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1 Genetic advancements and future directions in ruminant livestock breeding:

2 From reference genomes to multiomics innovations

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Abstract

Ruminant livestock provide a rich source of products, such as meat, milk, and wool, and play a critical role in global food security and nutrition. Over the past few decades, genomic studies of ruminant livestock have provided valuable insights into their domestication and the genetic basis of economically important traits, facilitating the breeding of elite varieties. In this review, we summarize the main advancements for domestic ruminants in reference genome assemblies, population genomics, and the identification of functional genes or variants for phenotypic traits. These traits include meat and carcass quality, reproduction, milk production, feed efficiency, wool and cashmere yield, horn development, tail type, coat color, environmental adaptation, and disease resistance. Functional genomic research is entering a new era with the advancements of graphical pangenomics and telomere-to-telomere (T2T) gap-free genome assembly. These advancements promise to improve our understanding of domestication and the molecular mechanisms underlying economically important traits in ruminant livestock. Finally, we provide new perspectives and future directions for genomic research on ruminant genomes. We suggest how ever-increasing multiomics datasets will facilitate future studies and molecular breeding in livestock, including the potential to uncover novel genetic mechanisms underlying phenotypic traits, to enable more accurate genomic prediction models, and to accelerate genetic improvement programs.

Keywords: ruminant livestock, genomics, domestication, genetic improvement

Introduction

Ruminant livestock include mainly taurine cattle (*Bos taurus*), zebu (*Bos indicus*), river- and swamp-type buffaloes (*Bubalus bubalis*), yaks (*Bos grunniens*), sheep (*Ovis aries*), goats (*Capra hircus*) and reindeer (*Rangifer tarandus*). Ruminants possess a unique digestive system that enables them to utilize plant cellulose more efficiently than other herbivores, such as camelids and horses. The largest livestock production systems worldwide rely on ruminants (Figure 1A), and these species provide major sources of products, such as meat, milk, and wool (Xu and Li 2017; Godde et al., 2021). The Food and Agriculture Organization (FAO) of the United Nations reported that more than 50% of protein and 17% of calories consumed worldwide come from animal sources, with ruminants as major providers (FAO, 2018). Ruminant meat and milk are important sources of calories, high-quality proteins, and micronutrients, including vitamins (A, B12, and B2), and minerals (calcium, iron, and zinc), and thus play critical roles in global food security and nutrition (Mottet et al., 2017). With the global population approaching 9.9 billion by 2,050, the demand for ruminant-sourced foods will continue to grow (Figure 1B) (Henchion et al., 2021). However, global climate change poses a significant threat to animal growth rates, milk production, reproductive performance, morbidity, and mortality, along with feed supply (Cheng et al., 2022). Breeding ruminant livestock with high productivity, resistance to diseases, and the ability to adapt to severe environments is necessary to address these challenges (Stranden et al., 2019). The keys to achieving these goals are developing and utilizing available genetic resources to implement advanced breeding

strategies (Abraham et al., 2019). Recent advances in sequencing technologies, data analysis algorithms, and pipelines for assembling genomes have greatly advanced our understanding of their genomes (Bovine et al., 2009; International Sheep Genomics et al., 2010; Canavez et al., 2012; Dong et al., 2013). Sequencing technologies such as PacBio single-molecule real-time and Oxford Nanopore sequencing can decrease error rates and increase the outputs of long reads (>10 kb) for the assembly of reference genomes. In addition, the application of “trio-binning” can achieve the *de novo* assembly of haplotype-resolved genomes, exceeding the quality and continuity of all previously assembled reference genomes (Koren et al., 2018). High-quality reference genomes facilitate gene annotation and reveal hidden genomic variations, which are crucial for studying chromosome evolution, genetic diversity and architecture and are essential for the practical application of gene editing technologies. From 2010 to 2023, reference genomes for representative ruminant livestock (Table 1), such as *ARS-UCD2.0* (Hereford) for taurine cattle, *Bos_indicus_1.0* (Nelore) for zebu, *NDDB_SH_1* (Murrah) for buffaloes, *BosGru_v2.0* for yaks, *ARS-UI_Ramb_v3.0* (Rambouillet) for sheep, *ARSI.2* (San Clemente) for goats, and *mRanTar1.h1.1* for reindeer, have improved our understanding of ruminant functional genomics.

Furthermore, the advent of comprehensive multiomics datasets encompassing genomic, proteomic, transcriptomic, metabolomic, and epigenomic information has significantly advanced our understanding of the domestication history and genetic underpinnings of economically vital and functional traits in ruminant livestock. Here,

we systematically review the research achievements in the genomic biology and breeding of domestic ruminants (Figure 2). Furthermore, we discuss the current situation of genomic studies for the genetic improvement of traits in ruminant livestock (Figure 2). Finally, we propose future directions for functional genomic studies and molecular breeding of ruminant livestock and thus provide a critical reference for advancing modern biological research and molecular breeding programs for domestic animals.

Ruminant livestock domestication

Animal domestication should be understood as a cumulative and gradual evolutionary process wherein animals are artificially selected, resulting in substantial phenotypic, behavioral, and physiological alterations for adaptation to captivity and to fulfill human needs (Diamond, 2002; Evin et al., 2015; Pitt et al., 2019a; McHugo et al., 2019; Chen et al., 2019; Wu et al., 2024a). The provision of meat, milk, wool, hides, and transportation has plausibly initiated the development of civilization (Mignon-Grasteau et al., 2005; Larson and Burger 2013; Larson and Fuller 2014). Three plausible pathways of domestication are described by Zeder (2012) and Larson and Burger (2013): *(i)* the commensal pathway, where wild animals were drawn to human habitats and developed a commensal relationship with humans; *(ii)* the prey pathway, involving species such as cattle, sheep, and goats, which were initially domesticated as food sources; and *(iii)* the direct pathway, where wild animals capable of performing specific tasks, such as horses for riding, were domesticated. We

proceed to summarize recent advances in understanding the origins and husbandry practices of several major ruminant livestock species, including bovines, sheep, goats and reindeer.

Origins

Archaeological evidence of the origins of taurine cattle, sheep, and goats traces back to approximately 10,500 years before present (YBP) in the Fertile Crescent (Figure 3).

Goats were probably the first animals to be domesticated in this area, followed immediately by sheep and taurine cattle. Taurine cattle in the *Bos* genus were the first to be domesticated from *Bos primigenius* (Verdugo et al. 2019; Zhang et al. 2020a).

Ovis is a complex mammalian genus that exhibits high interspecies variability in chromosome numbers ($2n=52$ to -58) and hybridization between wild and domestic sheep (Rezaei et al., 2010; Mereu et al., 2024). Domestic sheep originated from the ancestral Asian mouflon (*O. orientalis*) (Razaei et al., 2010; Kijas et al., 2012; Alberto et al., 2018; Her et al., 2022). Domestic goats (*C. hircus*) belong to the tribe Caprini, indicating a close resemblance to sheep. They are believed to descend from a mosaic of wild bezoar populations (*C. aegagrus*) (Naderi et al., 2008; Amills et al., 2017; Alberto et al., 2018; Zheng et al., 2020; Stiner et al., 2022).

The domestication of *B. primigenius namadicus* occurred in the Indus Valley, now in Pakistan, at approximately 8,500 YBP and resulted in humped indicine cattle (*Bo. indicus* or zebu cattle) (Figure 3) (Loftus et al., 1994; Dai et al., 2023). Zebu and

taurine cattle diverged approximately 137,000–317,000 YBP, suggesting descent from different auroch populations (Cubric-Curik et al., 2022; Pitt et al., 2019; Zhou et al., 2022). Domestic water buffaloes (*Bu. bubalis*) can be classified into two subspecies with distinct morphological, karyological and behavioral criteria: river buffaloes (*Bu. bubalis*, 2n=50), originally domesticated from the Indian subcontinent and Mediterranean countries between 4,000 and 5,000 YBP and used mainly for milk, and swamp buffaloes (*B. carabanesis*, 2n=48), likely domesticated around 4,000–5,000 YBP in a region adjacent to the border between China and Indochina and used primarily as draft animals (Figure 3) (MacGregor 1941; Nagarajan et al., 2015; Zhang et al., 2016). The two distinct types originated from different wild Asian water buffaloes (*B. arnee*) populations that diverged from approximately 860–900 kiloYBP and were subsequently domesticated in separate geographical regions (Zhang et al., 2011; Zhang et al., 2020b; Dutta et al., 2020). Domestic yaks (*Bo. grunniens*) were first domesticated from wild yaks (*B. mutus*) on the Qinghai–Tibet Plateau (QTP) during the early Neolithic period, around 7,300 YBP (Figure 3). This domestication was followed by a sixfold increase in the yak population size by 3,600 YBP (Guo et al., 2006; Qiu et al., 2015; Chen et al., 2023a; Liu et al., 2023a). Domestic reindeer (*R. tarandus*) originated from ancestral wild reindeer in the northern Fennoscandia at approximately 1500 YBP (Figure 3). However, approximately half of the global reindeer population is considered domesticated or semidomesticated.

Migratory pathways

Animal husbandry and food production contributed to the initial uneven division of labor within early human societies. With increasing demographic pressure, farmers and their animals began to spread beyond domestication centers into Europe, Asia, and Africa, leading to the global dispersal of agriculture. Currently, the rapid expansion of genomic resources, combined with archaeology, has revealed numerous unexpected insights into the hypothesized migration pathways of ruminant livestock species (Chen et al., 2018a; Zhang et al., 2020a; Dutta et al., 2020). For example, taurine cattle quickly spread across Europe from the northwest of the Fertile Crescent through Turkey into the Balkans and northern Italy, following either the Mediterranean coastline or part of the Danube River route (Figure 4A) (Beja-Pereira et al., 2006; Lenstra et al., 2014; Feliuss et al., 2014; Zhou et al., 2022). The migratory pathways of cattle across the European mainland are closely related to the expansion of Neolithic culture from southeastern Europe to Central/Western Europe (Scheu et al., 2015). Additionally, taurine cattle spread from Egypt westward along the northern coast of Africa, eventually reaching the Iberian Peninsula, which facilitated hybridization between taurine and local cattle (Figure 4A) (Anderung et al., 2005; Beja-Pereira et al., 2006; Decker et al., 2009; Zhang et al., 2020a; Günther et al., 2024). Additionally, archaeological records document the earliest introduction of cattle into East Asia from West Asia around 4,000–5,000 YBP (Chen et al., 2010, 2018). Similar migration routes worldwide, as indicated for cattle, are used for sheep and goats. Sheep migrated from their domestication center into other parts of Asia, Europe, Africa and the New World together with other livestock species (Figure 4B)

(Tapio et al., 2006; Singh et al., 2013; Niemi et al., 2013; Lv et al., 2014; Rannamae et al., 2016; Moradi et al., 2017; Zhao et al., 2017; Taylor et al., 2021; Lv et al., 2022). The first migration into Europe probably introduced mouflon-like hair sheep, which survived in a number of present semi-feral or feral North-European populations and in the European mouflon (Chessa et al., 2009; Ciani et al., 2020). The hair sheep were largely replaced by a second wave of wool sheep that also originated 3,000 YBP in the Middle East (Ryder 1987). A third important event was the emergence of fat-tailed sheep, which already occurred 3,000 YBP in Uruk (Moradi et al., 2012) and eventually spread to central Asia, southwest Asia and eastern Africa from Egypt to South Africa (Figure 4B). Following the north–southwest routes of Di-Qiang migration at approximately 3,000–5,000 YBP, Chinese sheep originating from the Mongolian Plateau spread throughout the upper and middle reaches of the Yellow River (Zhao et al., 2017). In addition to the fine-wool Merino sheep, several British breeds have become popular transboundary breeds (Porter et al. 2016). Domestic goats rapidly migrated from their domestication center into Europe via the Danubian and Mediterranean corridors (Figure 4B) (Daly et al., 2018; Zheng et al., 2020; Signer-Hasler et al., 2022). Compelling evidence suggests two independent dispersal corridors in the Asian region: the first pathway carried the Near Eastern goats’ gene pool to the Indian subcontinent and subsequently spread to Southeast Asia through overland and maritime routes; the second pathway traversed the Eurasian Steppe belt, linking the Middle East with Mongolia and northern China (Figure 4B) (Amills et al., 2017). Y chromosome variation revealed strong philographic contrasts in the male

domestic lineages. For example, goats separated eastward migrations of the Y1AB haplogroup into North Central Asia, Y1AA and Y2B into South Central Asia, Y1AB and Y1B into North Central Europe and Y2A into Africa (Vargoats et al., 2022). Much later, domestic goats were introduced to America and Oceania between the 15th and 18th centuries (Boyazoglu et al., 2005; Colli et al., 2018b). However, the migration route of goats to Southeast Asia remains unknown. Most dairy goats are derived from the transboundary Swiss Saanen, Alpine or Toggenburg breeds. The popular transboundary Boer and Anglo-Nubian breeds originated by crossing breeds from different continents (Porter, 1996).

Zebu cattle spread from their domestication site to Africa, East Asia and Southwest Asia between 1,300 and 4,000 YBP, resulting in hybridization between taurine and Zebu cattle across the landmass of Afro–Eurasia (Figure 4A) (Utsunomiya et al., 2019; Verdugo et al., 2019). In the nineteenth and twentieth centuries, zebu cattle were imported to the Americas and Oceania, where they formed large local populations and interbred with local Criollo cattle in the Americas (Ajmone-Marsan et al., 2010; Gautier and Naves 2011; Feliuss et al., 2015). River buffaloes migrated to Iran, Turkey, Egypt, the Balkans and Italy (Figure 4A) (Colli et al., 2018a; Zhang et al. 2020b). Following their domestication, the dispersal patterns of domestic swamp buffaloes, extended through peninsular Malaysia to islands in Indonesia (Sumatra, Java, and Sulawesi). From there, they moved north and northeast into central China, subsequently spreading across the Philippines and Borneo via an eastern island route

through Taiwan (Figure 4A) (Zhang et al., 2011). The yak range encompasses the entire Tibetan Plateau and the Pamir Mountains and extends to the Hangai Mountains (Jacques et al., 2021). Currently, reindeer hunting and herding have been conducted over most of the tundra and taiga areas of Eurasia (Fennoscandia, Siberia, and Mongolia) and North America (Canada, Alaska, and Greenland) (Pelletier et al., 2023). Two main independent reindeer domestication poles are present in Fennoscandia and western Russia (Pelletier et al., 2020). Two interbreeding subspecies of reindeer populations have been identified in Fennoscandia: mountain reindeer (*R. t. tarandus*), which are mainly distributed in the mountainous regions of southern Norway, and forest reindeer (*R.t. fennicus*), which live in the denser habitats of the taiga in southern Finland.

Genetic diversity during domestication and breeding

The evolution of domesticated animal species has contributed not only to genetic differentiation between domesticated species and their wild ancestors but also to increased phenotypic variation within species. This selection pressure was associated mainly with adapting the species to the local environment and increasing productivity. For example, domestic taurine cattle have been subjected to human- and environment-mediated selection, and since 200–300 YBP, they have diversified into more than 1,000 breeds (belonging to the European, African, and Asian lineages) displaying a diverse range of morphological and production phenotypes (McTavish et al., 2013; Felius et al., 2015; Campbell and Ranciaro 2021). As many as 1,400 breeds

of sheep have colonized worldwide via their adaptation to a broad range of climatic environments and varied production systems (Scherf 2000; Safari et al., 2005; Lv et al., 2014). Currently, more than 300 goat breeds are distributed worldwide with distinct morphological and production phenotypes, such as variations in horn, body size, cashmere and milk production, shaped by human selection, genetic isolation, the founder effect, and genetic drift (Ahmad et al., 2020; Panigrahi et al., 2022). The divergence of zebu cattle has led to different production phenotypes in term of milk yield, meat quality, stature, and coat color. Domestic water buffaloes have a global population exceeding 200 million and are distributed across 67 countries on five continents. Domestic yaks, with an estimated population of approximately 18 million individuals, typically live at elevations between 3,000 and 5,000 meters. These yaks exhibit unique adaptations to the low-oxygen conditions characteristic of the plateau (Meyer et al., 2009). In addition, ruminant livestock species also share several common features (*e.g.*, hooves and multi-chambered stomachs) while also displaying unique traits (*e.g.*, sheep for wool and tail types and goats for cashmere) that distinguish them from one another.

Notably, the timing of early breeding and corresponding human historical events are related primarily to shaping a rich source of phenotypic variation in ruminant livestock. Studying the timing of early breeding is crucial for understanding how genetic variations correspond to human activities and environmental conditions. For example, the selection pressures during the Neolithic Revolution (~10,000 YBP)

focused mainly on tameness and reproductive performance under human management. With the expansion of human civilizations in the Bronze Age (~1200–3300 YBP), selection for traits that increased meat yield, improved milk production, and wool quality was performed to meet the increased demand for livestock. In addition, agricultural expansion and trade routes, disease outbreaks and modern agricultural practices have played pivotal roles in shaping phenotypic variation in ruminant livestock (Morand et al., 2014). Understanding the factors related to past selection pressures is essential for predicting future individual and population responses to climate change.

With human selection for traits of interest for centuries, sex chromosome evolution and phenotypic convergence among ruminant livestock have fascinated evolutionary biologists. Sex chromosomes have significant implications for recombination, specialized gene content, dosage compensation and heteromorphic size (Abbott et al., 2017). Sex chromosome evolution affects animal genetic diversity and contributes to the development of unique adaptive traits in different environments. For example, Chen et al. (2018) detected strong selective footprints and related these signals to early domestication and accelerated genetic drift on the X chromosome in sheep (Chen et al., 2018). However, genetic drift may cause the loss of alleles over time, especially in small populations, which results from a reduction in genetic diversity that may diminish the capacity of animals to adapt to emerging environmental threats (Furlan et al., 2012). Similar traits evolve independently in distinct lineages during

convergent evolution. For example, ruminant livestock have evolved an efficient digestive system to degrade grass and obtain the necessary nutrients to maintain homeostasis (Stern 2013), as well as production traits such as reproduction, meat and dairy traits, and hornlessness. Yang et al. (2024) identified convergent selection targeting the *BMPRI1B* gene associated with fecundity traits in sheep and goats (Yang et al., 2024). Overall, understanding these molecular characteristics is essential for ensuring global food security and sustainable development in the future.

Genetic dissection of important traits in ruminant livestock

Advances in selection for production traits

The primary challenges to accommodate the growing global population are increasing the production of animal byproducts without compromising animal welfare and minimizing the environmental footprint (Grossi et al., 2019). For thousands of years, farmers have used selective breeding to improve desirable traits in ruminant livestock (Chen et al., 2019; Zheng et al., 2020). For example, milk is vital to the diets of millions of people worldwide because it provides important macro- and micronutrients (Visioli and Strata 2014). Various types of dairy livestock have been developed to meet consumer preferences and lifestyles for typical cheese, as well as to ensure higher quality and safety. These include cattle breeds such as Ayrshire, Brown Swiss, Guernsey, Holstein, and Jersey; sheep breeds such as East Friesian, Lacaune, and Awassi; and goat breeds such as the Saanen dairy goat (Adesogan and Dahl 2020; Moradi et al., 2021). Another example is the exceptional ‘double-muscled’ phenotype

of cattle resulting from mutations in the *MSTN* gene, which increase the number of muscle fibers and have attracted considerable attention from producers (Bittante et al., 2021; Guo et al., 2023). This phenomenon clearly demonstrates the intensive efforts by humans to improve the meatiness of both beef cattle and sheep. Economically important wool and cashmere traits in sheep and goats present distinct characteristics and have historically been bred for specific uses (Reis and Sahlu 1994; Li et al., 2017a; El et al., 2023).

The advent of affordable high-throughput sequencing technologies and the development of dense single nucleotide polymorphism (SNP) genotyping arrays have enabled the widespread adoption of genomic selection (GS) in livestock breeding programs. GS uses genome-wide marker data to predict the breeding values of selection candidates, allowing for more accurate selection at a younger age compared with traditional pedigree-based methods (Meuwissen et al., 2016). Many major livestock breeding companies now routinely use GS to accelerate genetic progress for important traits such as milk yield, growth rate, and disease resistance (Goddard and Hayes, 2009). Currently, selective breeding of ruminant livestock can be accelerated by advanced assisted reproductive technologies such as artificial insemination. As the costs of sequencing continue to decrease and the accuracy of genomic prediction models improves, the role of genomics in livestock improvement is expected to expand further in the future.

Identification of genes associated with phenotypic traits

Exploring the functional genes and genetic variants underlying economically important traits is foundational for innovations in modern animal breeding technology (Miglior et al., 2017). In the past decade, multiomics data, including genomic, proteomic, transcriptomic, metabolomic, and epigenomic data, have been explored to elucidate the genetic regulatory mechanisms underlying key traits related to meat, milk, reproduction and adaptation in ruminant livestock. Recently, genome-wide association studies (GWASs) have determined the associations between genomic variants, most commonly single nucleotide polymorphisms (SNPs), and phenotypic traits. Transcriptomic analysis is an efficient molecular genetic approach for identifying potential candidate genes, biological pathways, and noncoding RNAs associated with economically important traits. Additionally, proteomic and DNA methylation analyses have been proposed to incorporate genomic information on phenotypic traits. For example, Liu et al. (2022) detected expression/splicing quantitative trait loci in 23 distinct cattle tissues using a variety of omics data, including whole-genome sequencing, bulk RNA-Seq, DNA methylation, and ATAC-Seq data (Liu et al., 2022a). In addition, Yan et al. (2024) identified critical functional genes (*e.g.*, *HIF1A*, *PARG*, and *HMOX1*) associated with high-altitude adaptation in sheep during low-to-high-altitude translocation using multiomic data including whole-genome sequencing, bulk RNA-Seq, ATAC-Seq, and single-cell RNA-Seq data (Yan et al., 2024).

Comparative genomics, combined with multiomic data, can also serve as powerful tools for identifying the genes that are conserved among species, as well as those that endow each organism with its own unique characteristics. In this review, we summarize the common and unique genes and their genetic variations associated with economically important traits across cattle, sheep, and goats (Figure 5). The application of modern breeding systems, combined with advanced genomic knowledge, will facilitate omics-assisted breeding practices in ruminant livestock.

Meat and carcass traits

Meat is one of the most nutritious food products, supplying high-quality protein (essential amino acids), minerals (especially iron, selenium, and zinc) and essential vitamins, which are necessary for the growth and vitality of the human body (Maggiolino et al., 2022; Silva et al., 2023). As the demand for meat production grows in the ruminant livestock industry, geneticists and breeders are placing greater emphasis on improving growth and carcass traits. Recently, multiomics analyses have been developed to evaluate production qualities and improve meat production traits in ruminant livestock breeding (Wu et al., 2020a; Yu et al., 2023).

Many studies have identified the *MSTN* gene as a key regulator of muscle cell movement and growth in cattle, sheep, and goats (Figure 5) (Esmailizadeh et al., 2008; Ramayo-Caldas et al., 2016; Purfield et al., 2019; Sanchez et al., 2023). However, distinct genetic loci of the *MSTN* gene have been identified across cattle, sheep, and

397 goats. For example, a causative mutation (g.6723G > A) on chromosome 2 is
398 associated with the muscular hypertrophy by causing miRNA-mediated translational
399 inhibition of *MSTN* allele in the Texel sheep (Clop et al., 2006). A 5 bp
400 insertion/deletion is significantly associated with growth traits in goats (Bi et al.,
401 2020). *MSTN* belongs to the family of transforming growth factors, and its primary
402 function is to inhibit muscle mass gain (Figure 6A). By binding to activin type IIB
403 receptors, it inhibits AKT phosphorylation via the Smad2/Smad3 signaling pathway,
404 thereby increasing the expression levels of genes associated with atrophy. It also
405 blocks the expression of the factor MyoD, which enhances myogenesis (Aiello et al.,
406 2018). In addition, the common gene *IGF2* plays a role in intramuscular fat deposition
407 by activating the PI3K-AKT/AMPK signaling pathways (Duo et al., 2023). These
408 genes are worth considering in breeding work, as they can positively influence meat
409 yield and quality.

410
411 In addition, numerous unique candidate genes associated with meat and carcass
412 composition have been identified in cattle, sheep, and goats (Figure 5). In cattle, a
413 number of genes are associated with meat color, fat color, longissimus dorsi muscle
414 characteristics, and intramuscular fat content. For example, the *TRDN* gene has
415 previously been shown to be involved in muscle contraction and intramuscular
416 adipose accumulation. *TRDN* also participates in calcium signaling, which plays a
417 crucial role in skeletal muscle function (Sasaki et al., 2022). The *CAPNI* gene, which
418 encodes the enzyme μ -calpain, has been shown to induce changes in the expression

levels of certain regulators of myogenic factors. These myogenic factors play key roles in regulating muscle growth and development (Moyen et al., 2004; Lian et al., 2013). Notably, EGFR is implicated in regulating calpains through the ERK/MAPK signaling pathway (Galding et al., 2000). The *MUSTN1* gene is highly expressed in muscle tissue and is required for bone development, myotube establishment, muscle recovery, and regeneration (Hu et al., 2021). The transcription factor *PLAG1* was shown to affect the proliferation and apoptosis of primary myoblasts via the PI3K-AKT signaling pathway (Nishimura et al., 2012; Wang et al., 2022). Previously, a strong association of this gene with stature and growth traits was observed in diverse cattle breeds (Song et al., 2016; Abdelmanova et al., 2022). In sheep, multiple key genes are involved in growth and meat quality traits, such as carcass composition, muscle pH and marbling. For example, the TGF β 2 protein is an important member of the transforming growth factor beta 1 family and promotes F-actin polymerization in fibroblasts by stimulating myomerger expression (Girardi et al., 2021). The *ALDOA* gene encodes an enzyme that has been reported to be a glucose detector through interactions with mTORC1 and AMPK (Ren et al., 2011; Bai et al., 2022). *KDM4C* has been reported to play a critical role in muscle development by regulating H3K9me3 modification (Zhu et al., 2021). In goats, some genes have been identified as candidates related to meat quantity and quality. For example, HMGA2 regulates IGF2BP2 transcription and affects myoblast proliferation and myogenesis (Li et al., 2012). These candidate genes, regarded as important tools in shaping breeding programs, will increase our mechanistic

understanding of improving production efficiency and meat quality.

Reproductive traits

Reproductive performance is a critical factor determining the efficiency of flock production, especially in developing countries where ruminant livestock play a significant economic role (Martin et al., 2004; Abebe et al., 2023). Increased reproductive performance can lead to improved production efficiency in ruminant livestock. Therefore, genetic improvement can be achieved by identifying genetic loci that contribute to reproductive performance, which can increase the litter size and reproductive efficiency. This approach also provides valuable insights into the reproductive genetics and physiology of ruminant livestock.

Some common genes, such as *BMP15*, *BMPR1B*, *GDF9*, *PRLR*, and *ESR2*, are associated with reproductive performance in cattle, sheep, and goats (Figure 5). The well-known major fecundity genes *BMP15* and *GDF9* have been extensively studied (Våge et al., 2013; Chantepie et al., 2020; Calvo et al., 2020; Demars et al., 2013; Akhatayeva et al., 2022). The *BMP15* and *GDF9* genes play important roles in primordial follicle development, ovulation, corpus luteum formation, granulosa cell proliferation, and oocyte maturation through paracrine/autocrine signaling pathways (Swinerd et al., 2023). *BMPR1B* is expressed in granulosa cells and regulated by the BMP/SMAD signaling pathway (Figure 6B) (Abdurahman et al., 2019). Marchitelli and Nardone (2015) identified two nonsynonymous SNP mutations, g.6045 G>A

(p.V202I) in the *BMP15* gene and g.231 T>C (p.L66S) in the *GDF9* gene, which affect twinning in cattle (Marchitelli and Nardone 2015). The well-known variants, including the *BMP15* (FecX^B, FecX^G, FecX^H, FecX^I, FecX^L, FecX^O, FecX^R, FecX^{Bar}, and FecX^{Gr}), *BMP1B* (FecB^B) and *GDF9* (FecG^A, FecG^E, FecG^F, FecG^H, FecG^I, FecG^T, and FecG^V) genes, are associated with litter size in sheep (Mulsant et al., 2001; Campbell et al., 2006). Some mutations of the *BMP1B* (FecB) and *BMP15* (FecX^H, FecX^I, FecX^G, and FecX^B) genes are monomorphic in prolific goat breeds, indicating that the regulation of reproductive genetics may differ from that of sheep (Song et al., 2023). However, several high-fertility gene variants, such as those of *BMP15* and *GDF9* in sheep, are lethal if they are homozygous, which limits their frequency in the population (Derks and Steensma 2021). The *PRLR* gene belongs to the class I cytokine receptor family, which is critical for reproduction and shows high homology with the GHR. The binding of *PRL* to the receptor activates several signaling pathways, the most studied of which are the JAK 2–signal transducer and activator of transcription (STAT5) signaling pathway (Bouilly et al., 2012). Additionally, *ESR2* affects estrogen signaling, which contributes to folliculogenesis (Drummond and Fuller 2010). The functions of these genes significantly increase reproductive efficiency, and breeding work that utilizes them can significantly improve reproductive performance.

In addition, unique candidate genes have been reported to participate in regulating reproductive performance in cattle, sheep, and goats (Figure 5). In cattle, some genes

485 have been implicated as potentially linked to fertility. For example, *CRISP2* is
486 expressed in the testis and may regulate sperm motility via the RyR/Ca²⁺ channel (Lim
487 et al., 2019). The *PPP3CA* gene, a part of the serine/threonine protein phosphatase
488 superfamily, encodes the alpha isoform of a subunit of calcineurin and plays a role in
489 spermatogenesis via the Ca²⁺/CaN/NFAT signaling pathway (Silva et al., 2014).
490 *IGF1R* encodes the receptor of IGF1 and is involved in granulosa cell proliferation
491 and differentiation via the MEK/ERK or ATK/PI3K signaling cascade (Gusscott et al.,
492 2016). The expression levels of the *SRY* and *SOX9* genes are reduced in the IGF1R
493 knockout embryos, suggesting that insulin/IGF signaling is required for male
494 reproduction (Nef et al., 2003). The *SPEF2* gene, which encodes sperm flagellar
495 protein 2, is involved in the development of the sperm tail. Loss of SPEF2 function
496 may lead to defects in spermatogenesis (Li et al., 2022a; Sironen et al., 2011).
497 Moreover, numerous genes are associated with the age at first calving, calving
498 interval and conception rate in cows. For example, the *MEMO1* gene, which is
499 regulated by the kinase c-Src, controls estrogen receptor alpha, a hormone receptor
500 widely expressed in ovarian tissues and fallopian tubes that is responsible for
501 stimulating uterine myometrium growth and preparing the uterus for calving (Frei et
502 al., 2016). The *FST* gene plays a role in the formation of granulosa cells, and is
503 associated with the heifer and cow conception rates (Ortega et al., 2016). The *SMAD*
504 family genes, including *SMAD1*, *SMAD5*, and *SMAD8*, are also important factors in
505 the TGF- β /SMAD signaling pathway that participate in ovarian follicle development
506 and embryogenesis (Li et al., 2022b). Notably, *GHR* participates in the

GH/GHR-induced signaling pathway, which is required for IGF-1 production in granulosa cells and plays an important role in the regulation of fertility (Chang et al., 2022). Furthermore, the results of transcriptomic, proteomic, and methylomic analyses have identified several novel candidate genes that may serve as candidates for improving sheep fecundity (Gholizadeh et al., 2014; Pokharel et al., 2018; Hernández-Montiel et al., 2019; La et al., 2020; Gao et al., 2021a; Shariati et al., 2023; Dong et al., 2023; Chang et al., 2023). For example, CYP17A1 is an essential steroidogenic enzyme that is required for estrogen production in granulosa cells by regulating FSH (Heidarzadehpilehrood et al., 2022). In addition, the *BBX* and *CD47* genes were reportedly associated with the supernumerary nipple phenotype by regulating the Wnt and MAPK signaling pathways (Peng et al., 2017). In goats, numerous genes have been reported to be involved in reproductive processes such as follicle development. IGFBPs that bind to IGF-1 and IGF-2 induce steroidogenesis and luteinizing hormone production in granulosa cells (Zhou et al., 2013). *TGFBRI* encodes a TGF- β type 1 receptor that participates in the TGF- β and GDF9 signaling pathways involved in ovarian folliculogenesis (Li et al., 2011). A more recent testicular transcriptome study revealed tissue-specific genes (*e.g.*, *FSIP2* and *TDRD9*) related to male reproductive traits (Xu et al., 2024). *FSIP2* is an MMAF-associated gene associated with sperm flagella that plays a role in sperm motility (Fang et al., 2021). The TDRD9 protein is expressed in germ cells and plays a role in the ping-pong cycle of the piRNA pathway and spermatogenesis (Liu et al., 2022b). Therefore, these genes function to significantly improve follicle development and

spermatogenesis, and breeding programs that utilize them can greatly increase reproductive performance.

Dairy traits

Milk and dairy products are important elements in a healthy and balanced diet to ensure proper growth and development (Givens 2020). For example, milk proteins contribute to the expression of insulin-like growth factor-1, which is necessary for bone growth and bone mass formation in young children, thus reducing the risk of stunting (Pereira 2014). The dairy industry is often regarded as a large and dynamic economic sector, with dairy consumption continuing to increase in many countries and regions worldwide. Milk traits exhibit considerable phenotypic diversity, which has attracted the attention of animal geneticists and genomicists aiming to elucidate the underlying genetic and genomic determinants.

This research seeks to identify common genes (*e.g.*, *DGATI*, *CSN1S1*, *CSN1S2*, *CSN2*, *CSN3*, *LALBA*, and *ABCG2*) related to milk traits across cattle, sheep, and goats (Figure 5), and with the advancement of next-generation sequencing technologies, the understanding of the genetic bases underlying dairy traits has improved dramatically. Several authors have reported that the *DGATI* gene is a promising genetic marker for milk yield, fat content, and protein content (Grisart et al., 2002; Sanchez et al., 2017; Nayeri et al., 2016; Do et al., 2018; Jiang et al., 2014; Jiang et al., 2019). Notably, the mutation (K232A) detected in *DGATI* has been widely studied for its association with

551 milk fatty acids in dairy cattle (Houaga et al., 2018). A ruminant-specific enhancer of
552 *DGAT1* is also associated with the protein percentage (Chen et al., 2022). *DGAT1*
553 regulates triglyceride synthesis, thereby depositing excess fatty acids from the body
554 into lipid droplets. Silencing of the *DGAT1* gene significantly reduces the triglyceride
555 content in bovine mammary epithelial cells (Lu et al., 2012). The four primary casein
556 fractions have different genetic variants, including aS1 (CSN1S1), aS2 (CSN1S2), p
557 (CSN2), the k (CSN3), which regulate the expression of milk yield and protein in
558 cattle, sheep, and goat populations (Bovenhuis et al., 1992; Suárez-Vega et al., 2016;
559 Crisà et al., 2016; Suárez-Vega et al., 2017; Suárez-Vega et al., 2018; Mucha et al.,
560 2018; Hao et al., 2019; Corredig et al., 2019; Scholtens et al., 2020; Guan et al., 2020;
561 Michailidou et al., 2021; Massender et al., 2023). The *LALBA* gene encodes the main
562 milk protein that binds to Ca^{2+} and enables lactose synthesis in goats (Čítek et al.,
563 2023). The *ABCG2* gene has been shown to affect milk production and the milk
564 content in dairy cattle and sheep (Olsen et al., 2007; Garcia-Fernandez et al., 2011;
565 Iung et al., 2019). This gene plays a critical role in mammary gland differentiation and
566 branching of the mammary epithelial ductal system and participates in transporting
567 cholesterol into milk (Wei et al., 2012). In addition, unique candidate genes have been
568 suggested to be potentially linked to milk yield, the milk fat content, and protein
569 percentage in cattle, sheep, and goats (Figure 5), respectively. For example, an
570 integrated study of genome-wide DNA methylation and gene expression examined the
571 association of the *PIK3RI* gene with the milk fat percentage (Dong et al., 2021).
572 *PIK3RI* can relieve lipid disorders in adipocytes and may be linked to the AMPK,

mTOR, insulin, and Jak-STAT signaling pathways (Han et al., 2019). Some genes, including *SLC35A3* (milk fat and protein percentage), *CCDC152* (lactation persistency and somatic cell count), and *NT5DC1* (lactation persistency), are associated with milk traits in sheep. In goats, several milk yield-related genes, such as *VPS13C*, *RPL3*, and *ABCG2*, have been identified (Zhang et al., 2018; Amiri et al., 2023). Therefore, these genes provide new insights into the genetic basis of milk properties and can contribute to the design of ruminant livestock breeding programs that incorporate genomic information.

Feed efficiency

Feed efficiency is a highly complex trait that is described as the relative ability of animals to turn feed nutrients into products such as meat and milk (Kenny et al. 2018). The genetic selection of animals with low residual feed intake (RFI) not only improves overall profitability and decreases greenhouse gas emissions but can also optimize the use of food resources. Researchers have started to identify common genes (*e.g.*, *MC4R*, *UCP2*, and *FGF21*) associated with feed efficiency across cattle, sheep, and goats (Figure 5) (Taussat et al. 2020; Salleh et al. 2018; Yang et al. 2022). *MC4R* plays critical roles in the control of appetite, energy expenditure, and body weight (Krashes et al., 2016). *UCP2* is a mitochondrial anion carrier protein that plays a regulatory role in energy metabolism by uncoupling oxidative phosphorylation (Pierelli et al., 2017). *FGF21*, a novel polypeptide ligand, contributes significantly to regulating lipid storage and utilization in both adipose tissues and the liver in response

to energetic and nutritional cues (Lin et al., 2017).

In addition, unique genes have been suggested to be potentially linked to feed efficiency in cattle, sheep, and goats (Figure 5). For example, the common energy consumption controlled by the *ADAM12*, *CAMK2G* and *CXADR* genes is associated with RFI in cattle (de et al., 2014). *ADAM12* has been shown to regulate remodeling of the extracellular matrix, modulation of cell morphological changes, satellite cell activation, and ectodomain shedding during signaling in muscle and fat development (Coles et al., 2014). The *CAMK2G* gene has been implicated in the regulation of biological processes, such as osteogenic differentiation, maintenance of vascular tone, the cell cycle and protein amino acid phosphorylation (Panizza et al., 2019). *CXADR* plays a role in muscle organ development, the regulation of organ growth, muscle tissue development and the regulation of developmental growth (Shi et al., 2023a). Previous studies revealed that the genes *ARPC1A* and *TRRAP* are associated with predicted methane emission and valeric acid traits (Jalil et al., 2020). *ARPC1A* is involved in the regulation of actin polymerization and, together with a nucleation-promoting factor, affects the formation of branched actin networks (Fokin et al., 2024). *TRRAP* is a multidomain adapter protein that participates in histone acetyltransferase activity and interacts with a specific tag for epigenetic transcriptional activation (Cogne et al., 2019). In sheep, key candidate genes, such as *MEI*, *CAI*, and *ADCY8*, affecting feed efficiency have been identified (Zhang et al., 2021a; Yang et al., 2023). In goats, some genes (*e.g.*, *BAG4*, *POU3F4*, and *SMPX*)

participate in regulating metabolism, digestion, and nutrient absorption processes (Ncube et al., 2022). However, the identified candidate genes need to be validated in independent studies to provide a deeper understanding of the genetic architecture of feed efficiency.

Environmental adaptation

Indigenous ruminant livestock have adapted to their local conditions, including extreme natural environments, for hundreds or even thousands of years, achieving homeostasis that is optimally suited to the demands of their environments (Pitt et al., 2019b; Weldenegodguad et al., 2019; Tian et al., 2023a; Delandmeter et al., 2024). Recent advances in sequencing and genotyping technologies have enabled the identification of genomic changes in ruminant livestock associated with adaptation to diverse environmental conditions. Several genes (*e.g.*, *HSP70*, *HSP90*, *HSPB6*, *UCPI*, *PPAR γ* , *MHC*, and *EPASI*) are commonly associated with environmental adaptation across cattle, sheep, and goats (Figure 5). *HSP70*, *HSP90*, and *HSPB6*, which are heat shock proteins, are crucial for heat tolerance, especially in regions with high temperatures, as they regulate diverse vital physiological processes, such as smooth muscle relaxation and platelet aggregation (Li et al., 2017b; Taborda-Charris et al., 2023). The *UCPI* gene is involved in maintaining body temperature in animals exposed to cold climates by uncoupling oxidative phosphorylation in mitochondria (Tsubota et al., 2019). The *PPAR γ* gene plays a role in regulating fat metabolism and energy homeostasis (Wang 2010). The *MHC* genes (MHC class I and class II) play

integral roles in adaptive immune function and are crucial for pathogen resistance and adaptability to different environments (Day et al., 2024). *EPAS1* regulates the heterodimeric transcriptional complex HIF-1, which leads to increase angiogenesis, erythropoiesis, and certain metabolic changes, resulting in increased oxygen delivery to skeletal muscles (van Patot and Gassmann 2011). These genes should be highlighted to develop high-yielding ruminant livestock resistant to stressors associated with harsh environmental conditions through genomic selection procedures.

In addition, some unique genes allow cattle, sheep, and goats to adapt to a wide range of environmental conditions (Figure 5). Several studies have identified candidate genes related to stress or the immune response (*CCL14*, *PBRM1*, and *ADAMTS12*) (Vanvanhossou et al., 2020), cold shock response (*MSANTD4*), body thermoregulation (*EGR1* and *STING1*) (Igoshin et al., 2019; Huang et al., 2023), and adaptation to extensive tropical environments (*PLAG1*, *PLRL*, *MSRB3*, *AQP5*, and *RETREG1*) in cattle (Porto-Neto et al., 2014; Yurchenko et al., 2018; Pitt et al., 2019b). *ADAMTS12* plays a critical role in various inflammatory processes through the activation of the Wnt/ β -catenin signaling pathway (Li et al., 2020a). UQCR11 is a part of the mitochondrial respiratory chain and participates in thermoregulation (Lin et al., 2023). Lyu et al. (2024) investigated the adaptation of cattle to the high altitude of the QTP and reported that recent selection has targeted genes related to body size (*HMGA2* and *NCAPG*) and energy expenditure (*DUOX2*)

in Tibetan cattle (Lyu et al. 2024). Other variants from yaks occurring via adaptive
 introgression include variants in genes responsible for the hypoxia response (*EGLN1*),
 cold adaptation (*LRP11*), DNA damage repair (*LATS1*), and UV radiation resistance
 (*GNPAT*) (Wu et al., 2018). Whole-genome sequencing of yaks (Qiu et al., 2012) and
 the construction of bovine pangenomes (Liu et al., 2023a) suggested that genes
 involved in the high-altitude adaptation are enriched in functional categories and
 pathways related to sensing the extracellular environment, hypoxic stress, hypoxia
 and nutrient metabolism. A comparison of structural variants detected by long-read
 sequencing of wild and domestic yaks revealed genes that are potentially involved in
 domestication and are predominantly related to the nervous system, behavior,
 immunity, and reproduction (Zhang et al., 2021b; Liu et al., 2023a). In sheep, a
 meta-analysis identified 219 selective sheep genes related to adaptation (Fonseca et al.,
 2024). Several studies have identified candidate genes associated with high-altitude
 adaptation (Gorkhali et al., 2016; Wei et al., 2016; Hu et al., 2019; Zhang et al., 2021c;
 Wiener et al., 2021) and desert environments (Yang et al., 2016). For example, the
HIF1 α gene is a critical transcriptional regulator of the tissue response to low-oxygen
 stress (Lee et al., 2019). *MITF* co-regulates a subset of hypoxia-responsive genes and
 alters cellular metabolism to suppress pseudohypoxia (Loupphasitthiphol et al., 2019).
GPCPD1 is important for hypoxia-induced mitophagy and is regulated by
HIF1 α under hypoxic conditions (Liu et al., 2023b). Some structural variants in
EPAS1, *PAPSS2*, and *PTPRD* genes that involved in cardiac function and circulation
 were associated with the physiological response to hypoxia, which contributed to the

high-altitude adaptation of Tibetan sheep (Liang et al., 2024). Several goat genes are involved in high-altitude adaptation (Wang et al., 2016; Manunza et al., 2023), the adaptation to hot climates, immune response (Amiri et al., 2023), lipid metabolism, hypoxia stress/lung function, seasonal patterns or neuronal function (Serranito et al., 2021). For example, *TRAP1* participates in mitochondrial metabolism, induces the transcription of HIF1 α and inhibits its proteasomal degradation (Laquatra et al., 2021). *CDK2* also interacts with HIF-1 α , and plays a role in the cell cycle under hypoxic conditions (Hubbi et al., 2014). *DSG3* *FGF5*, and *PAPSS2* genes are key adaptive genes for Tibetans goat by regulating hypoxia response pathway (Wu et al., 2020b; Li et al., 2022c). Identifying these genes will clarify the genetic mechanisms responsible for successful domestication and provide a better understanding of the practical breeding strategies needed to increase productivity and resilience to environmental challenges.

Disease resistance

Improved disease control in ruminant livestock contributes to animal welfare (Berry et al., 2011; Knap and Doeschl-Wilson 2020), whereas veterinary biomedical studies may also be relevant for human medicine. Inflammatory factors and pattern recognition receptors play crucial roles in the pathogenesis of diseases in cattle, sheep and goats (Figure 5). For example, *IL-4* and *IL-13* have similar biological activities that regulate the proliferation and functional activity of B and T lymphocytes. The binding of IL-4 and IL-13 to their cell surface receptors activates the cytoplasmic

IL-4R α domain and the JAK1/STAT6 signaling pathway (Jiang et al., 2000). The chemokines encoded by *CXCL1*, *CXCL9*, *CXCL10*, and *CXCL11* are involved in leukocyte activity and inflammation by regulating the NF- κ B, PI3K/AKT, MAPK, and STAT3 signaling pathways (Zhou et al., 2023). The Toll-like receptors TLR5 and TLR9 are pattern recognition receptors that promote inflammatory cytokine secretion by activating the NF- κ B and MAPK signaling pathways (Oliveira-Nascimento et al., 2012).

Paratuberculosis, caused by *Mycobacterium avium paratuberculosis*, is a chronic and contagious granulomatous enteritis that leads to progressive weight loss, debilitation, and eventually death in cattle and other ruminants. Several candidate genes related to resistance to bovine paratuberculosis or tuberculosis have been identified (Ring et al., 2019; Sanchez et al., 2020; Canive et al., 2022; Xia et al., 2023). For example, *ABCC4* is a member of the ATP-binding cassette subfamily C subfamily and is also known as a multidrug resistance protein. *ABCC4* participates in ion transport, toxin extrusion, and signaling processes (Wang et al., 2021). IER3 is activated by cytokines or infections and is involved in the PI3K/AKT, NF- κ B, and MAPK/ERK pathways (Arlt and Schäfer 2013). Importantly, major genes (*DRA*, *DRB3*, and *DQ* family) that control humoral and cellular immune responses to a variety of antigens have been mapped to the region of bovine autosome 23 known as the major histocompatibility complex (Behl et al., 2012; Miyasaka et al., 2012). Bovine spongiform encephalopathy, commonly known as mad cow disease, is a progressive and fatal

nervous system disease in bovines caused by the accumulation of an abnormal protein called a “prion” in nervous tissue. Scrapie is also a degenerative and fatal disease that damages the central nervous system of sheep and goats. Some genes related to bovine spongiform encephalopathy and scrapie were identified. For example, the *PRNP* gene plays a critical role in the vulnerability to prion diseases (Won et al., 2020). The ability of genomics to identify previously unrecognized diseases was elegantly illustrated by Novosel et al. (2022). In their study on mitogenome diversity (Cubric-Curik et al., 2022), Cubric-Curik and colleagues identified the harmful T10432C mutation in the bovine mitogenome. A more detailed investigation revealed that this mutation, which is transmitted through homoplasmic maternal inheritance, results in clinical and histopathological changes similar to Leber's hereditary optic neuropathy in humans (Novosel et al., 2022). In sheep, a number of genes are associated with disease resistance (Arzik et al., 2022; Al Kalaldehy et al., 2019; Becker et al., 2020; Atlija et al., 2016; Ahbara et al., 2021). The *PADI2* gene is essential for antibacterial innate immunity in sheep (Cao et al., 2021). Furthermore, some genes, such as *TGF-β*, *MAPK*, and *CAMs*, contribute to nematode resistance in goats (Bhuiyan et al., 2017; Aboshady et al., 2021). Therefore, these genes significantly contribute to the overall health and disease resistance of ruminant livestock.

Wool traits of sheep and goats

The wool industry annually consumes approximately 1,160 million kilograms of clean wool produced from a global herd of over a billion sheep. The economic value of

wool production depends on various parameters, such as the fiber diameter, length, and strength. Generally, wool traits are influenced by diverse genetic and environmental factors and exhibit moderate to low heritability (Zhao et al., 2021). Several genes related to wool traits in sheep have been found to be involved in these traits (Figure 5). For example, major keratin-associated genes, such as the *FGF5*, *BMPRI1A*, *TNF*, and *KIT* genes, have been identified using RNA-Seq (Shi et al., 2022). More specifically, *FGF5* encodes a protein called fibroblast growth factor, which functions as an inhibitor of hair elongation. Loss-of-function mutations in the sheep *FGF5* gene created using CRISPR/Cas9 editing resulted in significantly longer wool staple and stretch lengths (Li et al., 2017a). *BMPRI1A* is a member of the bone morphogenetic protein family that is involved in triggering hair follicle initiation, and *BMPRI1A* has been shown to be critical for inner root sheath differentiation in mice (Yuhki et al., 2004). *TNF- α* is an inflammatory cytokine, and macrophages activated by *TNF- α* can promote hair growth in wounds via the AKT/ β -catenin cascade (Wang et al., 2017). By binding to its ligand *KITLG*, the *KIT* proto-oncogene receptor tyrosine kinase activates tyrosine kinases and plays a crucial role in the regulation of melanocytes. Mutations in *KIT* are involved in hair pigmentation (Guenther et al., 2014).

Cashmere goats contain two types of coats, a primary type of hair follicle producing coarse hair and a secondary type of hair follicle producing fine cashmere fiber, which is famous for being finer, softer, lighter, and more insulating than sheep wool, and is

thus regarded as a luxury fiber. Researchers have attempted to identify the genetic variants controlling higher cashmere quality and yield (Figure 5); for example, the *FA2H* gene has been suggested to influence cashmere fineness (Wu et al., 2022). *FA2H* stimulates the proliferation of dermal papilla cells in cashmere secondary hair follicle and is associated with cashmere traits (Wu et al., 2022). A member of the fibroblast growth factor family, *FGF12*, promotes hair growth by interacting with the Wnt and TGF- β signaling pathways (Mossahebi-Mohammadi et al., 2020). Keratins and keratin-associated proteins play important roles in hair growth (An et al., 2022). Keratin proteins are targeted by estrogen and ECM receptor signaling pathways in the regulation of cashmere growth (Gao et al., 2021b). *SOX2* has also been shown to regulate hair growth by fine-tuning the BMP signaling pathway (Clavel et al., 2012). These genes provide functional insights into the genetics of wool quality and production traits, which will be important for improving breeds with enhanced wool quality and production characteristics.

Horns

Horns are paired frontal appendages that are unique to bovid species that include cattle, sheep, and goats, comprising a bony core and an exterior keratin sheath. The primary functions of horns include defense against predators and competition between males for breeding access to females. Additionally, horns may play a role in thermoregulation (Algra et al., 2023). Nonetheless, domestic bovid species with horns pose a significant health risk to other livestock and handlers, and damage from horns

may result in economic costs due to bruised tissue, which must be trimmed when the meat is processed (Aldersey et al., 2020). In recent years, a series of research advances have improved our understanding of horn development. In cattle and sheep, the *RXFP2* gene has been reported to be associated with the development of horn size and shape (Figure 5) (Hu et al., 2019; Aldersey et al., 2020; Xu et al., 2021; Guo et al., 2021a). The RXFP2 protein is conjugated to G protein-coupled receptors, and its function triggers the cAMP and Wnt signaling pathways (Tian et al., 2023b). A recent study reported that deletion of the *RXFP2* gene reduced its expression in the skin. However, sheep exhibit apparent unilateral cryptorchidism, suggesting that the gene is associated with testicular descent and horn formation (Gao et al., 2023). This study also provides evidence for a hitherto ambiguous connection between both horn and testicular development. Previous studies have shown that the genes *IFNAR2*, *IFNGR2*, *OLIG1*, *OLIG2*, and *SOD1* might be related to the horn formation in cattle (Figure 5) (Stafuzza et al., 2018). In sheep, *HOXD* gene clusters (*HOXD1*, *HOXD3*, *HOXD4*, and *HOXD8-HOXD13*) reportedly participate in regulating the polycerate phenotype (Figure 5) (Ren et al., 2016). In goats, the *KCNJ15* and *ERG* genes might be major candidate genes influencing horned and polled phenotypes (Figure 5) (Guo et al., 2021b). Collectively, these genes could improve our understanding of the genetic mechanisms of horn formation.

Tail

The fat-tail phenotype is a unique adaptation in sheep that emerged around 3000 YBP

to withstand harsh environmental conditions, such as steppe and desert environments, and food scarcity in Central Asia (Dong et al., 2020). However, this phenotype has become less desirable for both producers and consumers because of several negative effects. Fat tails can significantly impact animal locomotion, mating efficiency, food conversion rates, and breeding costs, among other factors (Luo et al., 2021; Kalds et al., 2022). Compared to traditional husbandry practices such as tail docking, genetic improvement is a promising approach for reducing tail size in sheep. It is reliable, long-lasting, and may improve animal welfare (Dong et al., 2020). Identifying genetic variants underlying fat-tail phenotypes is crucial for this approach (Figure 5). For example, the *PDGFD* gene has been identified as a causal gene for fat deposition in the tails of sheep (Wei et al., 2015; Li et al., 2020b; Dong et al., 2020; Kalds et al., 2023). *PDGFD* regulates the proliferation and migration of adipose-derived stem cells through the PI3K/AKT signaling pathway, which is involved in preadipocyte differentiation (Figure 6C) (Hye Kim et al., 2015). Additionally, the *BMP2* gene has been proposed to be associated with tail types (Pan et al., 2019; Zhao et al., 2020; Xu et al., 2023). *BMP2* participates in white adipogenesis through the induction of PPAR γ (Schreiber et al., 2017). Recently, studies of sheep revealed that the *HOXB13* and *TBXT* genes (Figure 6D) are responsible for the long-tail trait (Li et al., 2022d, 2023). Additionally, the role of the *FABP4* gene in fat deposition in the tails of some sheep breeds has been examined (Li et al., 2018; Bakhtiarizadeh et al., 2013). The gene is expressed in adipocytes and participates in regulating PPAR γ activity (Garin-Shkolnik et al., 2014). Collectively, these genes not only help researchers

elucidate the molecular mechanism of the fat-tail phenotype but also provide valuable theoretical insights into sheep evolution.

Coat color

With domestication, specialized elite breeds for milk, meat, or fibers as well as breeds with unique coat color phenotypes adapted to different habitats, climate conditions, or human preferences, have been produced. The variation in coat color phenotypes primarily involves three major mechanisms: *i*) melanocyte migration and differentiation, *ii*) melanocyte signaling and regulation, and *iii*) melanin production and transport (Fan et al., 2013; Bhat et al., 2019). With the emergence of high-throughput sequencing technologies, we identified common genes affecting coat color phenotypes across cattle, sheep and goats (Figure 5). In recent years, major genes have been confirmed to be associated with spatial and temporal pigment-type switching (*MC1R* and *ASIP*), pigment dilution (*TYR* and *TYRP1*) and the regulation of the migration and survival of melanocytes (*KIT*, *MITF*, and *KITLG*) (Durkin et al., 2012; Schmutz and Dreger 2013; Meszaros et al., 2015; Rajawat et al., 2023; Gebreselassie et al., 2020; Zhang et al., 2023). For example, *MC1R*, a factor driving of cutaneous pigmentation and cortisol production, is involved in the regulation of melanogenesis and pigmentation by binding to its ligand α -melanocyte stimulating hormone (Herraiz et al., 2021). Furthermore, different alternative promoters of the agouti signaling gene (*ASIP*) regulate the temporal and spatial expression of the gene, producing diverse pigmentation patterns of eumelanin and pheomelanin synthesis

(Norris and Whan 2008; Henkel et al., 2019; Trigo et al., 2021). *MITF* plays crucial roles in melanocyte differentiation and pigment production. *TYR* and *TYRP1* have been reported to be involved in regulating the melanin biosynthesis pathway (Wagatsuma et al., 2023). *MC1R* has also been shown to regulate the expression of *TYR* and *TYRP1*, which synthesize melanin via the cAMP pathway (Saternus et al., 2015). However, while extensive evidence for positive selection driving the choice of coat color in ruminants (*e.g.*, white fleece in sheep) is available, evidence also indicates the relaxation of selective constraints on coat color genes upon domestication, *e.g.*, the tyrosinase–kinase ligand locus *KITLG* in goats, where constraints in coat coloration in the wild became irrelevant under human-managed settings under domestication (Alberto et al., 2018). Therefore, these genes are crucial for enhancing the efficiency of artificial selection for a desirable coat color and for studying evolutionary changes related to phenotypic variation in farm animals.

Genome design in ruminant livestock breeding

Conventional breeding has made significant contributions to the agrarian economy, particularly in the development of elite domestic animal breeds. The accelerated growth and availability of genomic resources for domestic animals has improved the efficiency of genetic improvement (Georges et al., 2019; Gong et al., 2023). Future advances in the genome design of ruminant livestock in the genomics era will rely on three major avenues, *i.e.*, the selection of natural alleles from germplasms, the creation of novel genes/alleles by genetic modification, and interspecific hybridization

between ruminant livestock and their wild relatives. However, the latter can be controversial within the context of the need to preserve genomic resources from genetic erosion through hybridization according to the AICHI target 13 of the Convention on Biological Diversity (<https://www.cbd.int/aichi-targets/target/13>).

Molecular markers

The use of DNA markers via marker-assisted selection has become a powerful and effective strategy to localize genes contributing to desirable traits in the genomes of domestic animals. Over the past few decades, the development of molecular markers has been time-consuming, laborious, and cost-ineffective because of the absence of specific genomic resources. Recent advances in omics technologies have significantly contributed to the application of molecular marker assays (*e.g.*, simple sequence repeat (SSR), insertion and deletion (InDel), and SNP markers) for the mapping and discovery of genes associated with phenotypic traits in ruminant livestock (Laoun et al., 2020). For example, Xu et al. (2017) identified 11,676 SSRs that overlapped with functional genes and quantitative trait loci (QTLs) by using high-throughput sequencing in dairy cattle (Xu et al., 2017). Many InDel markers associated with growth traits in ruminant livestock have also been identified and subsequently applied in practical breeding (Mesbah-Uddin et al., 2018; Li et al., 2021a; Zhou et al., 2022; Li et al., 2023a). Due to their ubiquitous presence, uniform distribution, and biallelic nature, however, SNP markers have become the best choice for genomic studies that demand high-density markers with whole-genome coverage (Laoun et al., 2020). On

the other hand, large structural variations (SVs) have been identified by long-read sequencing and pangenome construction (see below) and were found to be causative for or significantly associated with desirable traits (Low et al., 2020; Zhou et al., 2022; Guo et al., 2022; Li et al., 2023b).

Gene and genome editing

Gene editing provides new opportunities for genetic improvement by engineering genetic variation (*e.g.*, fixing desirable allelic variants, generating novel alleles, breaking deleterious genetic linkages) and supports prebreeding for the introgression of beneficial variants into elite lines (Park 2023).

Genetic modification of farmed animals to increase productivity, increase disease resistance, and reduce the environmental footprint has been a long-standing goal. Recently, genome-editing technologies, such as FokI-based zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and, more recently, CRISPR-Cas9-based gene editing, have been applied to introduce desirable traits in ruminant livestock. For example, the *MSTN* gene, a major regulator of muscle development, was first identified in heavily muscled cattle breeds (*e.g.*, Belgian Blue and Piedmontese) and sheep breeds (*e.g.*, Texel) by targeting QTLs for meat traits. The CRISPR/Cas9 system was subsequently used to edit *MSTN* mutations in cattle, sheep, and goats (Proudfoot et al., 2015; Proudfoot et al., 2015; Crispo et al., 2015; Wang et al., 2018). These mutations significantly enhanced growth and muscle

development in ruminant livestock and could be considered markers for the genetic testing of meat traits. The *PDGFD* gene was reported to be associated with the fat-tail phenotype in sheep via a comprehensive genomic analysis (*e.g.*, genomic, transcriptomic, and metabolomic analyses) (Wei et al., 2015; Li et al., 2020b; Dong et al., 2020; Xu et al., 2023). Furthermore, histological and gene expression analyses, combined with the CRISPR/Cas9 system, were conducted to determine the association of gene expression with fat deposition in sheep by regulating adipogenesis and maintaining the hemostasis of mature adipocytes (Li et al., 2020b; Dong et al., 2020; Kalds et al., 2023). This gene could be used for molecular marker-assisted selection of sheep tail phenotypes. Clearly, genetic modification can provide substantial benefits to the livestock sector, resulting in faster, cheaper, healthier, and more efficient livestock production with reduced environmental impacts. Another application is the generation of polled cattle (Schuster et al., 2020; Mueller et al., 2021). However, we also summarize the gap between trait resolution and genome design. The main challenge is that quantitative traits are influenced by multiple genes that often interact within regulatory networks. Additionally, environmental factors significantly affect the formation of traits, making the identification of the exact genetic variations involved difficult. Additionally, the precision of gene editing tools still needs to be improved.

An interesting concept is the application of genome editing to artificial interspecific hybridization. The effects of selection during domestication and breeding reduce

genetic diversity and diminish disease resistance in all domestic animals (Groeneveld et al., 2010). These limitations have been counteracted by hybridization with wild relative species, especially during the earliest stages of domestication (Larson and Fuller, 2014). The application of genomic technology has advanced to artificial interspecific hybridization between domestic animals and their wild relatives, with the exception of cattle, which could transfer favorable domestication traits to wild ancestral species (Jian et al., 2022). This process would also allow a dissection of the genetic basis of complex phenotypes in domestic animals. This goal was accomplished by the identification of genetic variation associated with important production traits in an argali–sheep hybrid population (Li et al., 2022d). The identification of candidate genes will provide novel options for CRISPR/Cas9-based genome editing techniques to introduce a variety of precise modifications in ruminant livestock genomes (Figure 7). For example, the tail volume of TBXT-edited sheep produced using the CRISPR/Cas9 system was significantly reduced (Li et al., 2022d). We envisage a more widespread use of CRISPR/Cas9-based genome editing techniques, which will significantly expedite the examination of gene functions and elucidate the mechanisms underlying important traits.

Pangenome and telomere-to-telomere (T2T) gap-free genome assembly

Although high-quality chromosome-scale assembly reference genomes for domestic animals (*e.g.*, cattle, sheep, and goats) have been established, the reference genome assembled from a single individual cannot fully represent the extent of genetic

variation at the species level, especially for genetically divergent or admixed populations. Furthermore, approximately 10–15% of nonrepetitive, high-quality DNA sequences from an individual animal fail to map to a single reference genome pattern (Sherman and Salzberg 2020). A pangenome displays the variation of a representative panel of individuals (Golicz et al., 2020). Exploiting the new technology of accurate long-read sequencing (Hon et al., 2020), this technique has been implemented for humans and several domestic plants and animals. This technique has revealed many unidentified large SVs, several of which are associated with genetic diversity and phenotypic variation (Golicz et al., 2020; Sherman and Salzberg 2020; Shi et al., 2023b; Talenti et al., 2022). The pangenome provides a more complete catalog of genes and their variants across different populations, allowing a better understanding of how various gene variants contribute to phenotypic traits (Gong et al., 2022; Gong et al., 2023).

Pangenomes reveal SVs and putative genes that play crucial roles in the processes of ruminant livestock domestication, migration, and biological adaptation. For example, six integrated reference-quality assembly-based pangenomes added 70, 30, and 10.1 million bases of putative genes from nonreference sequences compared with the *Bo. taurus*, *Bo. grunniens*, and *Bo. indicus* reference genomes, respectively (Crysnanto et al., 2021). Additionally, haplotype-resolved assemblies have improved contiguity, completeness, and accuracy over the current *Bo. taurus* reference genome by combining *de novo* assembled genomes from three bovine trios with varying

heterozygosity into a structural variant-based pangenome (Leonard et al., 2022). A pangenome involving 898 cattle genomes from 57 breeds identified 83 Mb of base sequences not included in the reference genome that were associated with traits such as the immune response, olfactory functions, cell proliferation, and glucose metabolism in muscle (Zhou et al., 2022). Furthermore, multispecies pangenomes incorporating the *Bo. taurus* reference sequence and eleven haplotype-resolved assemblies from taurine and indicine cattle, bison, yaks, and gaur revealed 221,000 nonredundant SVs affecting the expression of proximal genes and noncoding RNAs (Leonard et al., 2023). A graph pangenome of 47 bovine genomes representing seven cross-fertile bovine species identified 334 genes overlapping with SVs, contributing to the hypoxic adaptation, yak domestication, and adaptive introgression from cattle in domestic yaks (Liu et al., 2023a). An international collaboration, the Bovine Pangenome Consortium, was recently launched to provide a more comprehensive representation of cattle genomic diversity (Smith et al., 2023). For sheep, graph pangenomes integrate high-quality genome assemblies with low-coverage short-read sequencing data for large panels of breeds (Wang et al., 2023). Li et al. (2023) built a graph-based ovine pangenome and identified a number of genetic variations, which provides a fundamental resource for understanding trait biology in sheep (Li et al., 2023a). Despite the completeness of pangenomes, gaps still exist within repetitive centromeres and telomeres, preventing researchers from fully exploring these complex genomic regions.

High-quality genomes are critical for understanding functional, evolutionary, and comparative genomics. The T2T assembly uses state-of-the-art long-read sequencing technologies and assembly algorithms and allows the reconstruction of gap-free genome assemblies. The production of the first T2T reference assembly of a human genome motivated similar efforts for livestock (Church 2022). Recently, the T2T gap-free genomes of Hu sheep and cashmere goats were assembled, providing novel insights into domestication and selection in ruminant livestock (Luo et al., 2024; Wu et al., 2024). In addition, Smith et al. (2024) assembled complete and gapless T2T Y chromosomes from cattle and sheep (Smith et al., 2024). The T2T gap-free genome could reveal species-specific differences in chromosomal structure and length, repetitive elements and evolutionary processes among cattle, sheep, and goats. These differences provide valuable resources for studying ruminant biology and improving animal breeding practices.

Future prospects of ruminant livestock biology and breeding in the genomics era

The ongoing advancement of high-throughput sequencing technologies, such as next-generation sequencing, has led to an exponential increase in the amount of genomic data available for ruminant livestock. These data provide valuable insights into the genetic basis of domestication and phenotypic traits. Future integration of multiomics data—including transcriptomic, proteomic, metabolomic, lipidomic, metagenomic, phosphoproteomic, acetylproteomic, ubiquitylproteomic, epigenomic, and immunomic data—will reveal novel associations between genetic variants and

phenotypic traits, identifying functional genes and relevant signaling pathways (Figure 7). Moreover, the development of novel technologies and algorithms is important to increase the prediction accuracy of the GS. Global data-sharing and collaborations will also be essential for generating, organizing, and curating related information and resources to effectively utilize this extensive omics data.

Enhancing GS efficiency

Currently, the benefits of GS over traditional breeding methods have been demonstrated in livestock breeding. However, the prediction accuracy of GS still needs to be improved by developing novel technologies and algorithms. For example, artificial intelligence techniques such as deep learning can manage complex, high-dimensional data and improve prediction models by learning from vast amounts of data and adapting to new patterns to identify nonlinear relationships between genetic markers and traits. CRISPR technology enables precise gene editing, and when combined with functional genomics, it can be used to validate the roles of specific genes in trait expression. This experimental validation contributes to refining prediction models by confirming causative variants and their effects on traits. Furthermore, employing other novel strategies—such as improving genomic data quality and density, considering epigenetic factors, optimizing statistical models, and integrating genotype-by-environment interactions—is crucial for enhancing the prediction accuracy of GS in improving production traits such as meat and milk.

Super-pangenomes for trait improvement

A super-pangenome that includes genomic information from diverse species, particularly wild relatives within a genus, can significantly expedite the improvement of production traits (Li et al., 2023a). For example, constructing reference-quality genome assemblies for many distinct cattle breeds, including both taurine (*Bo. taurus*) and indicine (*Bo. indicus*) subspecies, is essential. Advances in third-generation sequencing technologies, genomic analysis pipelines, and algorithms will facilitate the integration of transgenus pangenomes into *de novo* assemblies. This process will enable precise mapping of genes and SVs associated with important traits and provide deeper insights into animal domestication and migration.

Integration of multiomic data to identify key regulatory genes for important traits

The recent explosion of omics datasets (*e.g.*, transcriptomic, proteomic, metabolomic, lipidomic, metagenomic, phosphoproteomic, acetylproteomic, ubiquitylproteomic, epigenomic, and immunomic data) potentially allows researchers to explore causal genetic variations associated with complex traits. Comparative genomics can provide a comprehensive view to better identify potential causal variations in complex traits. However, further integration of multiple omics approaches is needed to narrow the range of targets underlying complex traits. In particular, the genetic mechanisms of the well-known genes associated with important traits (*e.g.*, *IGF2* for meat traits, *BMP15* and *GDF9* for reproductive performance, *DGAT1* for milk traits, and *VEGFA* for tail fat deposition) still need to be clarified by integrating multiomic data and

biological experiments (e.g., CRISPR technology).

Leveraging public omics data to reveal the genetic basis of traits

In recent years, large-scale resequencing studies combined with omics datasets have elucidated the molecular mechanisms and regulatory networks underlying complex trait formation (Figure 7). Despite many insightful studies, such as FarmGTEx, varGoats, the Bovine Pangenome Consortium, and Ruminat-T2T published from secondary analyses of public data, the sharing of genomic data from public archives remains inadequate (Byrd et al., 2020; Hardcastle et al., 2024). Diversifying population-level genetic datasets has shown significant potential for reuse in various applications, such as meta-GWASs (Sanchez et al., 2023) and the identification of regulatory elements (Fang et al., 2019). However, the reuse of public population genomic datasets is still relatively uncommon, partly due to the difficulty in accessing these datasets compared with omics datasets.

A growing number of researchers advocate for a more open and collaborative approach to promote comprehensive analyses and deeper exploration of large-scale population genomic datasets. Future population genomic studies could perform meta-analyses using these datasets to gain further insights into ruminant livestock domestication, responses to human selection, and environmental changes. Reusing publicly available genomic datasets can generate novel insights and hypotheses related to ruminant livestock breeding. Efforts should focus on promoting data sharing

and reuse by addressing technological challenges and encouraging collaboration among researchers to facilitate such analyses. Enhancing data accessibility will be crucial for reproducing published analyses, reducing redundant work, and fostering secondary analyses through data compilation.

Compliance and ethics

The author(s) declare that they have no conflict of interest.

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2422 **Table Legends**

2423 **Table 1.** Currently available chromosome-level genome assemblies for ruminant livestock

Species	GenBank accession	Breeds	Assembled length	Contig N50 size	Sequencing technology	References
<i>Bos taurus</i>	GCA_002263795.4	Hereford	2.8 Gb	26.4 Mb	PacBio; Illumina NextSeq 500; Illumina HiSeq; Illumina GAI	USDA ARS
	GCA_947034695.1	Charolais	3.2 Gb	84.1 Mb	PacBio; Hi-C; 10× Chromium	INRAE
	GCA_028973685.2	Hanwoo	3.1 Gb	64.7 Mb	PacBio	Jang et al.,2023
	GCA_021234555.1	Jersey	2.6 Gb	50.6 Mb	PacBio	USDA ARS
	GCA_034097375.1	Yunling cattle	3.1 Gb	36 Mb	PacBio	Yunnan Agricultural University
	GCA_905123885.1	Africa N'Dama	2.9 Gb	18.7 Mb	PacBio; Illumina	Talenti et al.,2022
	GCA_905123515.1	Africa Ankole	2.8 Gb	11.1 Mb	PacBio; Illumina	Talenti et al.,2022
	GCA_021347905.1	Holstein-Friesian	2.7 Gb	8.7 Mb	PacBio; Illumina	Jang et al.,2023
	GCA_000003205.6	Hereford	2.7 Gb	276.3 Kb	Sanger; PacBio RS II	Cattle Genome Sequencing International Consortium
	GCA_000003055.5	Hereford	2.7 Gb	97 Kb	Sanger	Merchant et al.,2014
<i>Bos indicus</i>	GCA_000247795.2	Nelore	2.7 Gb	28.4 Kb	SOLiD	Canavez et al.,2012
	GCA_030269505.1	Jinjiang cattle	2.9 Gb	84.3 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030272235.1	Dabieshan cattle	2.8 Gb	74.6 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030272135.1	Lincanggaofeng cattle	2.7 Gb	67.6 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030267375.1	Yiling cattle	2.8 Gb	67.5 Mb	PacBio; Illumina HiSeq	Dai et al.,2023

	GCA_030271795.1	Wenshangaofeng cattle	2.7 Gb	66.8 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030269815.1	Leiqiong cattle	2.7 Gb	54.8 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_029378745.1	Sahiwal × Tharparkar	2.7 Gb	42.1 Mb	PacBio	USDA ARS
	GCA_030271805.1	Weizhou cattle	2.7 Gb	38.7 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030267355.1	Xiangxi cattle	2.7 Gb	34.6 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030267345.1	Weining cattle	2.8 Gb	18.4 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_030270715.1	Guanling cattle	2.7 Gb	12.8 Mb	PacBio; Illumina HiSeq	Dai et al.,2023
	GCA_002933975.1	Gir	2.7 Gb	64.5 Kb	454; IonTorrent; Illumina NextSeq; Illumina MiSeq	Naji et al.,2021
	GCA_003121395.1	Mediterranean	2.7 Gb	22.4 Mb	PacBio	Low et al.,2019
<i>Bubalus bubalis</i>	GCA_019923925.1	Murrah	2.6 Gb	5.4 Mb	PacBio; 10× and BioNano Optical Map	National Dairy Development Board, India
	GCA_016772045.2	Rambouillet	2.7 Gb	43.2 Mb	Oxford Nanopore PromethION; PacBio RSII; Illumina HiSeq	University of Idaho
	GCA_033439445.1	East Friesian sheep	3 Gb	104.1 Mb	PacBio RSII; Oxford Nanopore PromethION; DNBSEQ	Inner Mongolia University
	GCA_022416915.1	Polled Dorset sheep	2.9 Gb	92.4 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_018804185.1	East Friesian	2.9 Gb	85.3 Mb	PacBio; HiFi CCS reads	Li et al.,2023
<i>Ovis aries</i>	GCA_022432835.1	Kermani sheep	2.8 Gb	80.3 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416755.1	Ujimqin sheep	2.9 Gb	75.7 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416685.1	Qiaoke sheep	2.9 Gb	75 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_017524585.1	Tibetan sheep	2.7 Gb	74.6 Mb	PacBio Sequel; Illumina NovaSeq	Li et al.,2022
	GCA_024222265.1	Waggir sheep	2.9 Gb	73.6 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022432845.1	Kazak sheep	2.9 Gb	73.4 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_019145175.1	Dorper sheep	2.6 Gb	73.3 Mb	Oxford Nanopore GridION; Illumina	Qiao et al.,2023

	GCA_022416785.1	Yunnan sheep	2.9 Gb	71.9 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022538005.1	Romney sheep	2.9 Gb	68.3 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416745.1	Charollais sheep	2.9 Gb	65.1 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416725.1	Suffolk sheep	2.9 Gb	64.5 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022244705.1	Romanov sheep × White Dorper sheep	2.7 Gb	62.3 Mb	PacBio; Oxford Nanopore	University of Kentucky
	GCA_022432825.1	Chinese Merino sheep	2.8 Gb	60 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416775.1	Texel sheep	2.8 Gb	47.6 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_024222175.1	Romanov sheep	2.9 Gb	31.8 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_022416695.1	White Dorper sheep	2.8 Gb	17.9 Mb	PacBio; HiFi CCS reads	Li et al.,2023
	GCA_011170295.1	Hu sheep	2.8 Gb	8.7 Mb	Oxford Nanopore PromethION; Illumina HiSeq	Li et al.,2021b
	GCA_002742125.1	Rambouillet	2.9 Gb	2.6 Mb	HiSeq X Ten; PacBio RS II	Baylor College of Medicine Human Genome Sequencing Center
	GCA_000298735.2	Texel sheep	2.6 Gb	150.5 Kb	Illumina GAII; 454; PacBio RSII	International Sheep Genomics et al., 2010
	GCA_000005525.1	mixed	2.9 Gb	685 bp	454 FLX	International Sheep Genomics et al., 2010
<i>Capra hircus</i>	GCA_001704415.2	San Clemente	2.9 Gb	26.2 Mb	PacBio; Hi-C	Bickhart et al.,2017
	GCA_015443085.1	Saanen Dairy Goat	2.7 Gb	46.2 Mb	PacBio; Hi-C; Illumina	Li et al.,2021c
	GCA_026652205.1	Xinong Saanen Dairy goat	2.6 Gb	42.6 Mb	Oxford Nanopore PromethION; Illumina; PacBio; Hic; BGI	Northwest A&F University
	GCA_000317765.2	Yunnan black goat	2.8 Gb	73.5 Kb	Illumina	Dong et al.,2013
	GCA_004361675.1	Black Bengal goat	3 Gb	819 bp	Illumina HiSeq	Siddiki et al.,2019

	GCA_949782905.1	Svalbard reindeer	3 Gb	22.5 Mb	PacBio; Illumina	Norwegian Institute for Nature Research
	GCA_019903745.2	Rangifer tarandus caribou	2.6 Gb	168.8 Kb	PacBio; Illumina HiSeq	Laval Univeristy
	GCA_963422255.1	Fennoscandian reindeer	2.7 Gb	146.8 Kb	Illumina	Pokharel et al.,2023
<i>Rangifer tarandus</i>	GCA_022457185.1	Multispecies	2.8 Gb	128.6 Kb	Illumina	Northwestern Polytechnical University
	GCA_004026565.1	Reindeer	2.9 Gb	77.7 Kb	Illumina HiSeq	Broad Institute
	GCA_014898785.1	Caribou	2.5 Gb	231.3 Kb	Illumina HiSeq	Louisiana State University
	GCA_902712895.1	Norwegain reindeer	2.5 Gb	195.7 Kb	Illumina	Institute of clinical molecular biology (Kiel)

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Figure Legends

Figure 1. (A) Overview of the gridded ruminant livestock of the world (GLW 3) datasets for cattle, zebu, buffaloes, sheep and goats. (B) Annual meat production by the top six countries in the last twenty years. Mt: Millions of tons.

Figure 2. Schematic representation of genetic advancements in ruminant livestock breeding

Figure 3. The phylogenetic relationships and domestic processing of taurine cattle, zebu, river- and swamp-type buffaloes, sheep and goats.

Figure 4. Migratory pathways for (A) taurine cattle, zebu, river-type and swamp-type buffaloes, including the ① routes from Ajmone-Marsan et al. (2010), the ② routes from Beja-Pereira et al. (2006), the ③ routes from Chen et al. (2023b), the ④ routes from Zhang et al. (2020), and the ⑤ routes from Zhang et al. (2016); and (B) sheep and goats, including the ① routes from Lv et al. (2022), the ② routes from Lv et al. (2015), the ③ routes from Fernandez et al. (2006), the ④ routes from Pereira et al. (2009), and the ⑤ routes from Zheng et al. (2020).

Figure 5. Common and unique candidate genes associated with economically important traits across cattle, sheep and goats.

Figure 6. Potential regulatory mechanisms of genes associated with economic traits.

(A) Myostatin and its signaling pathways participate in skeletal muscle development

(Chen et al., 2021; Abati et al., 2022). The myostatin dimer first undergoes proteolysis

into two monomers, and then binds to ActRIIB before interacting with ALK4/5 to

form a complex. Smad2/3/4 enter the nucleus to regulate the expression of target

genes. Smad7 can inhibit the phosphorylation of R-Smad by ActRI, thereby blocking

the myostatin signaling pathway, which is mediated through Smad. The Smad2/3/4

complex interacts with various transcription factors, leading to diverse roles of the

Smad signaling pathway. The nonclassical myostatin signaling pathway integrates the

PI3K/AKT/mTOR and MAPK signaling pathways, with the MAPK pathway

encompassing ERKs, JNKs, and p38MAPK. Collectively, these pathways regulate the

expression of myogenic regulatory factors, as well as MuRF-1 and atrogin-1, thereby

influencing myogenic differentiation. ActRIIB: activin receptor kinase II-B; ALK4/5:

activin receptor-like kinase 4/5; R-Smad: receptor-regulated Smad; PI3K:

phosphoinositide 3-kinase; AKT: protein kinase B; mTOR: mammalian target of

rapamycin; p38MAPK: p38 mitogen-activated protein kinase; ERK: extracellular

signal-regulated kinase; JNK: c-Jun N-terminal kinase; MuRF-1: muscle RING-finger

protein-1. MRFs: myogenic regulatory factors. **(B)** BMPR1B and its signaling

pathway are involved in fecundity (Abdurahman et al., 2019). FKBP1A is tightly

bound to BMPR1B; when the ligand BMP binds to BMPR1B, the spatial

conformation of BMPR1B changes, leading to the complete dissociation of FKBP1A.

The phosphorylation sites in the GS domain of the BMPR1B protein are exposed and

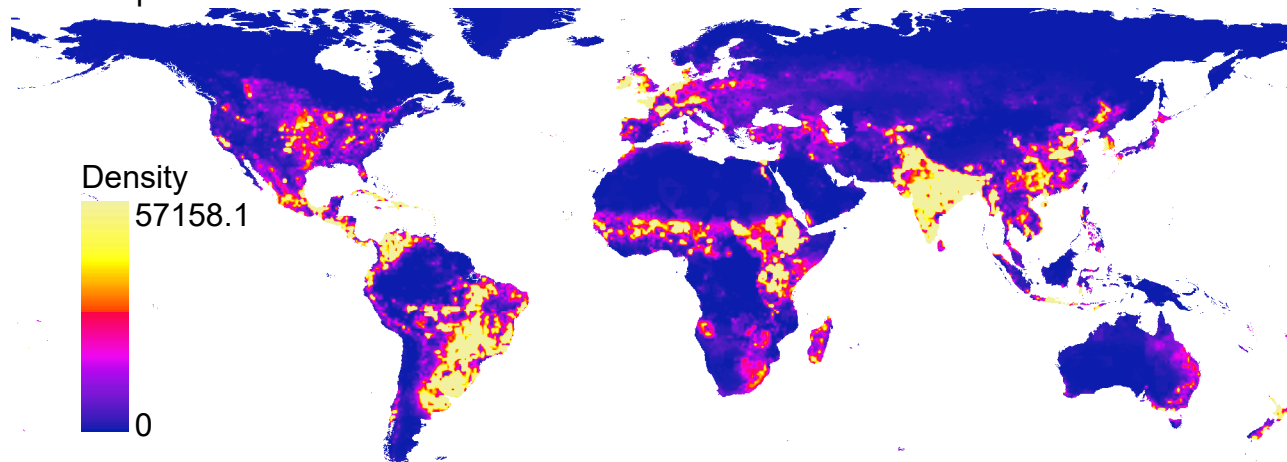
become phosphorylated, and activated BMPR then activates Smad1, Smad5, and Smad8, via a phosphorylation mechanism; subsequently, SMAD1/5/8 forms an oligomeric complex with Smad4. Finally, this complex enters the nucleus to control the transcription of target genes and thus acts as a specific transcriptional effector and influences various biological functions. (C) PDGFD and its signaling pathway are involved in fat deposition (Li et al., 2020b; Dong et al., 2020; Xu et al., 2023). PDGFD first binds to the PDGFR- β receptor and then activates signaling pathways, integrating the PI3K/AKT/mTOR and PPAR γ signaling pathways with the PPAR γ pathway encompassing RXR and LPL. Collectively, these pathways can induce the expression of adipose-specific cells, thereby regulating the generation, proliferation, and differentiation of adipocytes. PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; ERK: extracellular signal-regulated kinase; PPAR γ : peroxisome proliferator-activated receptor γ ; RXR: retinoid X receptor. (D) TBXT and its signaling pathway are involved in osteogenesis (Kalds et al., 2021; Li et al., 2022d). They regulate the transforming growth factor and Wnt signaling pathways during vertebrate development. TGF- β binds to activin receptor kinase II-B to form a complex; Smad2/3/4 enter the nucleus to regulate the expression of target genes. The activation of the Wnt signaling pathway involves the binding of the secreted ligand protein Wnt binding to the receptor protein Fzd and the subsequent activation of the intracellular proteins Dsh. Dsh then inhibits the activity of the β -catenin degradation complex formed by proteins such as GSK3 β , stabilizing the free β -catenin protein in the cytoplasm. β -catenin stably accumulates in the

cytoplasm and then enters the nucleus. FGF binds to FGFR to activate downstream cascades (RAS-MAPK and PI3K-AKT) and then enters the nucleus. Collectively, the activation of the Wnt and TGF- β signaling pathways leads to an increase in the expression of TBXT, and abnormally truncated versions of FGF result in a decrease in TBXT expression. These pathways ultimately participate in the formation of vertebrae. R-Smad: receptor-regulated Smad; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; MAPK: mitogen-activated protein kinase; Fzd: Frizzled family receptor; Dsh: dishevelled; GSK3 β : glycogen synthase kinase 3 β .

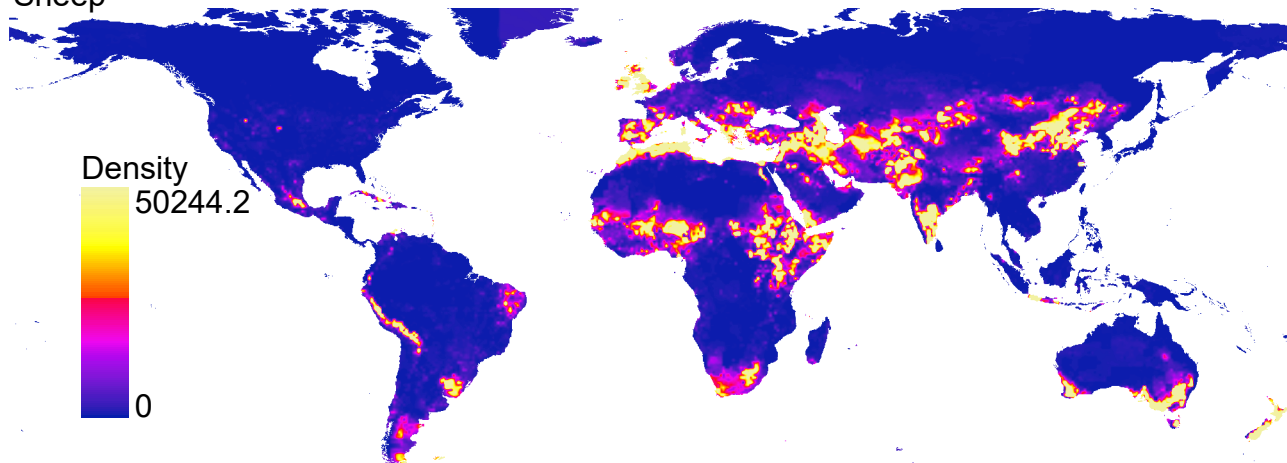
Figure 7. State-of-the-art biotechnologies for ruminant livestock breeding.

A

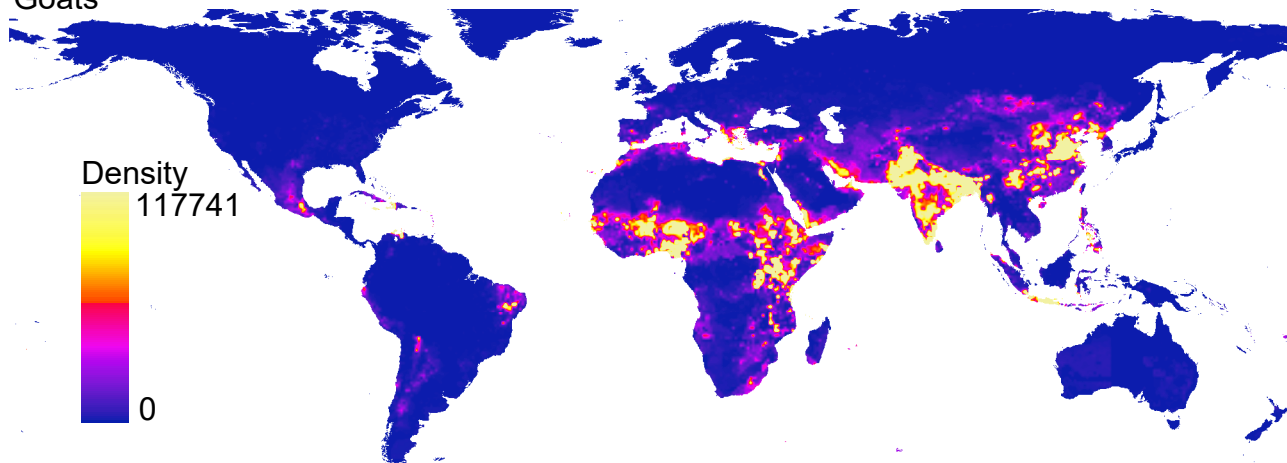
Bovine species



Sheep

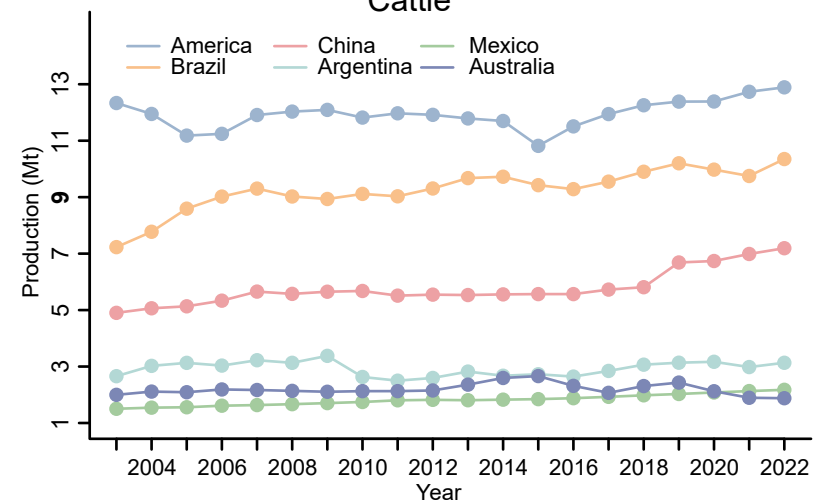


Goats

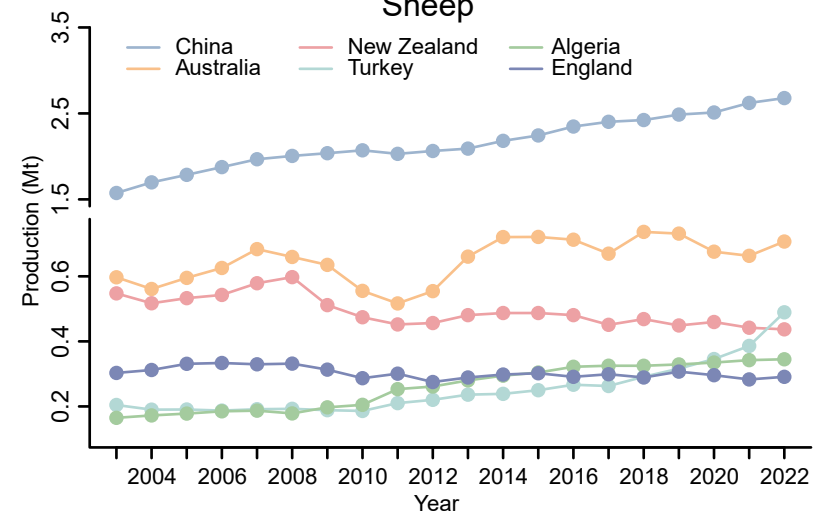


B

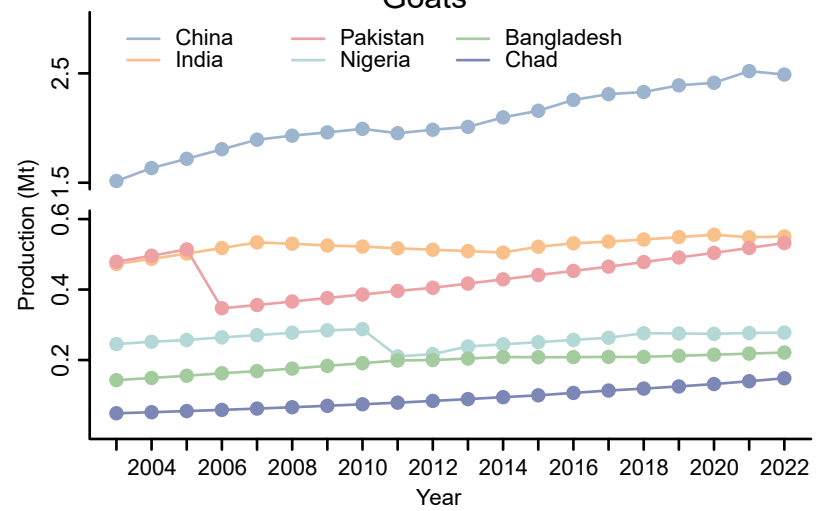
Cattle

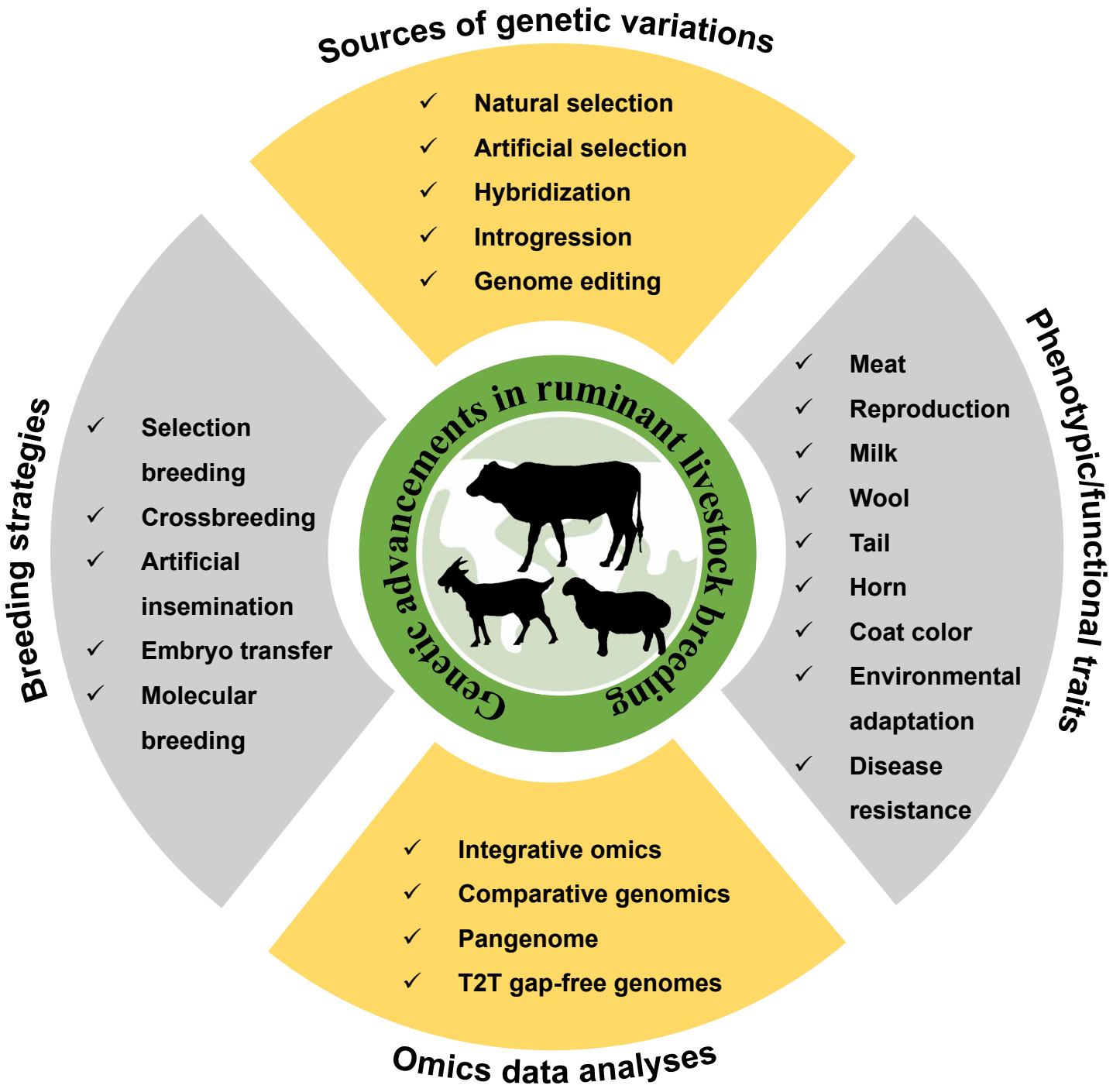


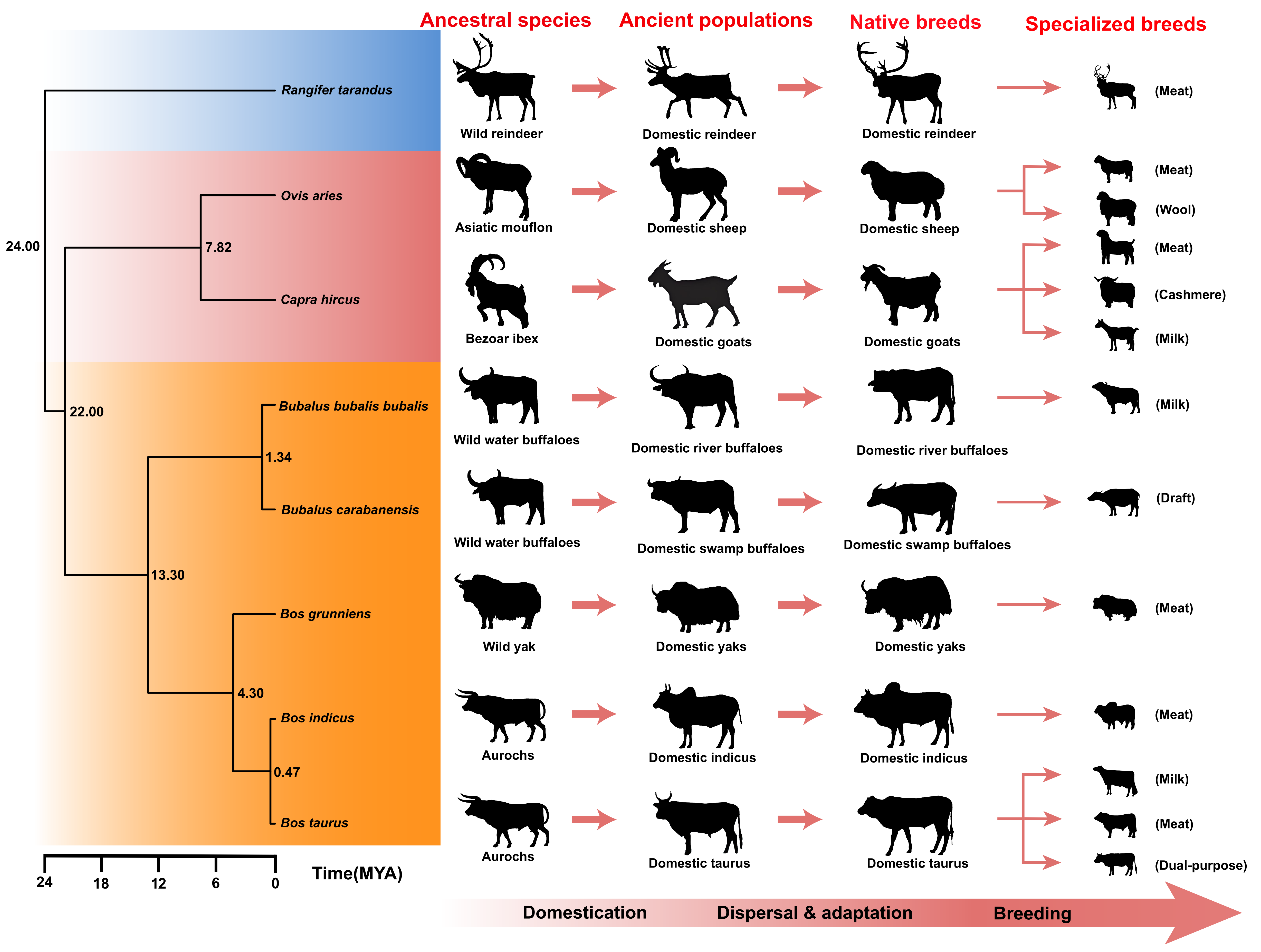
Sheep



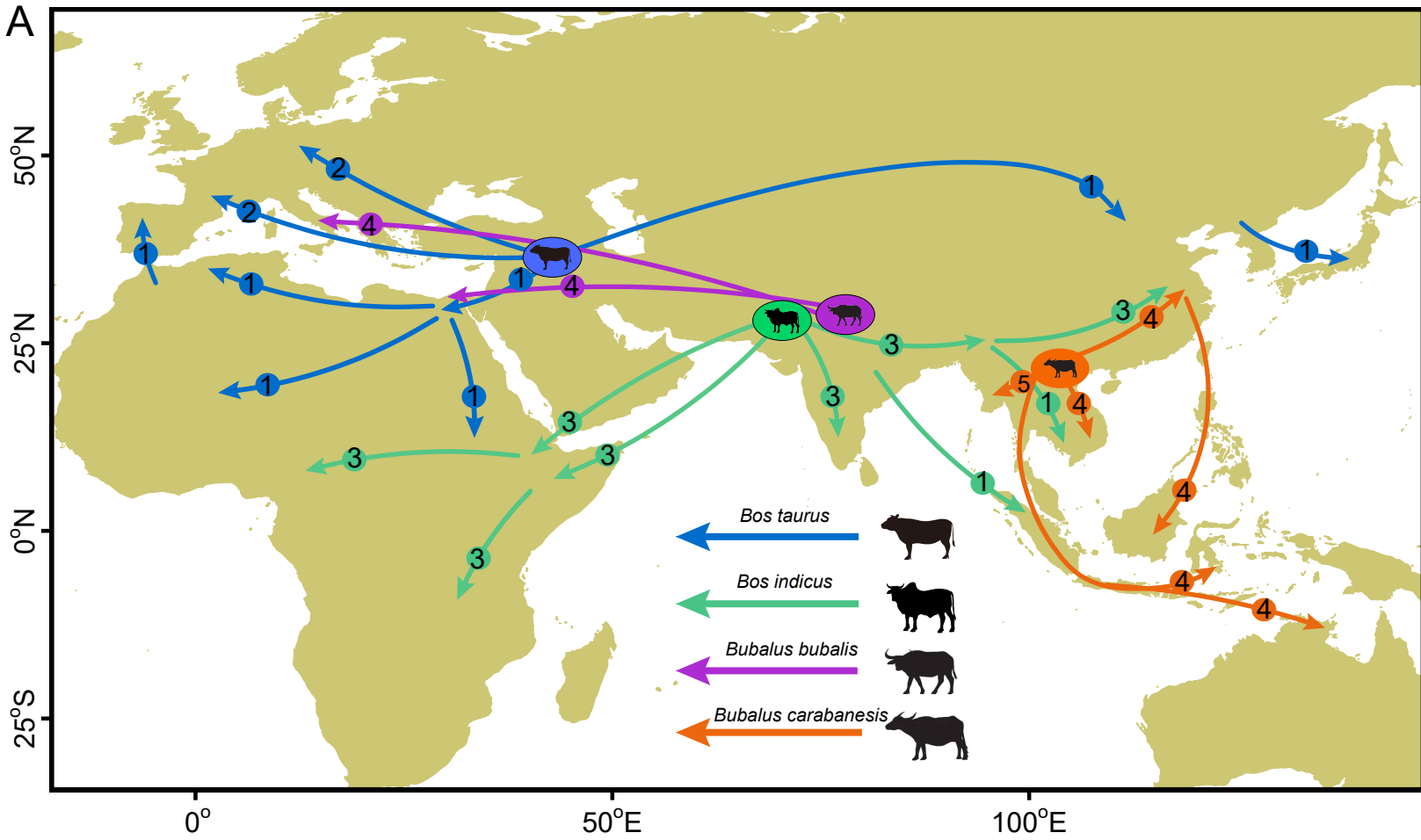
Goats



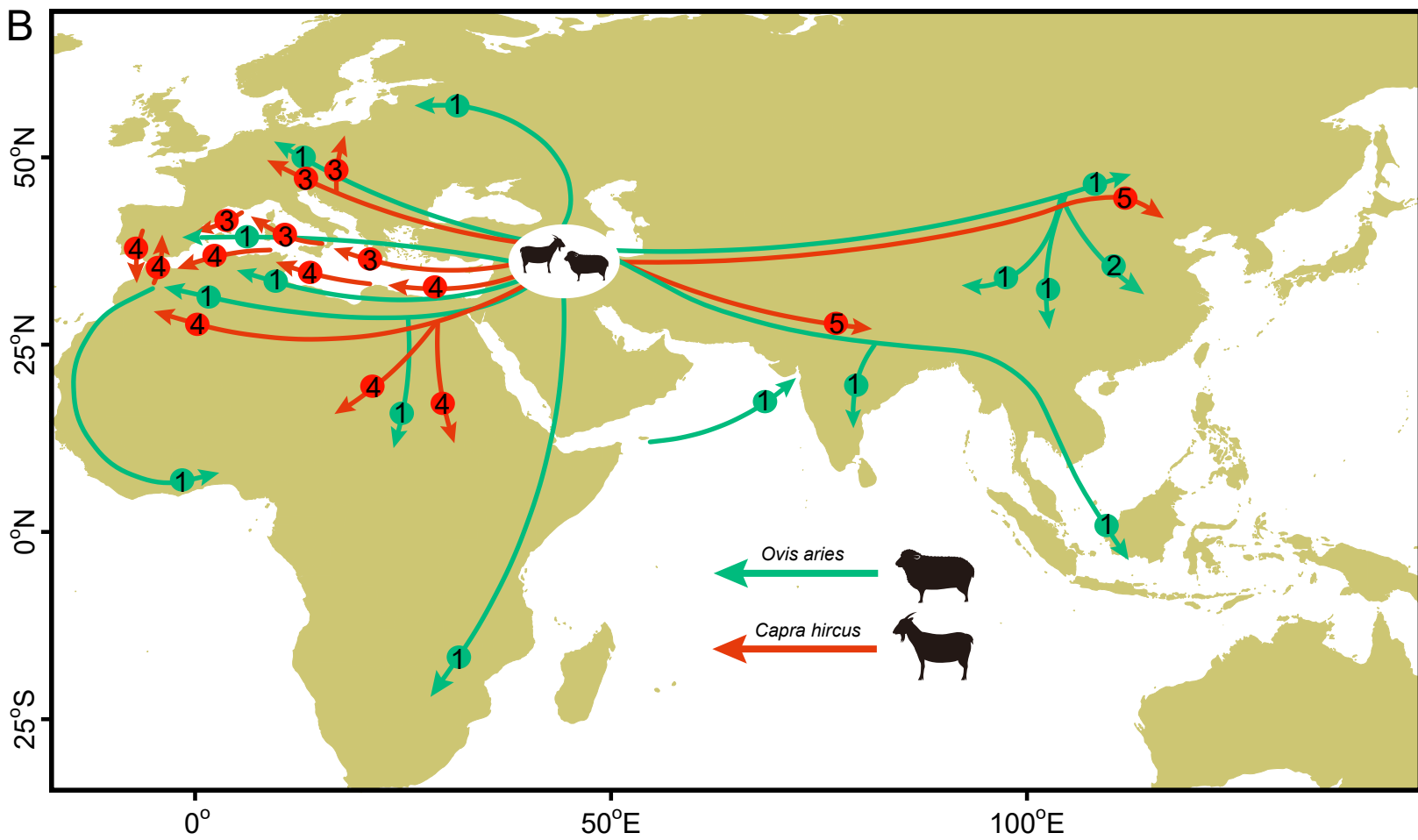


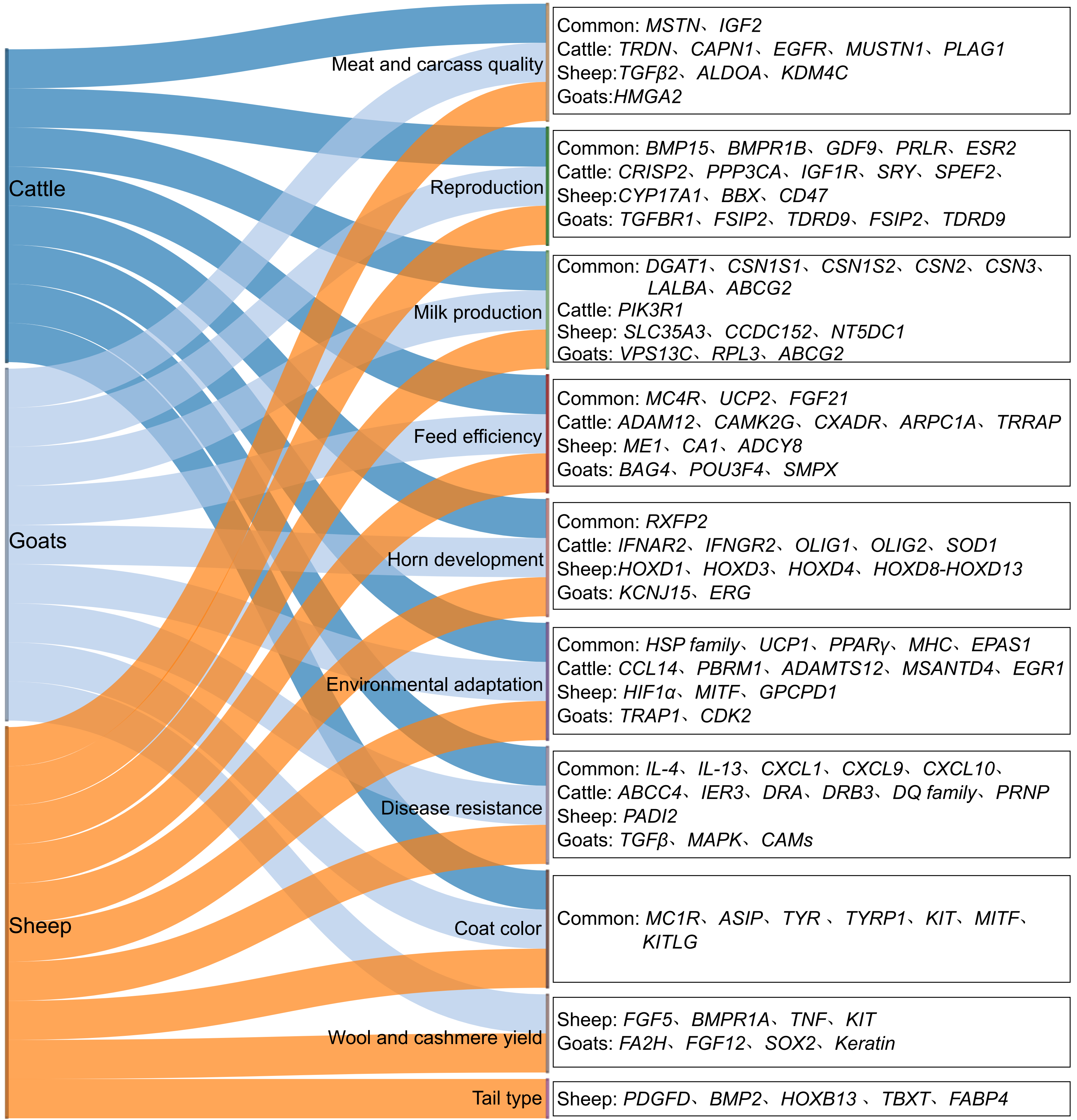


A

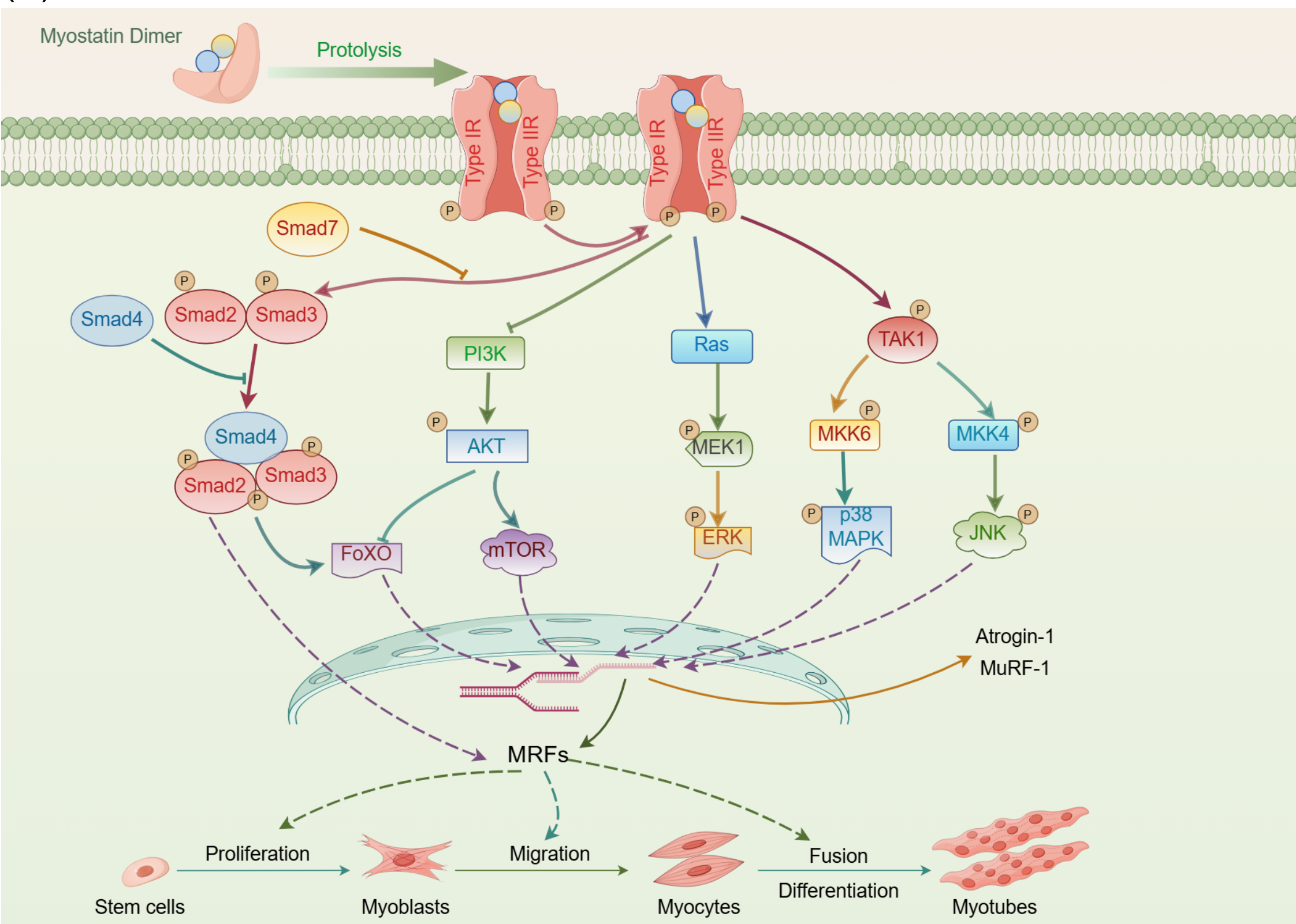


B

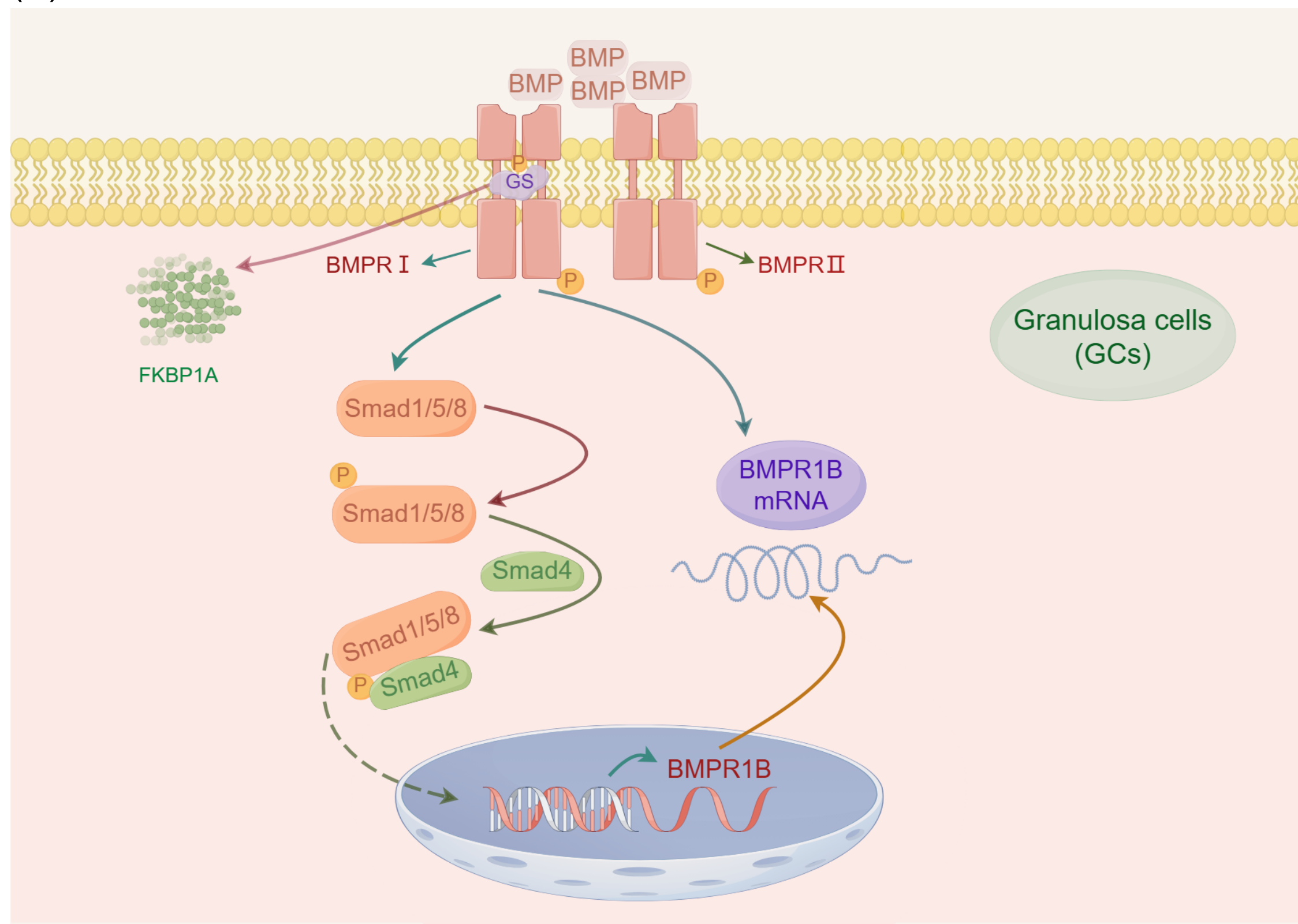




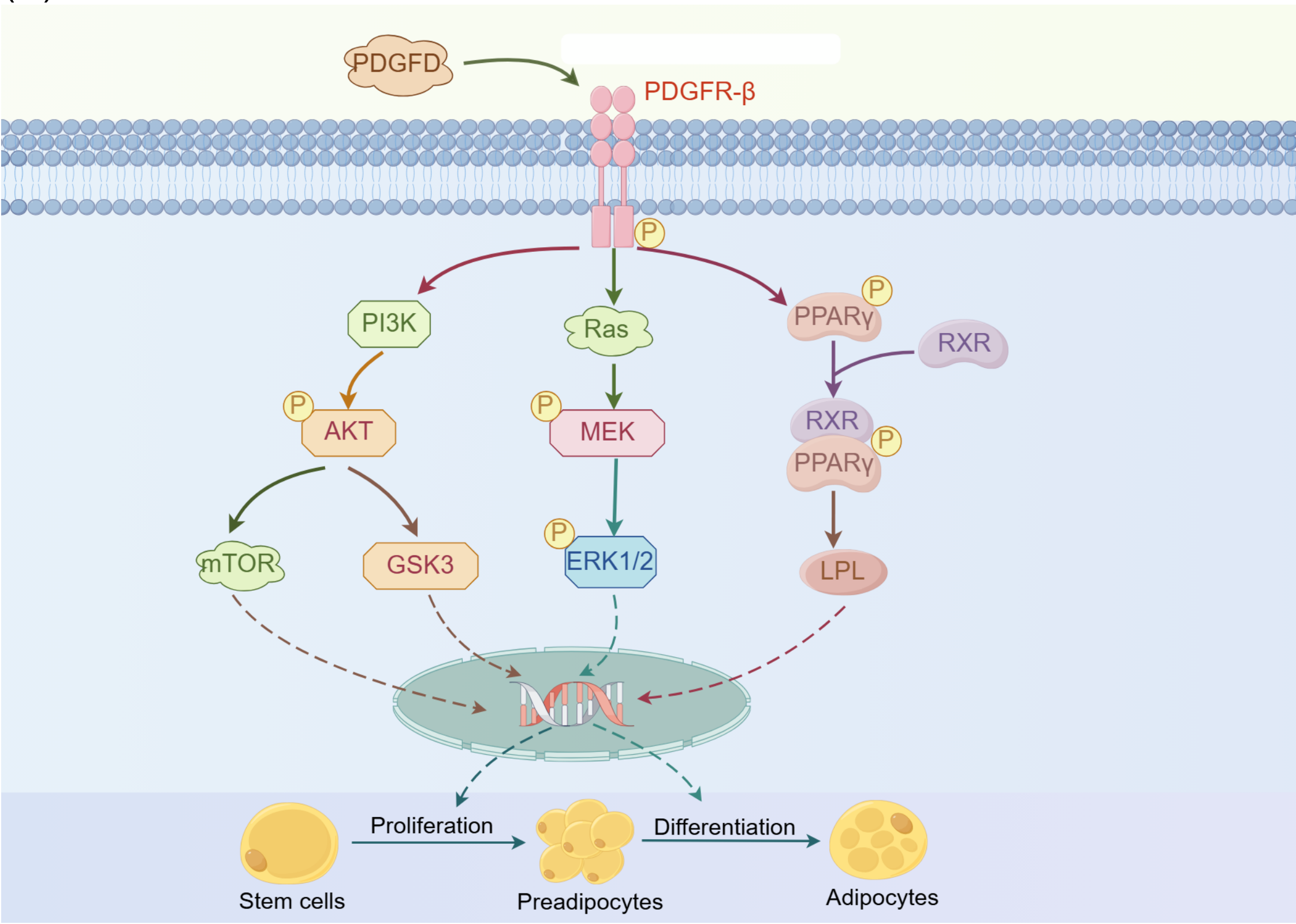
(A)



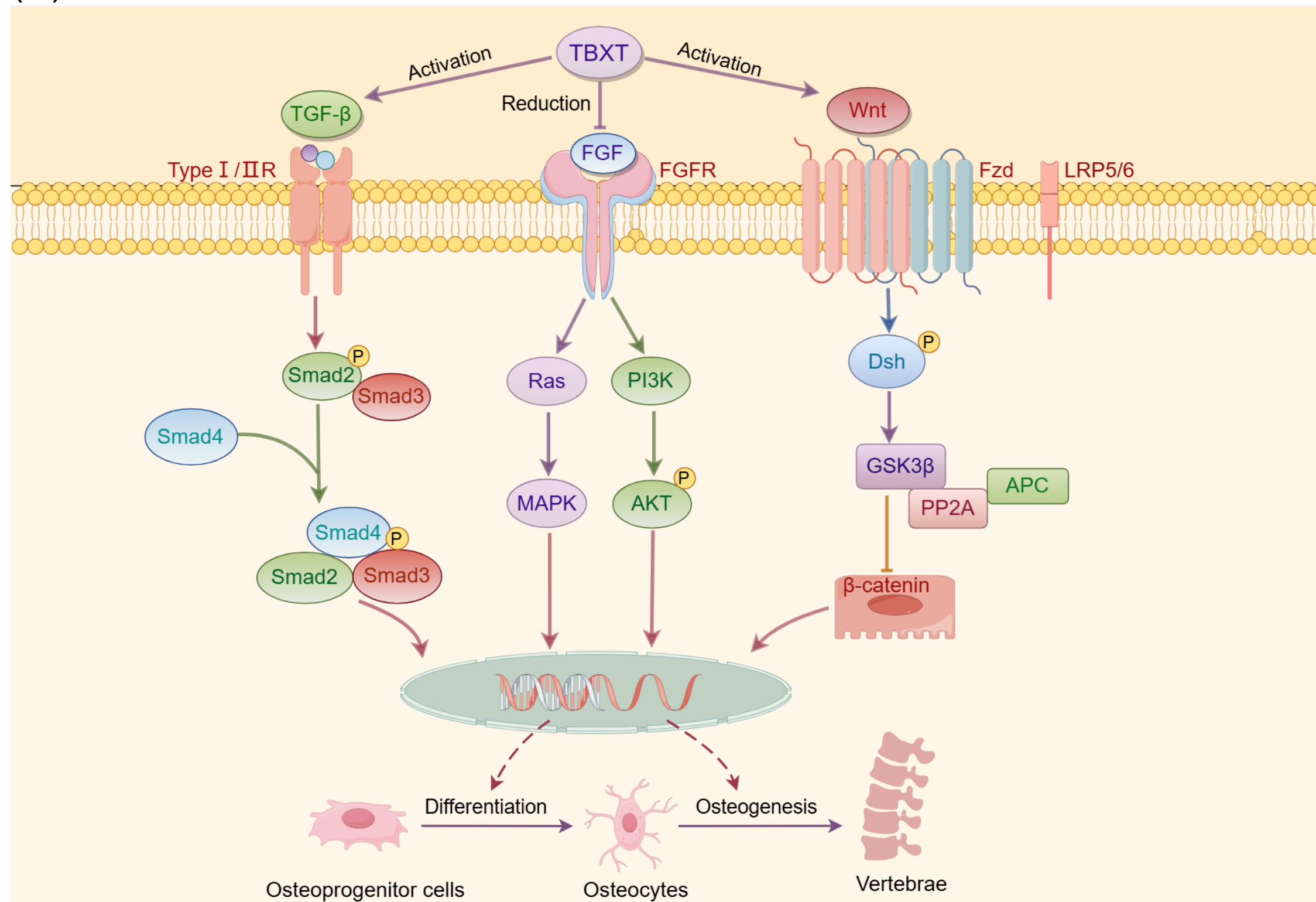
(B)



(C)

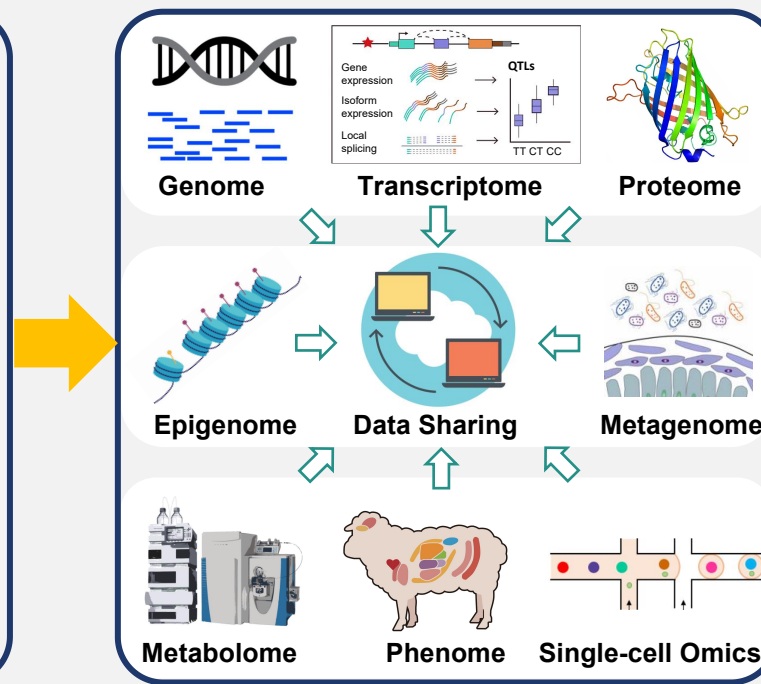


(D)

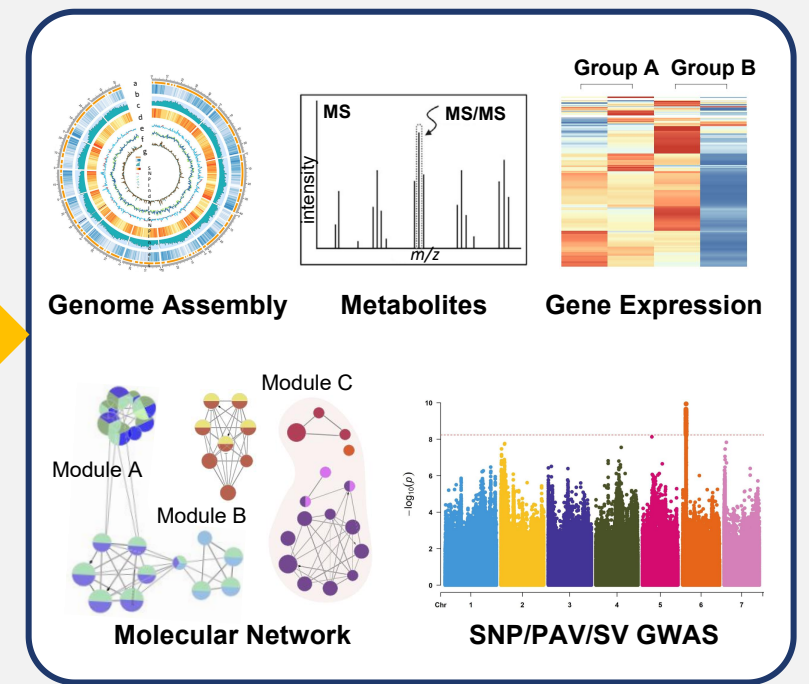




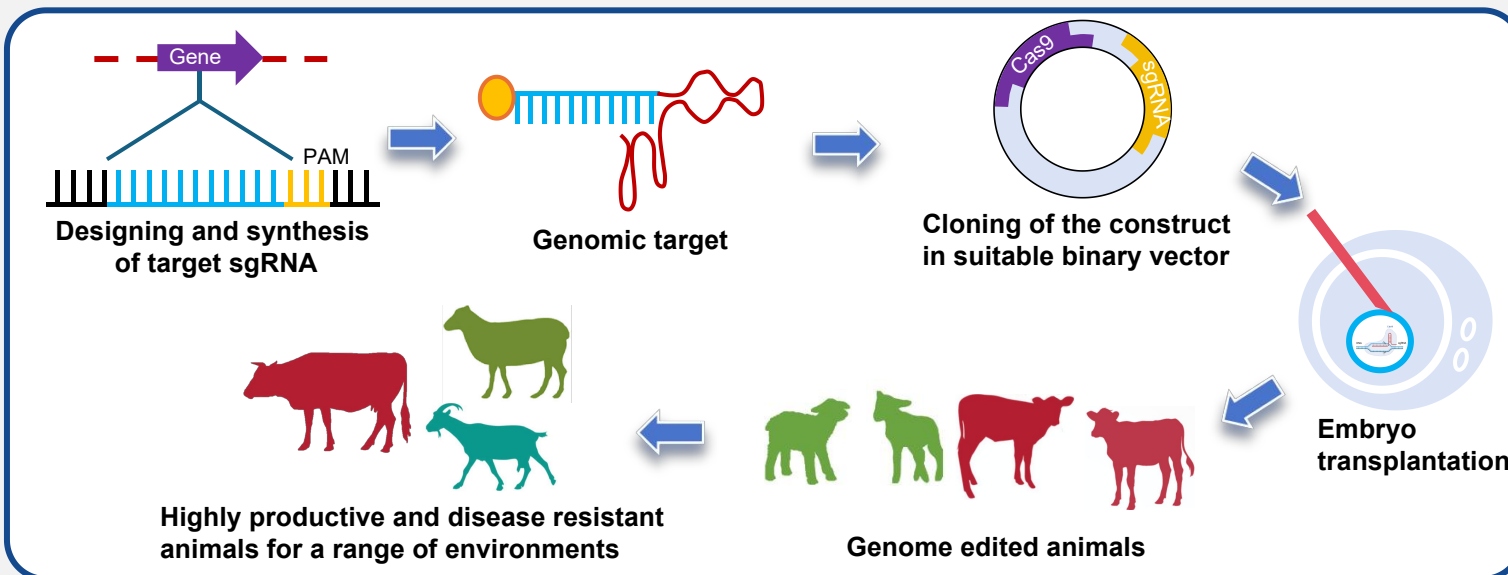
Ruminant Germplasm



Multi-omics Datasets



Association Testing



Molecular Design Breeding



Casual Variation Identification