TREATMENT FOR EQUINE JOINT DISEASE WITH REGENERATIVE MEDICINE PRODUCTS

Author: Jessica Madueño Caballero

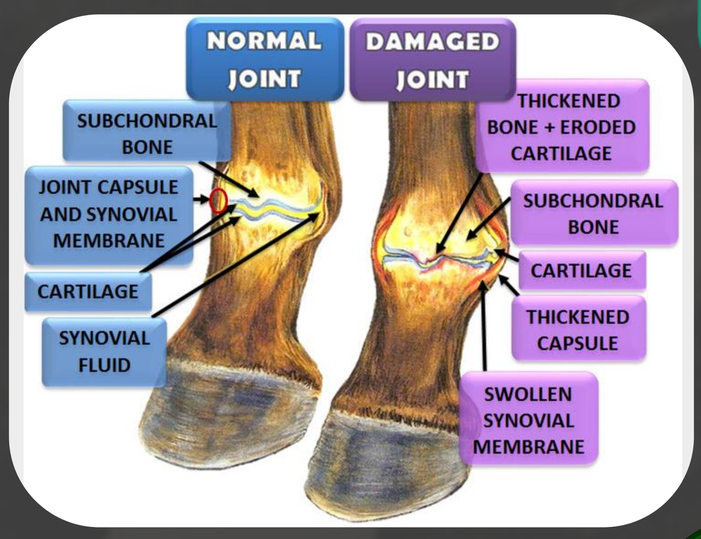
UAB Universitat Autònoma de Barcelona

DEGENERATIVE JOINT DISEASE (DJD)

DJD is the most prevalent joint pathology in horses. It is a chronic, irreversible degenerative process, based on progressive cartilage erosion, joint space narrowing, subchondral bone remodeling, marginal osteophytosis, synovitis and joint capsule fibrosis .

CLINICAL SIGNS

- Lameness
- Thickening of joint capsule
- Pain on manipulation
- Progressive loss of joint function
- Muscle atrophy
- Behavioural changes
- Decrease in athletic performance

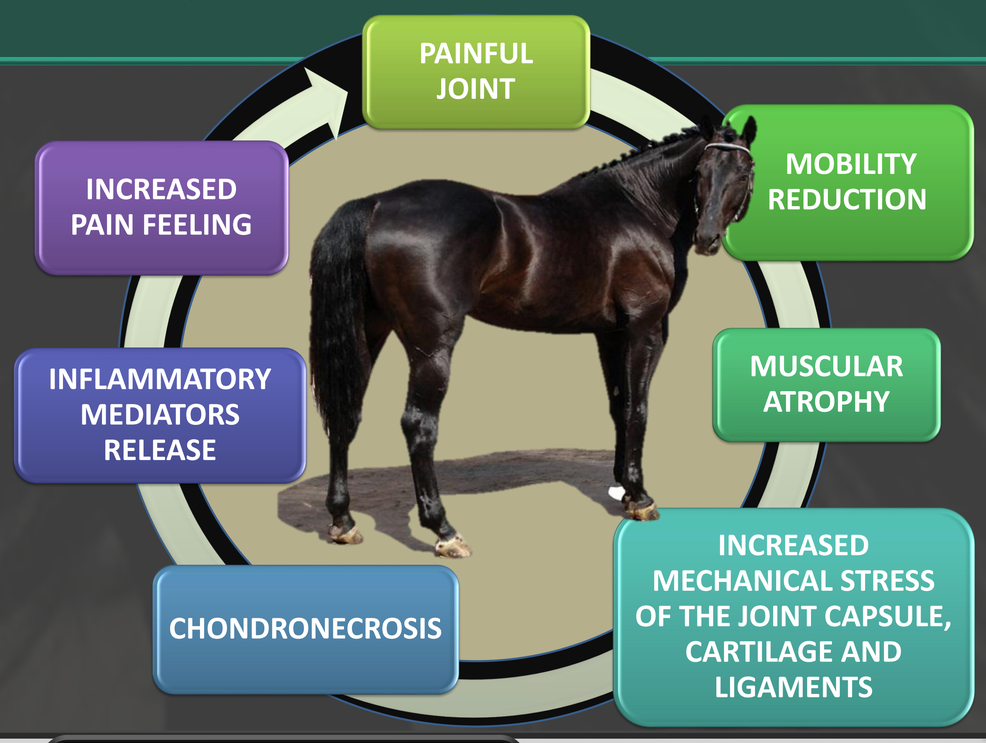


PATHOPHYSIOLOGY

INTERLEUKIN IL–1 + MATRIX METALLOPROTEINASES (MMPs) + E2 PROSTAGLANDINE + B4 LEUKOTRIENE + NITRIC OXIDE (NO) → DJD CLINICAL SIGNS

OBJECTIVES

- To assess the advantages and disadvantages of using different origin mesenchymal stem cells (MSCs) and compare their effectiveness in the horse with DJD.
- To establish an own judgement of clinical use , as well as a treatment proposal.



STEM CELLS

DEFINITION

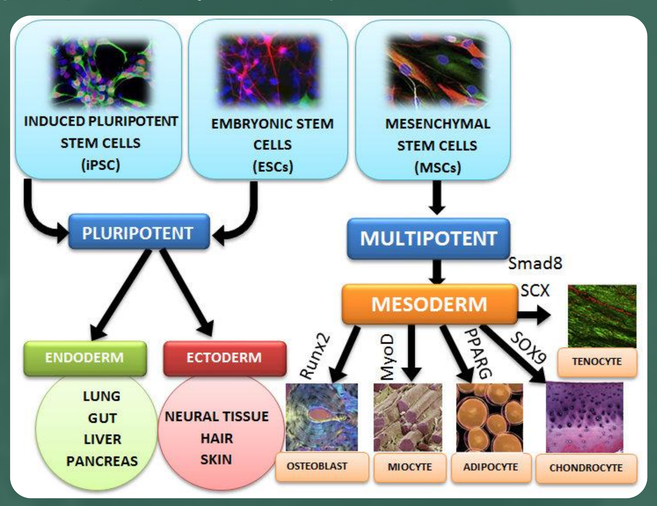
A stem cell is an undifferentiated cell capable of dividing indefinitely and differentiate into several specialized cell types, not only morphologically but also functionally. Stem cells main features are :

1. **Self-renewal** due to telomerase activity
2. **Pluripotentiallity** ability to differentiate into other cell types

CLASSIFICATION

ACCORDING TO ORIGIN:

- **Embryonic stem cells (ESCs):** properties of self-renewal and pluripotency, offer the possibility of an unlimited, renewable source of cells that can be induced to differentiate into any cell of the body.
- **Adult stem cells:** found within the majority of tissues. MSCs hold the greatest therapeutic potential.
- **iPSC:** generated from adult, terminally differentiated cells, re-programme cells into very similar ESCs by the introduction of four genes (Oct4, Sox2, cMyc and Klf4).



ACCORDING TO POTENTIAL DIFFERENTIATION:

- **Totipotent:** able to create an entire organism
- **Pluripotent:** capable of differentiating into cells of the 3 germ lines (endoderm, mesoderm and ectoderm).
- **Multipotent:** capable of differentiating into a limited lineages but also more specialised cell types
- **Unipotent:** capable of differentiating into a unique cell type.

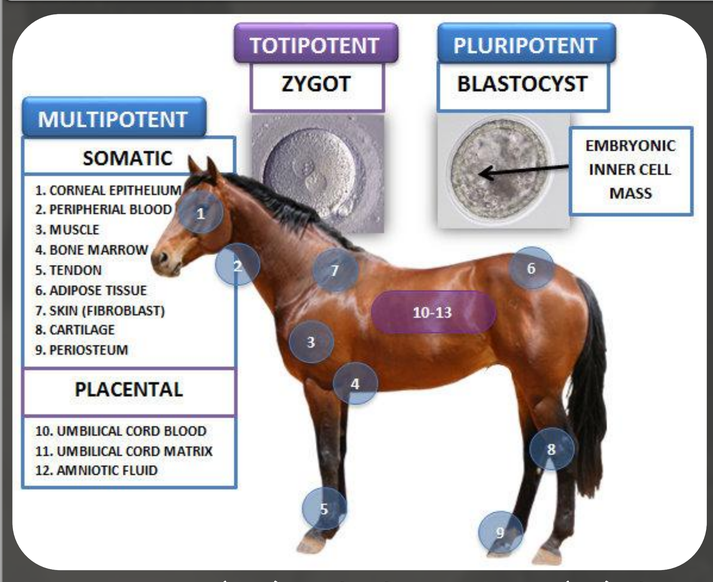
AUTOLOGOUS VS ALLOGENEIC MSCs

Autologous MSCs are obtained from the individual itself. The main disadvantage is that their expansion process takes 10 -21 days, so the treatment start is delayed and difficult as a result of the growth kinetic variations . In addition, some collection techniques are invasive and might be not be suitable for all patients.

Allogeneic MSCs are obtained from a different donor. They allow immediate treatment of acute orthopedic lesions. Some security studies done in horses by intraarticular administration in healthy joints, have shown promising prospects due to the similar response to autologous MSCs.

CELL THERAPY

MSCs TISSUE COLLECTION AND DIFFERENTIATION *IN VITRO*



Bone marrow (BM) and adipose tissue (AT) have been the most common sources of MSCs from years. Nevertheless, umbilical cord blood (UCB) as well as peripherial blood (PB), gum and periodontal ligament may be rising alternatives.

	ADVANTAGES	DISADVANTAGES
BM-MSCs	▪ Great rate of isolating ▪ Shortest culture period ▪ Tri-potential differentiation ▪ Best regenerative behaviour	▪ Highly invasive donation procedure ▪ Decline MSCs number and differentiation potential with increasing age. ▪ Less proliferation capacity
AT-MSCs	▪ Great rate of isolating ▪ Higher colony frequency (UFC-F) ▪ Higher inmunomodulatory effect.	▪ Relatively invasive technique in some athletic horses
UCB-MSCs	▪ Less invasive method ▪ Higher proliferation capacity ▪ Lowest colony frequency (UFC-F)	▪ Less isolating ratio ▪ Longest culture period ▪ Without adipogenic capacity

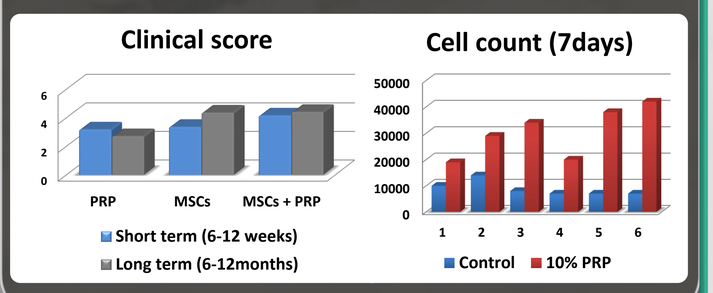
MSCs EFFECT ON CARTILAGE REPAIR

A study of the literature makes it apparent that MSCs injected intraarticularly do not engraft into the endogenous cartilage and directly affect repair. Nevertheless, they do appear to have analgesic and chondroprotective benefits retarding the progression of cartilage destruction by reducing inflammation. Treatment timing seems to be a key factor in the degree to which MSCs modulate the progression of cartilage destruction.

However, recent advances in tissue engineering technologies have allowed to create scaffolds for regenerative medicine. such as HR007, which is composed of sulphated glycosaminoglycans (sGAGs) and hyaluronic acid (HA). HR007 scaffolds induce cell proliferation, enhance the expression of specific gen markers, induce the tissue production and have chemotactic effects over the MSCs

MSCs + PRP COMBINED THERAPY

A study compared the conventional regenerative therapies based on the use of PRP or native MSCs alone, with the combined treatment (MSCs + PRP) The results shown that PRP enhances MSCs proliferation and chondrogenic differentiation.



TREATMENT/ STUDY PROPOSAL

Combined intraarticular administration of BM-MSCs + AT-MSCs + PRP charged in a biocompatible matrix

CONCLUSIONS

* Allogeneic MSCs are safe even administrating more than a single dose. They allow us to establish an early treatment without having to wait for their expansion. Patients age and exposure to invasive techniques become irrelevant.
* BM-MSCs are characterized by a great rate of isolation, good regenerative behaviour, the shortest culture period and tri-potential differentiation capacity .
* AT-MSCs are characterized by great inmunomodulatory behaviour. It would be interesting to combine with BM-MSCs to determine possible synergistic effects.
* PRP enhances MSCs proliferation and chondrogenic differentiation so it improves the regenerative results short (6-12weeks) and long term (6-12months) when combined.
* Tissue engineering based on sGAGs and HA might allow horse MSCs to engraft cartilage, decrease the expression of matrix degradation factors and make chondrogenic differentiation.