



Effect of carcinogenic agents in the Wnt/ β -catenin pathway as inducers of colorectal cancer

Final Degree Project
Bachelor's Degree in Biochemistry

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COLON STRUCTURE

The colon tissue consists in an epithelial layer, which contains different kind of cells organized in villi shape, called Crypts of Lieberkühn (Fig. 1). These cells regulate the absorptive and protective functions of the gut. The epithelial colon suffers a self-renewal process every 35 days throughout our entire lifetime. This process is required by the extremely harsh conditions that exist within the colon lumen. The resident stem cells are located in the base of the crypts and produce progenitor cells, which expand through multiple rounds of cell division as they move upwards as a column toward the crypt boundary. Differentiation of these cells continues during its upward migration and stops when they exit the crypts after two days.

WNT PATHWAY

Inactive - Wnt/ β -catenina pathway remains inactive in absence of Wnt protein (Fig. 2A). In this situation, β -catenina is bound to the cytoplasmic complex (Axin-APC-CK1-GSK3 β). CK1 and GSK3 β phosphorylate conserved Ser and Thr residues in N-terminus of β -catenin, respectively. These phosphorylations generate a binding site for ubiquitin-ligase E3 (β -TrCP), which subsequently target the β -catenina and send it to proteasomal degradation.

Active - Wnt promotes the proliferation of stem cells and the differentiation of Paneth cells. Wnt signal binds to Paneth cells membrane receptor (Frizzled) and Dishevelled (Dsh). This complex stimulates the union of Axin to it. When Axin is recruited to the membrane, the β -catenin phosphorylation complex (Axin-APC-CK1-GSK3 β) cannot be formed, and β -catenin cannot be neither phosphorylated nor degraded. The elevation of β -catenin levels in cytoplasm leads it to enter to the nucleus, promoting the transcriptional activation of Wnt target genes (Fig. 2B).

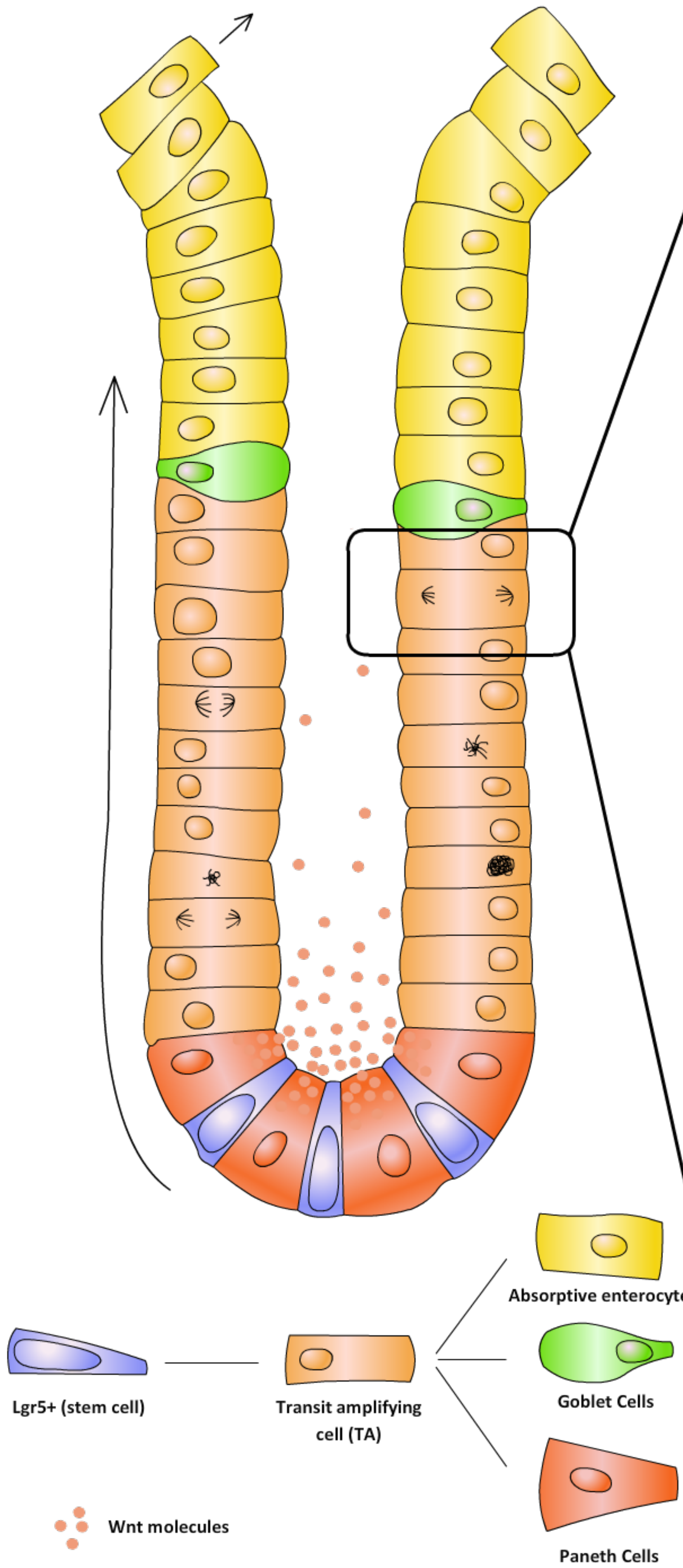


Figure 1. The common crypt structure

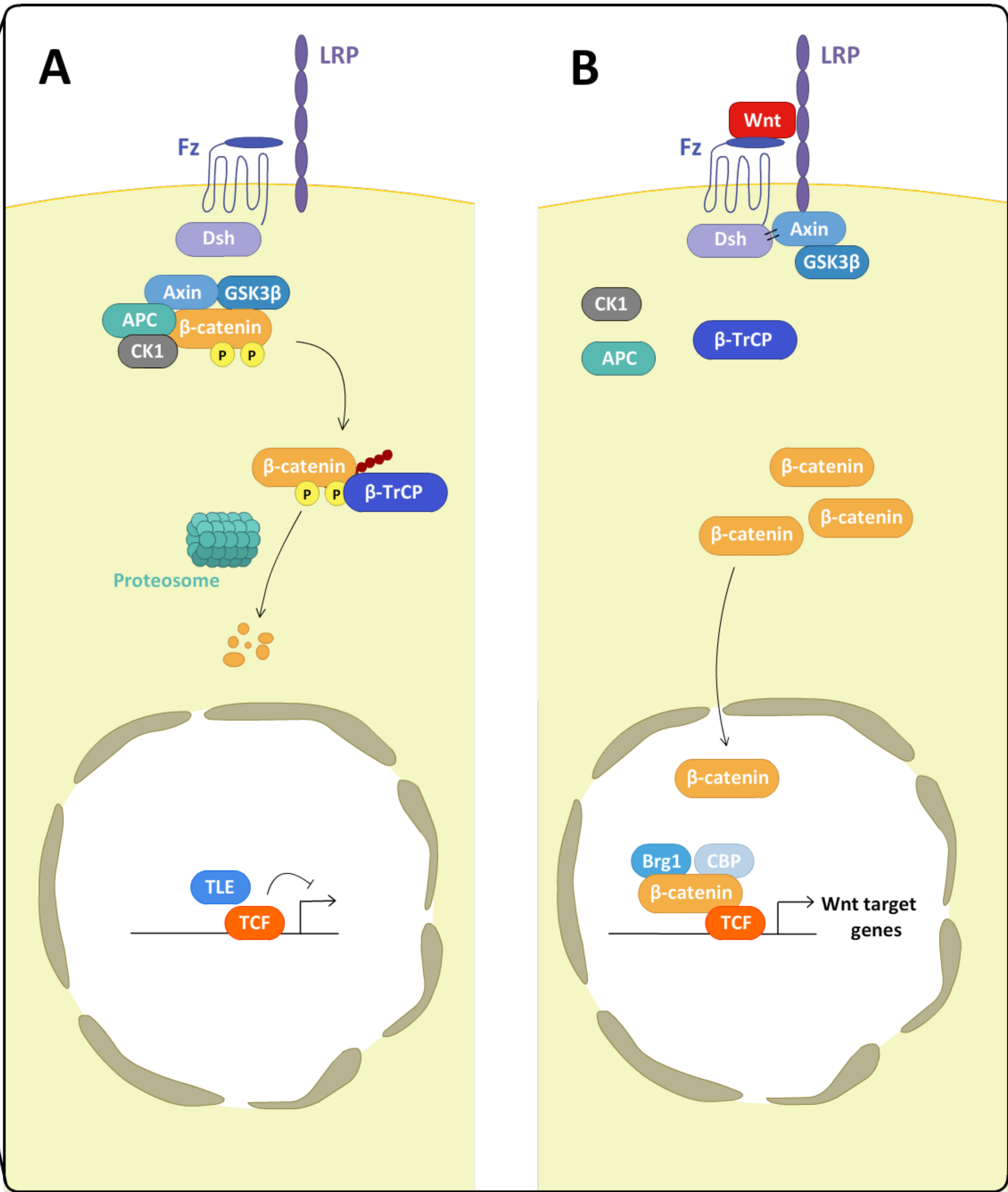


Figure 2. The canonical Wnt pathway. A- Inactive pathway, B - Active pathway

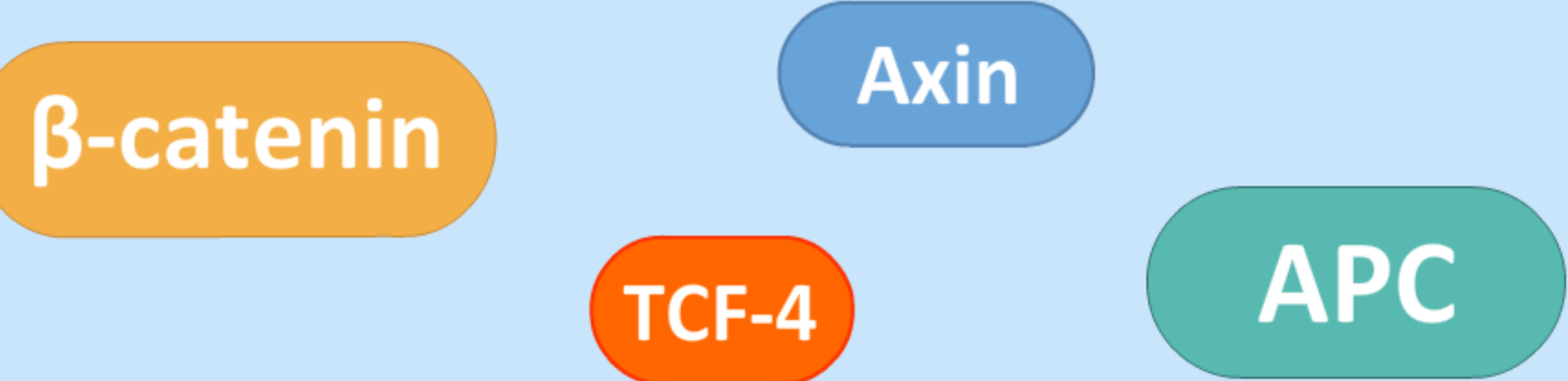
WNT TARGET GENES

Once β -catenin enters in nucleus it binds to TCF/Lef DNA-binding proteins, where TCF is a transcriptional factor, which was inactivated by TLE. With transcriptional complex activated, CBP histone acetylase and Brg-1 bind to the it to form the chromatin-remodeling complex, which may induce chromatin accommodation that favours target gene transcription. These genes maintain both the proliferative cell compartment and driving maturation of the Paneth cells.

Cyclic D1. Its promoter contains a LEF-1 binding sequence)
C-myc. Increased in adenomas with APC mutated)

ErphB2. Down-regulated with activated pathway)
Others. Gastrin, MMP7, uPAR, COX-2, Axin 2, connexin-43)

MUTATED PROTEINS

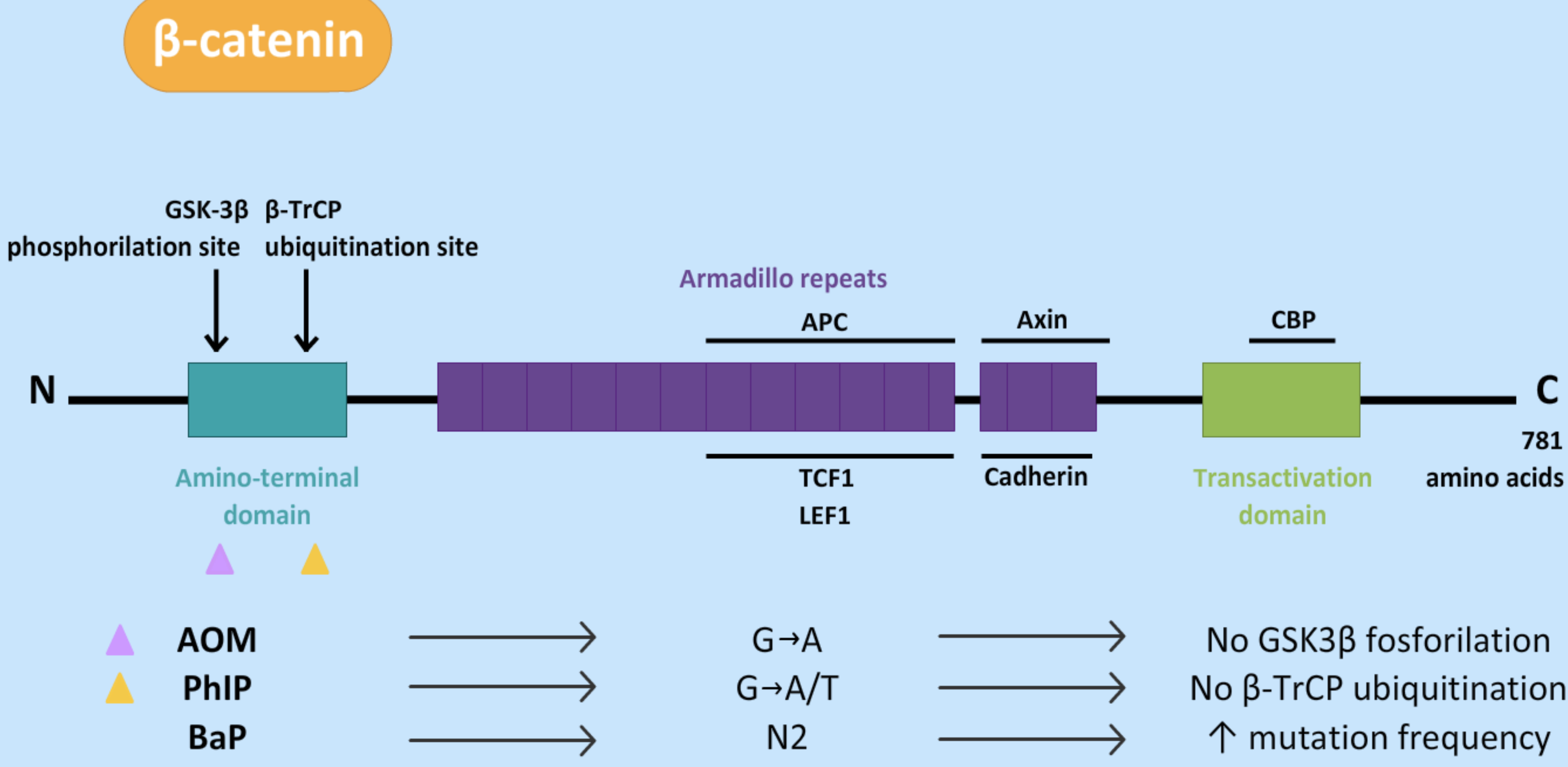
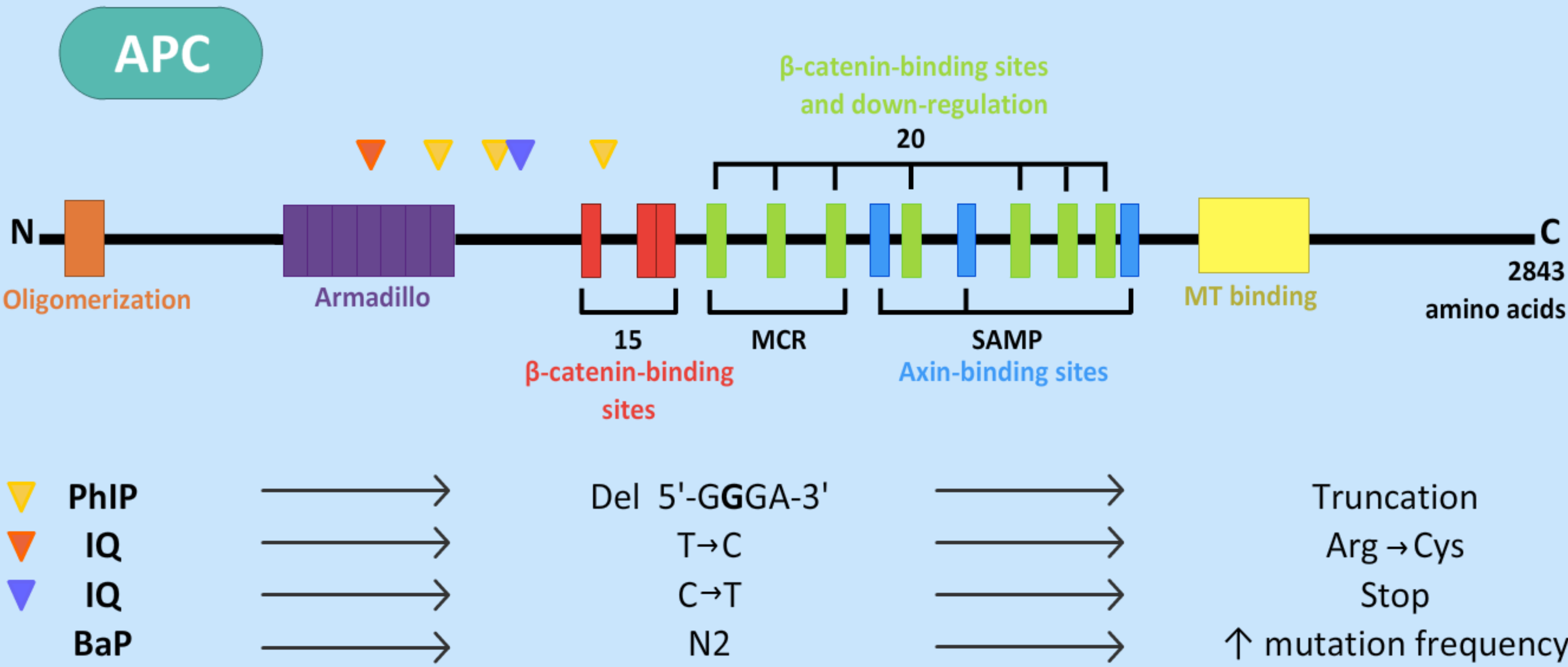


CARCINOGENS

- **Azoxymethane (AOM).** Used in labs to induce colorectal cancer in rats o mice
- **1,2-Dimethylhydrazine (1,2-DMH).** Used in labs to induce colorectal cancer in rats
- **Heterocyclic amines (HCA).** Present in red meat, processed meat and cooked fish
- **Benzo[a]pyrene.** Present in cigarette smoke and cooked meat (PAH)
- High **alcohol** consumption + folate and B vitamins deficiency
- **EPTC.** Main component of pesticides
- **Microbiota.** Acts as activator of latent carcinogens to bioactive compounds

- **PhIP**
- **IQ** (Broiled fish, fried bacon and cigarette smoke)
- **MelQx** (Fried fish, chicken skin and red meat)

MUTATED PROTEINS BY CARCINOGENS



CONCLUSIONS

Wnt/ β -catenin pathway is essential in cycle control in colon cells and main point in cancer development. This pathway signaling can be a mutational target for several reasons; this pathway has different proteins, which can be mutated by genetic causes or acquired, being liable of colon cancer development. Heterocyclic amines are, probably, the most studied carcinogens in CRC development via Wnt/ β -catenin present in large amount of daily food. It would be necessary further investigation of some compounds before been considered as carcinogens.

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