# β-CATENIN STABILIZATION IN THE WNT PATHWAY AND ITS IMPLICATION IN COLON CANCER

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## 1. Objective

This work aims to explain how β-catenin is stabilized upon activation of the Wnt pathway and also its implication in the colon cancer development.

## 2. β-catenin in context

β-catenin is an integral structural component of cadherin-based adherent junctions, and the key nuclear effector of canonical Wnt signalling in the nucleus. Imbalance in the structural and signalling properties of β-catenin often results in disease and deregulated growth connected to cancer and metastasis.

## 4. Intestinal Crypts and the involvement of the Wnt pathway in their development and maintenance

The epithelium of colon is organized in crypts and displays a remarkable self-renewal rate. This intense proliferation is confined to the crypts. Resident stem cells are located to the crypt bottom and they give rise to transit-amplifying (TA) cells which move upward towards the crypt border. During this migration, these TA cells begin to differentiate and subsequently exit the crypt.

In the intestine, two models of intestinal stem cell identity have been formulated: the stem cell zone model and the +4 model.

| The stem cell zone model | +4 model |
|---|---|
| • In the crypt base there are crypt base columnar cells (CBC cells) | • Rare DNA-label-retaining cells (LRCs) reside above the Paneth cells (+4 position) |

The pluripotency and proliferation of the stem cells is maintained by Wnt signal supplied by Paneth cells and stromal cells near the bottom of the crypt. Thus, Wnt signals are required for maintenance of adult crypt proliferation.

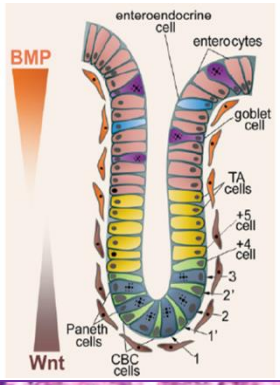


Figure extracted from [3] – Cellular architecture in the crypt of the small intestine.

## 3. The canonical Wnt pathway and the different components implicated

Absence of ligand: β-catenin that is not bound to the cytosolic tail of cadherin proteins becomes bound by a degradation complex containing APC, axin, GSK3β and CK1. In this complex, β-catenin is phosphorylated by GSK3 triggering its ubiquitylation and degradation in proteasomes.

Presence of ligand: Wnt binds to Frizzled and LRP, resulting in the recruitment of the degradation complex to the plasma membrane. Then β-catenin can accumulate and translocate to the nucleus. Once is in the nucleus, β-catenin binds to LEF1/TCF and acts as a coactivator to stimulate the transcription of Wnt target genes.

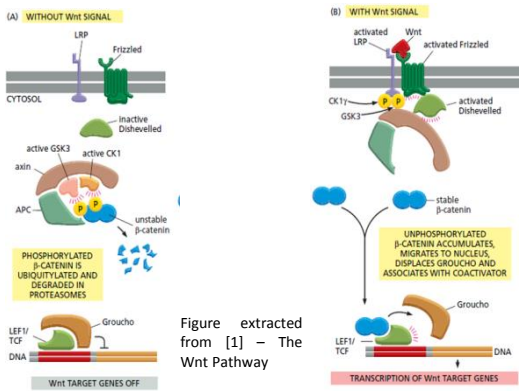


Figure extracted from [1] – The Wnt Pathway

## 5. Colon Cancer

More than 95% of colon cancers are sporadic and their origin is due to Wnt effectors' mutations. The inactivation of APC leads to an accumulation of free β-catenin and this can be observed in about 80% of sporadic colon carcinomas. The rest of sporadic colon carcinomas carry wild-type APC alleles, but some of these carry point mutations in the gene which encodes for β-catenin or mutations in Axin2. In some cases, the APC gene promoter is hypermethylated and rendered inactive. These mutations will lead to an accumulation of β-catenin too.

The accumulation of β-catenin in enterocyte precursor due to the mutations explained above, causes to the enterocyte precursor to retain a stem cell-like phenotype, which excludes it from migration out of the crypts. This leads to the accumulation of large numbers of relatively undifferentiated cells in a colonic crypt, which eventually form adenomatous polyps.

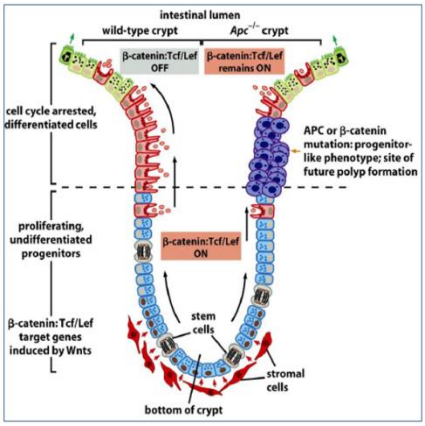


Figure extracted from [4] – The colonic crypt

Most of colon carcinomas develop from a benign non-invasive adenoma. The earliest histologically recognisable precursor lesion is the monocryptal adenoma or aberrant crypt focus (ACF). ACF expand through crypt fission. This lead to the formation of an adenoma, which has a higher rate of crypt fission. Then, a carcinoma will be developed.

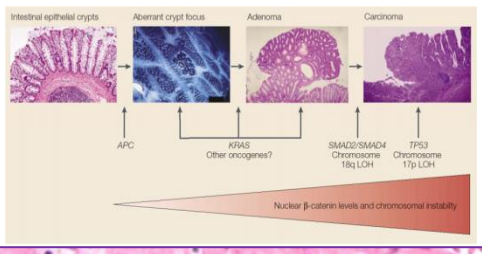


Figure extracted from [2] – colon carcinoma development

## 6. Therapy

Nowadays there isn't a cure for colon cancer. However, there are some therapies that can help to treat this cancer:

| | |
|---|---|
| Vitamin D | • Calcitriol is the most active vitamin D metabolite and inhibits Wnt-β-catenin signaling. |
| Celecobix | • is a selective COX-2 and COX-2 inhibition leads to an increase in β-catenin 's phosphorylation. |
| Resveratrol | • is a long-term inhibitor of COX-2 and COX-2 inhibition leads to an increase in phosphorylation of β-catenin. Also, resveratrol reduces ornithine decarboxylase expression and is a moderately selective inhibitor of COX-1. |

## 7. Conclusions

β-catenin has different roles in the cell and one of them is its implication in the Wnt pathway. This pathway is very important because its correct functionality is required for the development and maintenance of the intestinal crypts. However, if an alteration in a component of this pathway is presented, then there will be an up-regulation because the correct function won't be possible and an alteration in the crypts will be observed and this will lead to initiate tumours.

Nowadays, a pharmacologic treatment for colon cancer does not exist. Thus, it is important to know exactly the molecular mechanism of the Wnt pathway.

## 8. References

[1] - Alberts A, Johnson A, Lewis J, Raff M, Roberts K, and Walter Peter. (2008). Molecular Biology of the cell. Garland Science. Fifth Edition.

[2] - Fodde R, Smits R, and Clevers H. (2001). APC, signal transduction and genetic instability in colorectal cancer. Nat Rev Cancer. 1(1),55-67.

[3] - Krausova M. And Korinek V. (2014). Wnt signaling in adult intestinal stem cells and cancer. *Cellular signaling*. 26(3),570-9

[4] - Weinberg R.A. (2007). The Biology of Cancer. *Garland Science.*