

# Fighting colorectal cancer: Wnt/ $\beta$ -catenin pathway

UAB

Universitat Autònoma de Barcelona

Jiménez Herrera, Mireia

Degree in Biomedical Sciences · Faculty of Bioscience · Universitat Autònoma de Barcelona

## INTRODUCTION

### Epidemiology

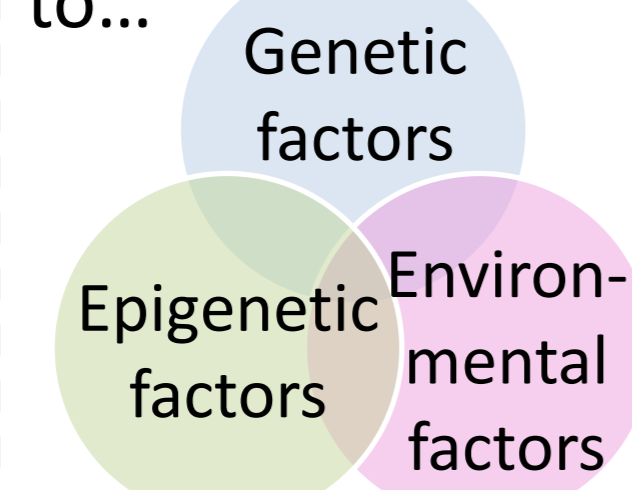
Colorectal cancer (CRC)...

- Most common malignant tumor in women and men considered together
- Second most frequent cause of cancer death
- Survival decreases with tumor stage

Importance of early detection  
Need for treatment

### Etiology

Alterations are due to...



CRC is classified into...

- Sporadic (70-75%)
- Heritable (5-10%)
- Familial (20%)

### Adenoma – carcinoma sequence

CRC is a **multistep process**. The order of genetic changes can vary, but activating mutations of Wnt/ $\beta$ -cat pathway always happen **at the beginning** of the neoplastic process.<sup>1</sup>

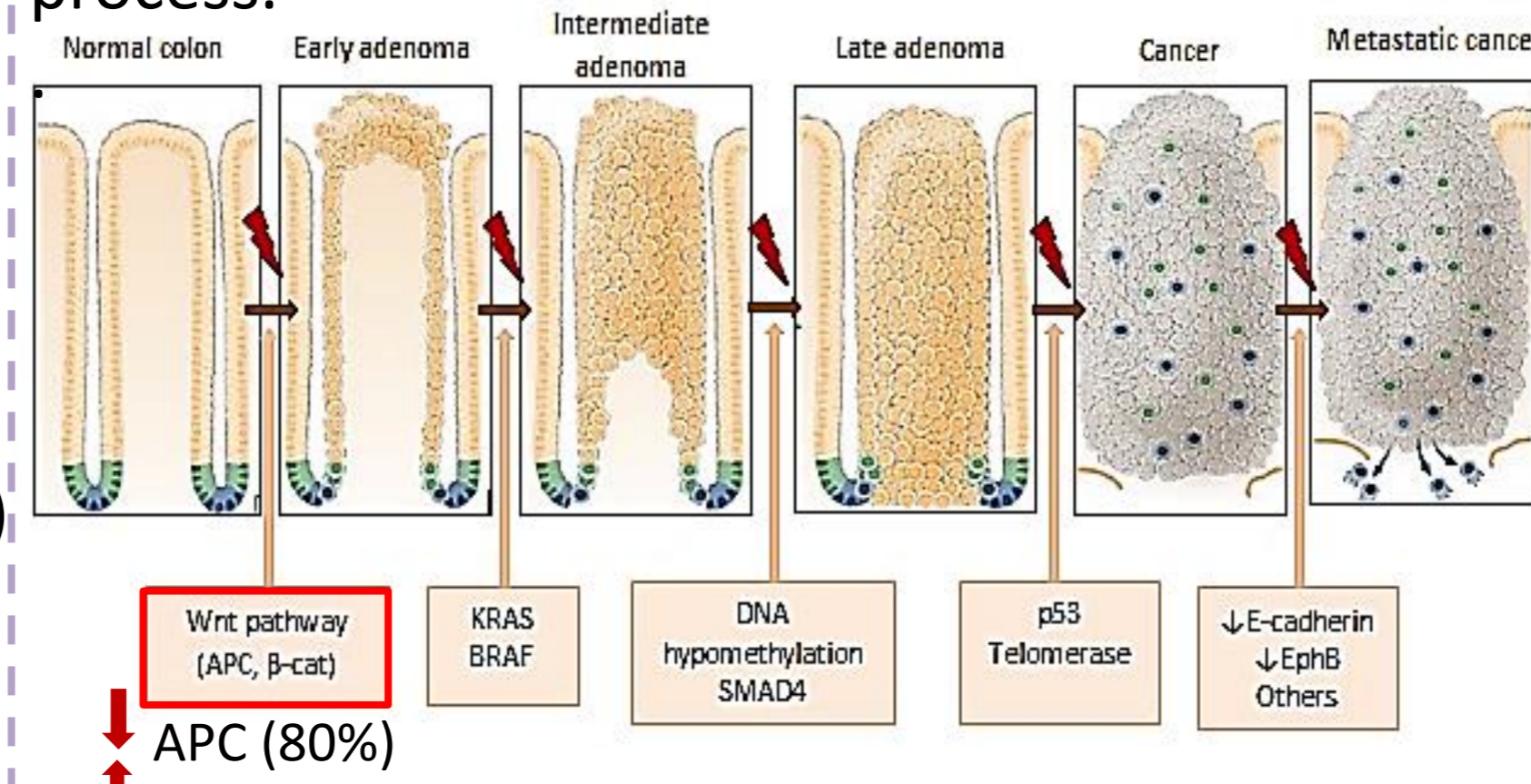


Fig.1. Changes through adenoma – carcinoma sequence. (Modified from Todaro, M., et al. (2010). *Gastroenterology*, 138(6), 2151-2162).

## AIM

The aim of this project is to analyze the **implication of Wnt/ $\beta$ -catenin signaling in colorectal cancer development** and show the most **promising therapies targeting this pathway**.

## MATERIALS AND METHODS

This scientific review has been achieved using books and articles obtained from **ScienceDirect**, **Scopus** and **Pubmed** databases. Articles were selected according to their **publication date**, even if some of them are older but very relevant, and the **journal impact factor**, although articles about therapy has lower impact factor because consist in researches paid by private institutions. **Main keywords:** colorectal cancer, Wnt pathway,  $\beta$ -cat, EphB, ephrinB, cryptogenesis, cancer stem cells, colorectal cancer therapy, Wnt inhibition.

## COLON CRYPTS

Maintenance of colonic mucosa is given by two processes regulated by Wnt/ $\beta$ -cat pathway: **cell production**<sup>5</sup> within a crypt by proliferating stem cells and **new crypt production**<sup>6</sup> by fission.

### Crypt renewal

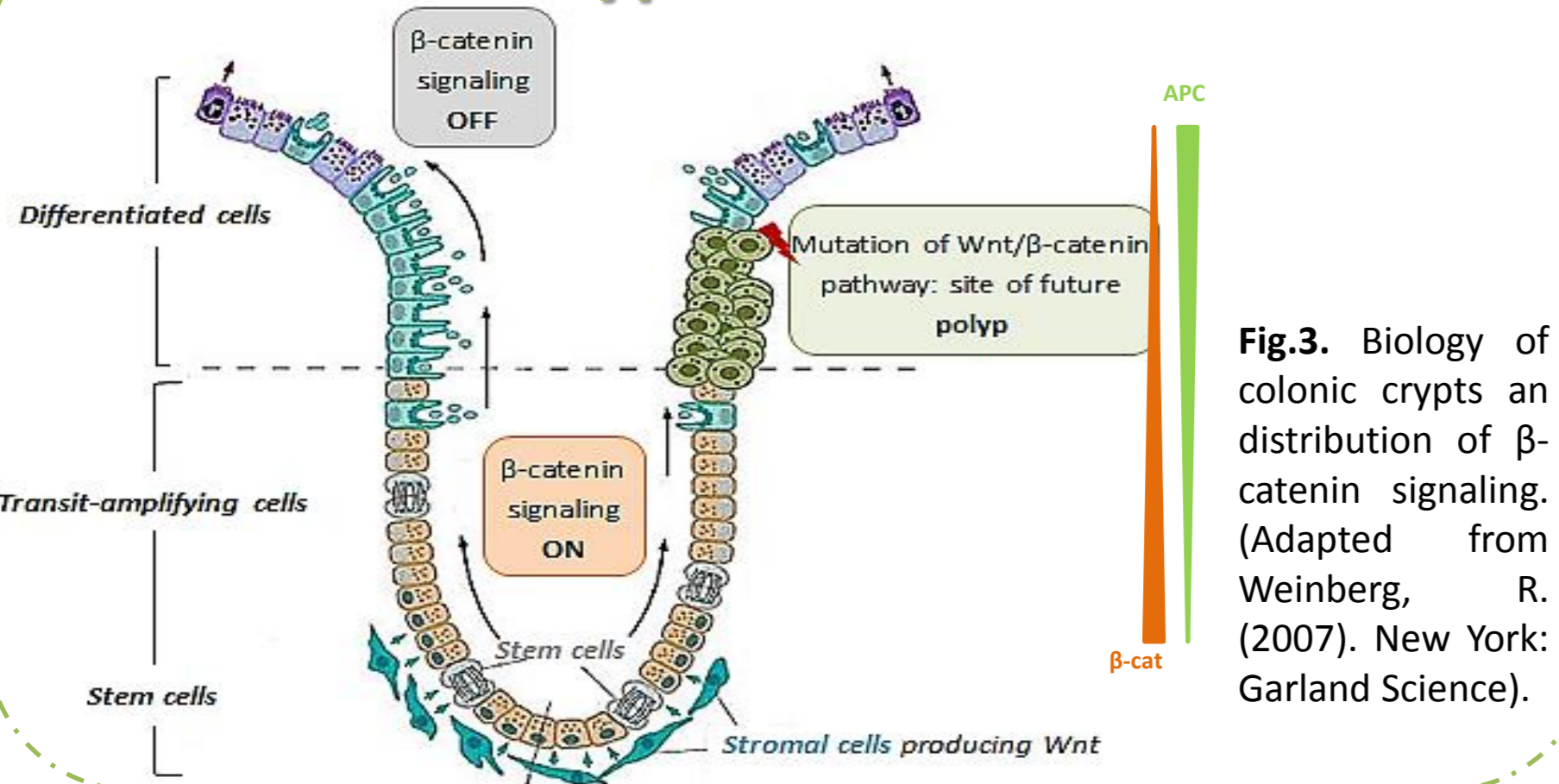


Fig.3. Biology of colonic crypts an distribution of  $\beta$ -catenin signaling. (Adapted from Weinberg, R. (2007). New York: Garland Science).

### Crypt fission

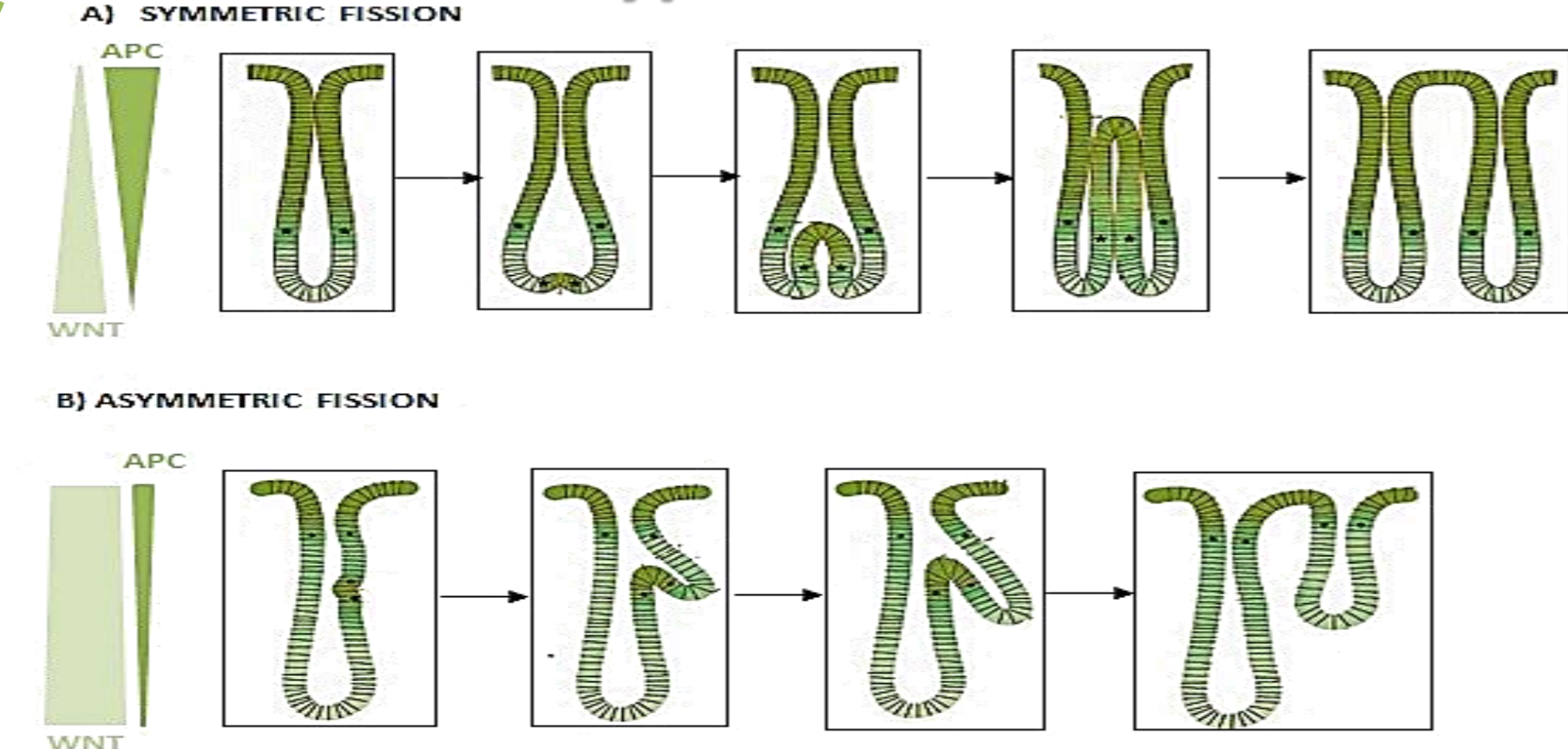
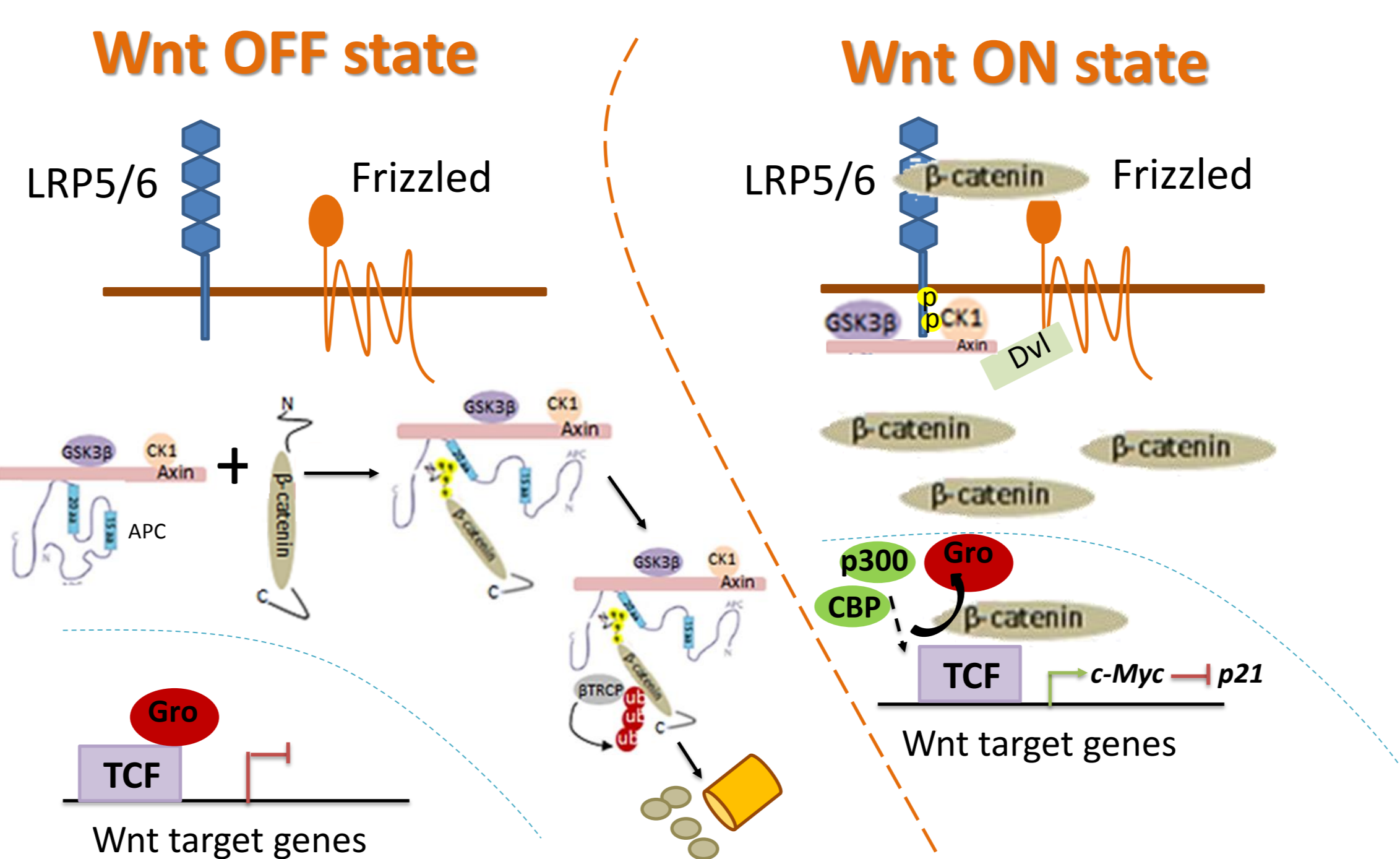


Fig.4. Normal (A) and aberrant (B) crypt fission. A. (Adapted from Boman, B. & Fields, J. (2013). *Front. Oncol.*, 3, 244).

## WNT/ $\beta$ -CATENIN PATHWAY

Wnt/ $\beta$ -catenin pathway is involved in important processes like **SC maintenance, cell proliferation, survival and differentiation**.<sup>2</sup>



### Cancer (Constitutively active)

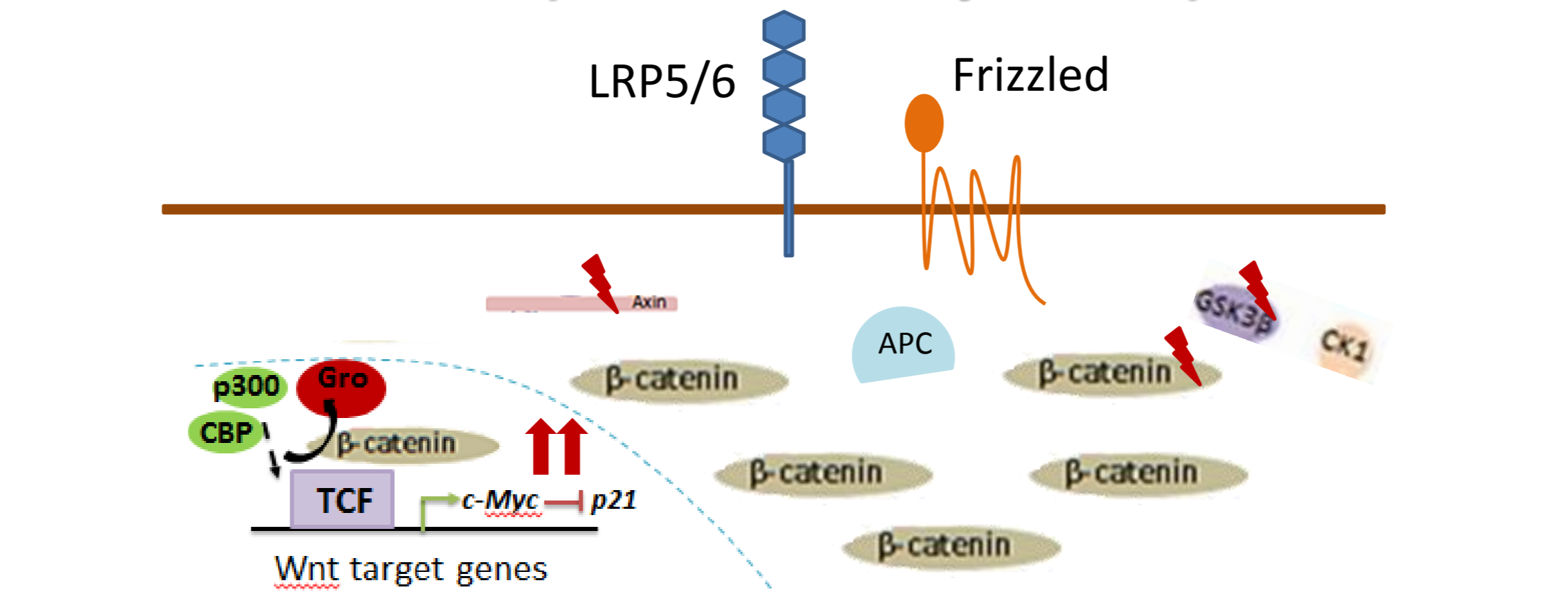


Fig.2. Wnt/  $\beta$ -catenin signaling in three possible scenarios: Wnt OFF state<sup>3</sup>, Wnt ON state and constitutively active state due to mutations of pathway components resulting in cancer.<sup>4</sup>

## EPHB-EPHRIN B SIGNALING

$\beta$ -cat/TCF also regulates compartmentalization and migration of cells along the crypt by promoting expression of EphB receptors and inhibiting ephrinB.<sup>7</sup>

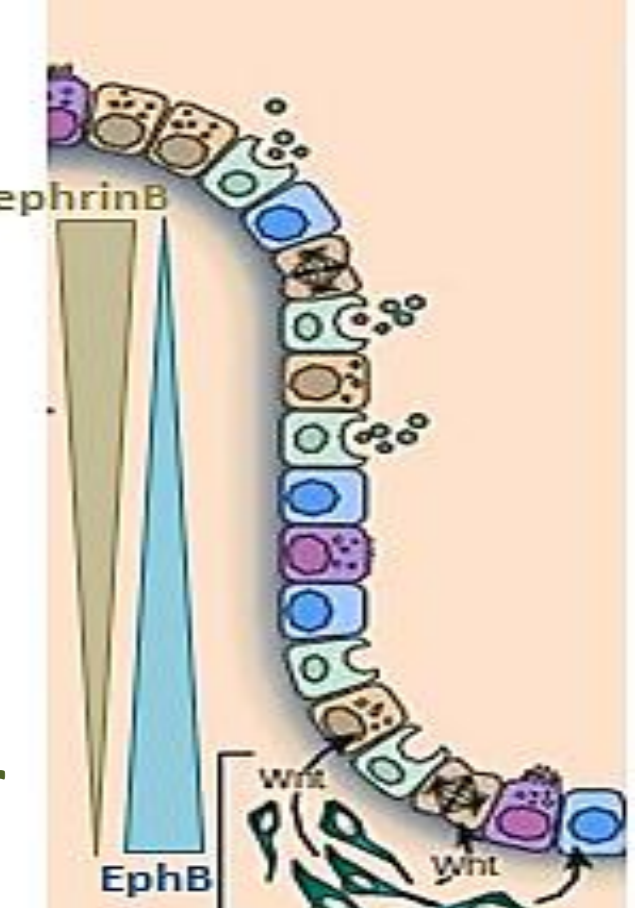
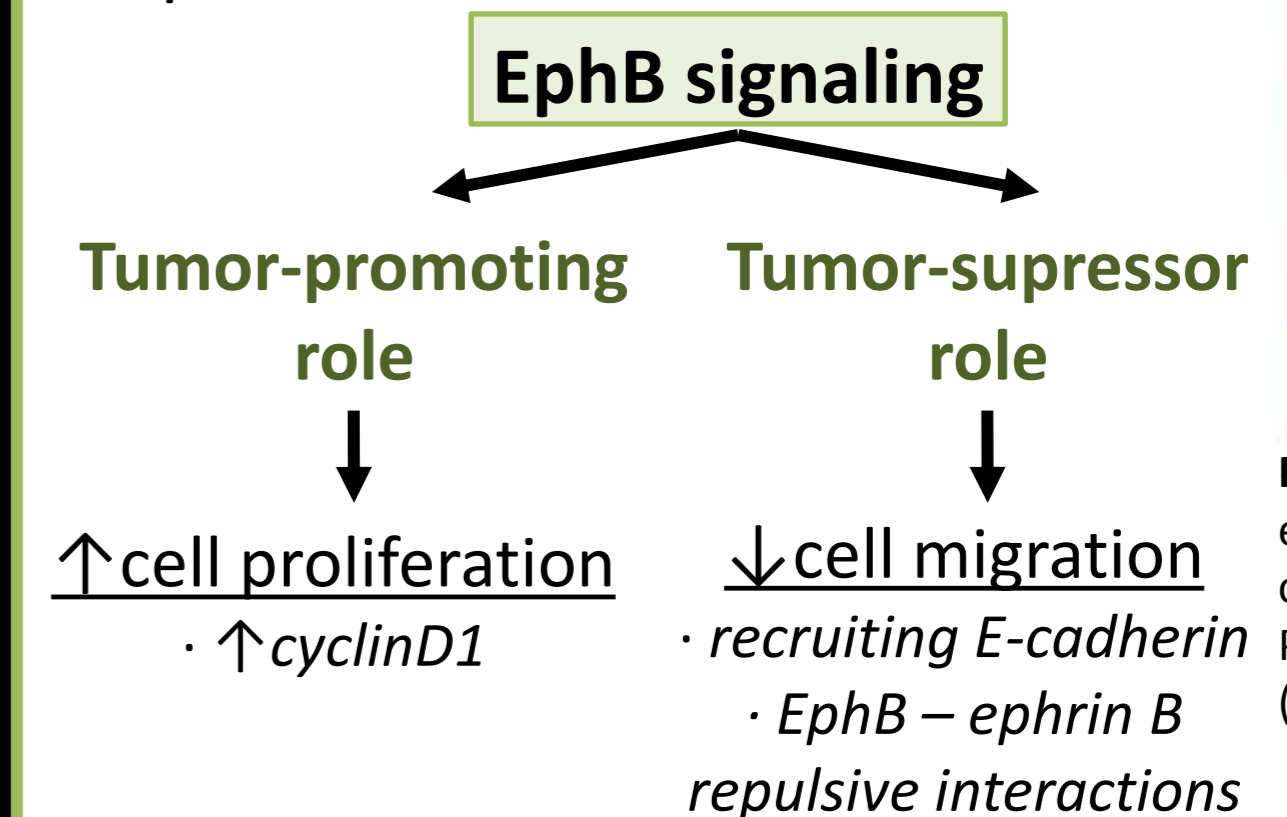


Fig.5. Eph receptors and ephrin ligands distribution in colon crypts. (Adapted from Peifer, M. (2002). *Nature*, 420 (6913), 274-276).

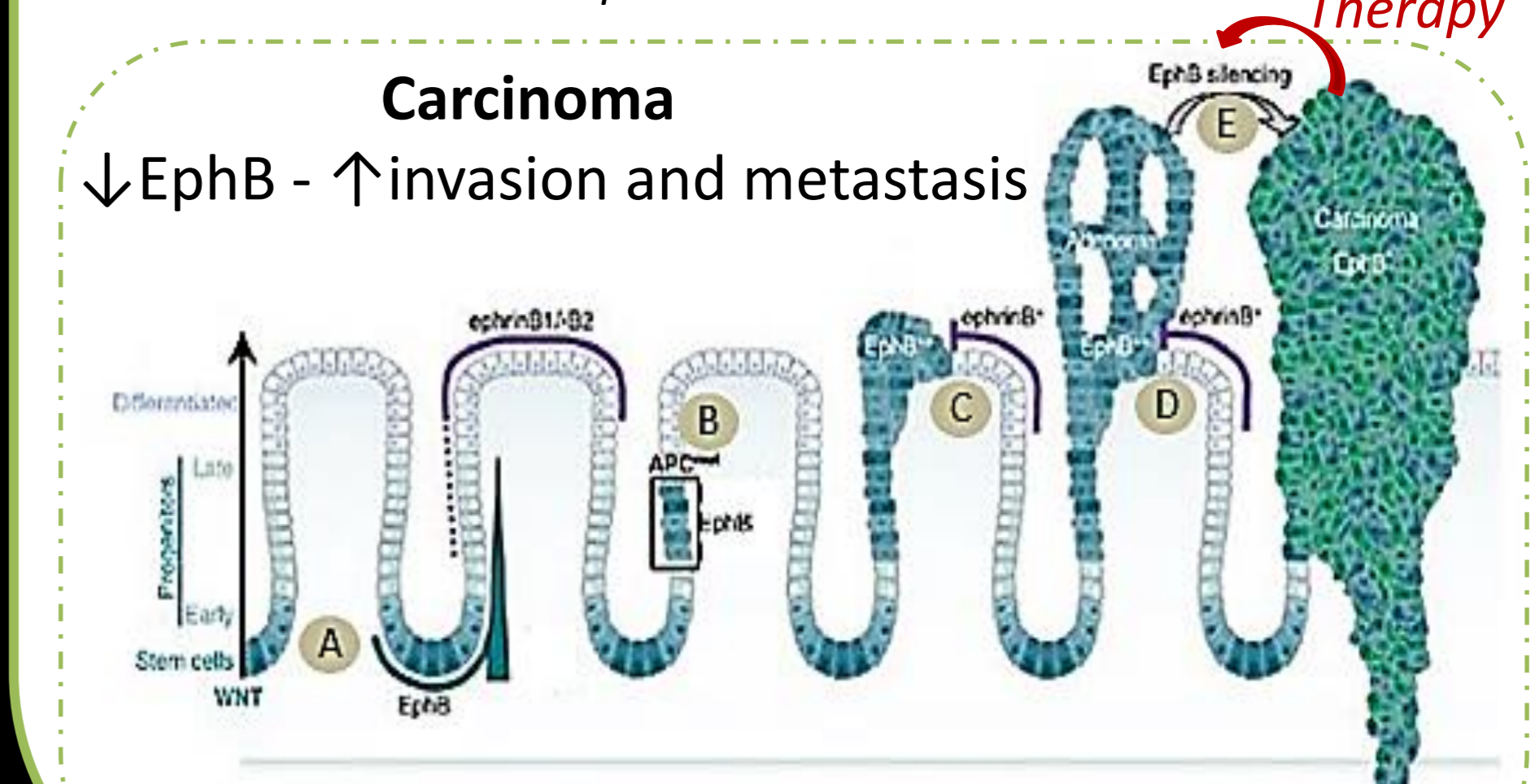


Fig.6. EphB – ephrin B signaling involved in CRC invasion and metastasis. (Adapted from Merlos-Suárez, A. & Batlle, E. (2008). *Current Opinion In Cell Biology*, 20(2), 194-200).

## THERAPEUTIC STRATEGIES

Resistance to conventional therapeutics is caused by presence of cancer stem cells (CSCs) and optimal therapies are those that **target this population**. Current treatment consists in surgical intervention along with chemotherapy and radiotherapy but it cannot kill all CSC. Therefore, there is a great interest in developing strategies targeting selectively Wnt signaling in CSCs.

### 1 $\beta$ -cat/TCF antagonists

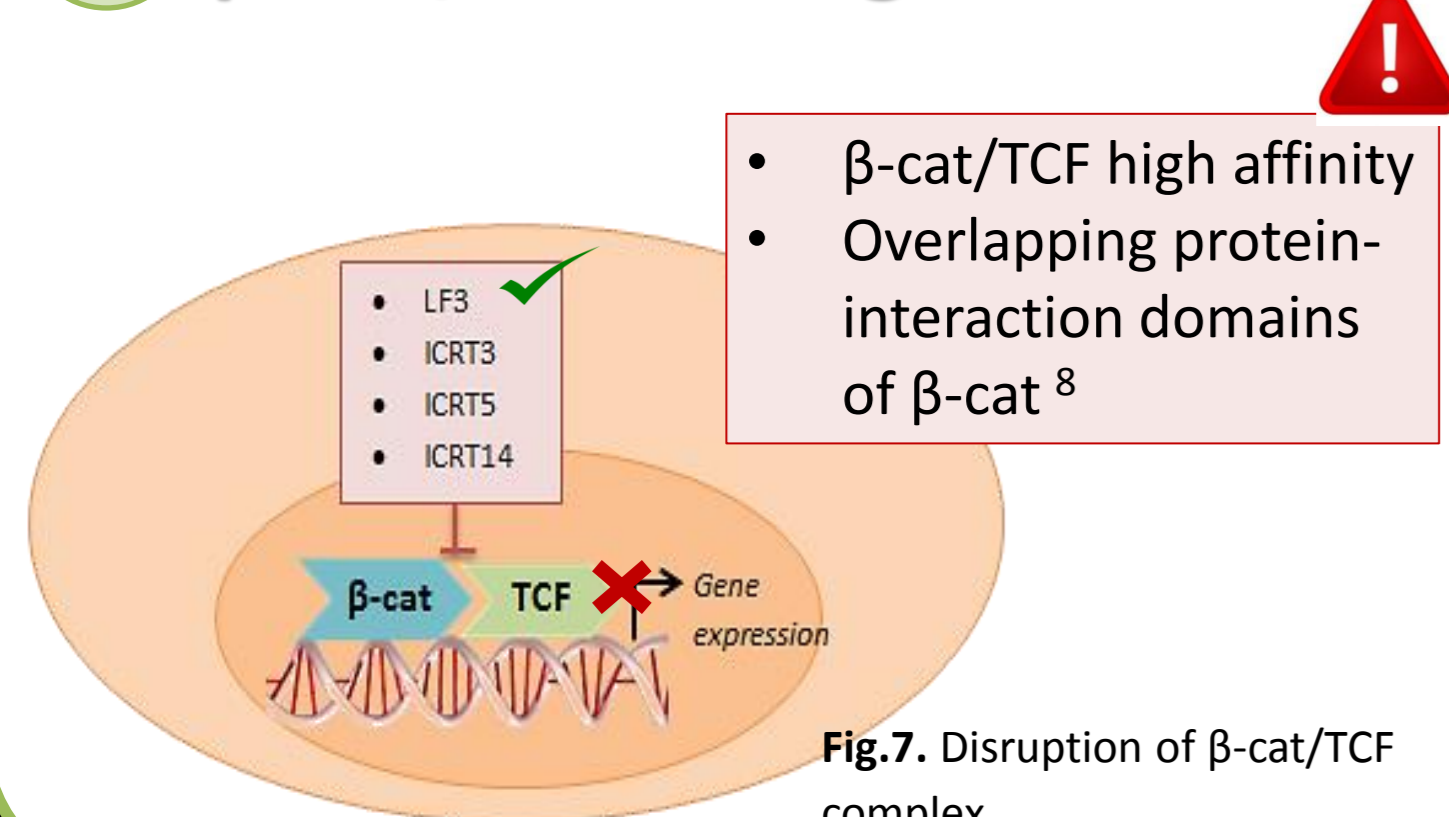


Fig.7. Disruption of  $\beta$ -cat/TCF complex.

### 2 $\beta$ -cat/CBP switch to $\beta$ -cat/p300

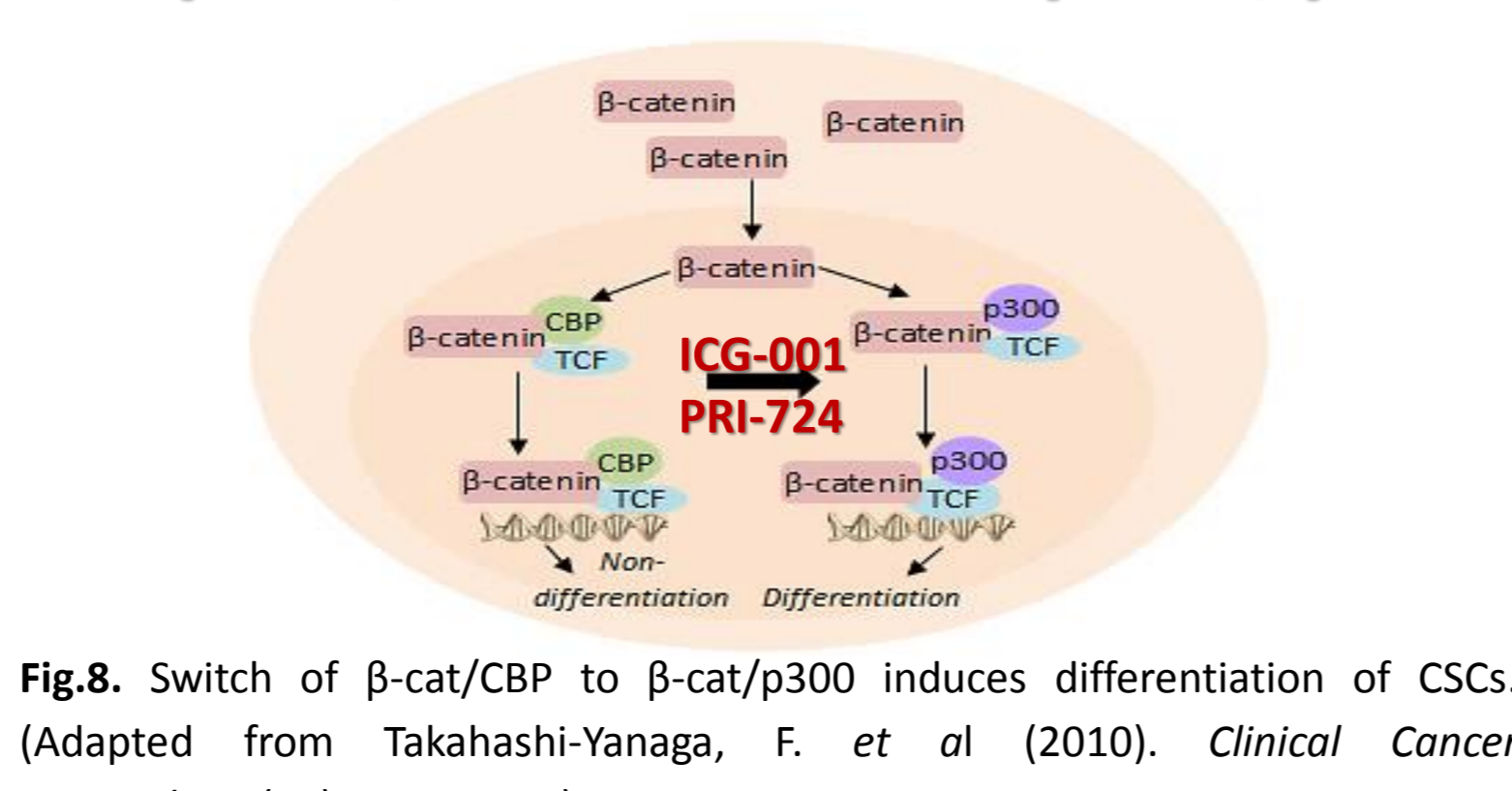


Fig.8. Switch of  $\beta$ -cat/CBP to  $\beta$ -cat/p300 induces differentiation of CSCs. (Adapted from Takahashi-Yanaga, F. et al (2010). *Clinical Cancer Research*, 16(12), 3153-3162).

### 3 CSC differentiation by retinoids

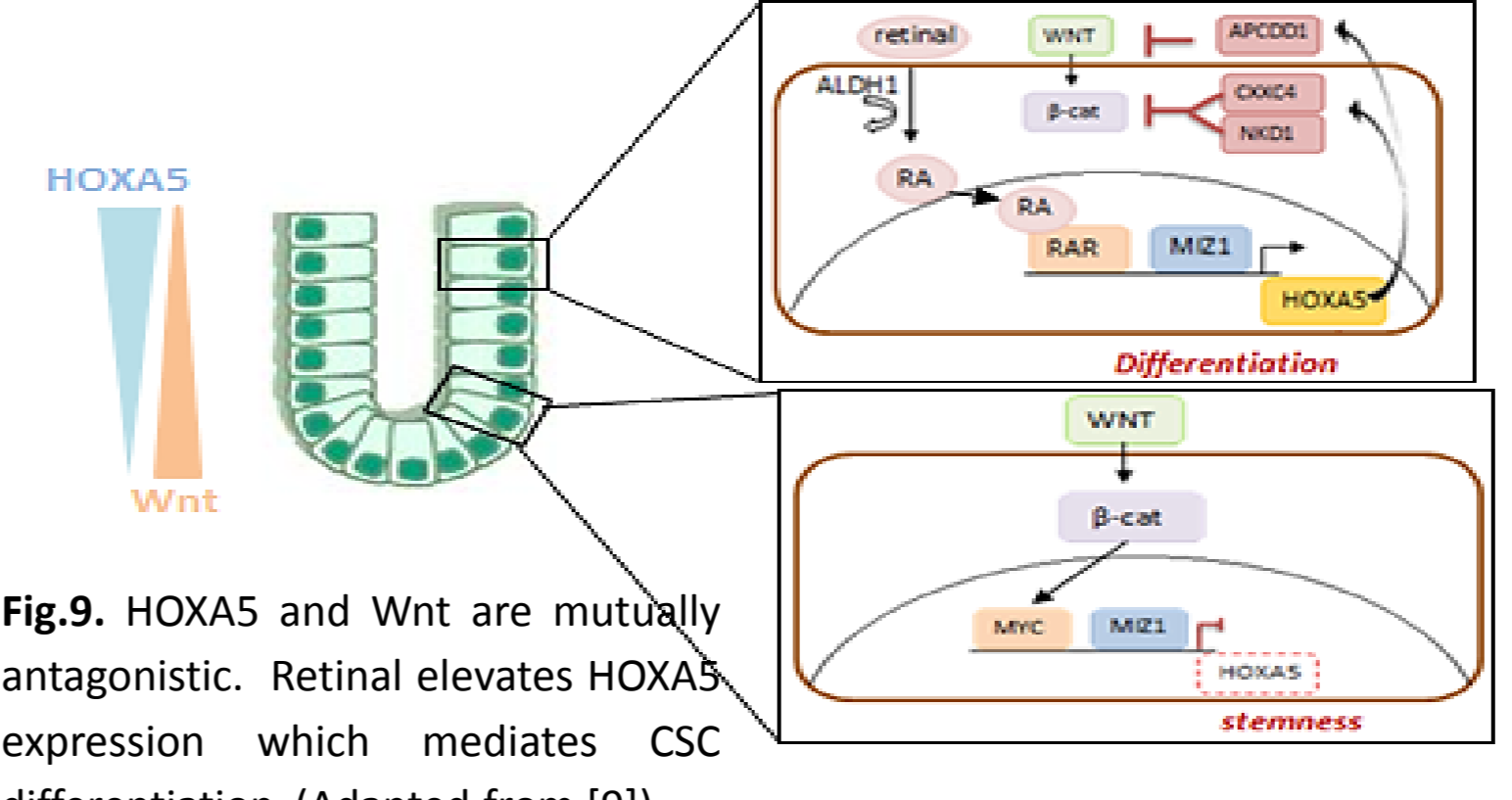


Fig.9. HOXA5 and Wnt are mutually antagonistic. Retinal elevates HOXA5 expression which mediates CSC differentiation. (Adapted from [9]).

### 4 $\beta$ -cat phosphorylation by PKC $\alpha$

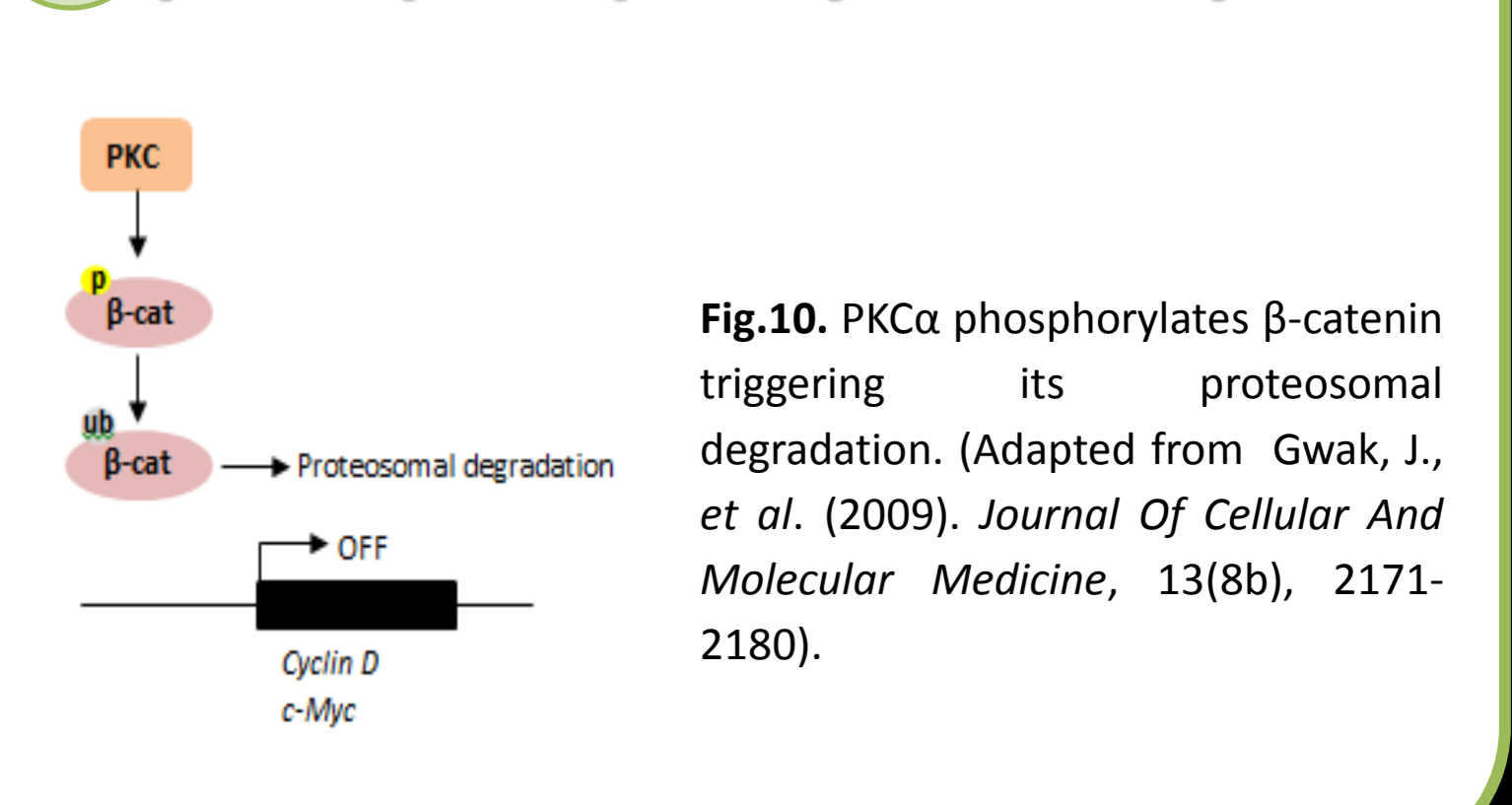


Fig.10. PKC $\alpha$  phosphorylates  $\beta$ -catenin triggering its proteosomal degradation. (Adapted from Gwak, J., et al. (2009). *Journal Of Cellular And Molecular Medicine*, 13(8b), 2171-2180).

## CONCLUDING REMARKS

- Wnt/ $\beta$ -catenin pathway controls maintenance of colon crypts production and renewal by inducing SC proliferation. Thus, its alterations are responsible of CRC initiation and progression.
- Wnt pathway also regulates cell positioning along the crypts by controlling EphB-ephrinB expression. EphB signaling inhibition during transition to carcinoma induces tumor invasion and metastasis.
- There are promising current research strategies that target Wnt signaling. However, there is still much work to do in order to downregulate Wnt pathway specifically in CSCs, preventing tumor progression and cancer relapse after treatment.

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