Fighting colorectal cancer: Wnt/β-catenin pathway

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INTRODUCTION

Epidemiology
Colorectal cancer (CRC)... is the fourth most common cause of cancer death worldwide. The incidence and mortality of CRC are increasing, and the disease is responsible for a significant number of deaths worldwide. The incidence of CRC increases with age, and the disease is more common in developed countries. The risk factors for CRC include age, family history, diet, and lifestyle. Prevention strategies include screening programs, lifestyle modification, and the use of drugs that inhibit the Wnt/β-catenin pathway.

Etiology
Alterations are due to...
- Genetic factors
- Epigenetic factors
- Environmental factors
CRC is classified into...
- Sporadic (70-75%)
- Heritable (5-10%)
- Familial (20%)

Adenoma – carcinoma sequence
The order of genetic changes can variate, but activating mutations of Wnt/β-catenin pathway always happen at the beginning of the neoplastic process.

AIM
The aim of this project is to analyze the implication of Wnt/β-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, β-catenin, 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/β-catenin pathway: cell production within a crypt by proliferating stem cells and new crypt production by fission.

WNT/BETA-CATENIN PATHWAY
Wnt/β-catenin pathway is involved in important processes like SC maintenance, cell proliferation, survival and differentiation.

EPHB-EPHRIN B SIGNALING
β-catenin/TF target genes are also regulated by EphB-ephrinB signaling, which is involved in the cell proliferation and migration of cells along the crypt by promoting expression of EphB receptors and inhibiting ephrinB.

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. β-catenin/TF antagonists
2. β-catenin/CBP switch to β-catenin/p300
3. CSC differentiation by retinooids
4. β-catenin phosphorylation by PKCs

CONCLUDING REMARKS
- Wnt/β-catenin pathway controls maintenance of colon crypts production and renewal by inducing SC proliferation. Thus, its alterations are responsible for 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.

REFERENCES