Review

From Molecular Biology to Clinical Trials: Toward Personalized Colorectal Cancer Therapy

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Abstract

During the past years, molecular studies through high-throughput technologies have led to the confirmation of critical alterations in colorectal cancer (CRC) and the discovery of some new ones, including mutations, DNA methylations, and structural chromosomal changes. These genomic alterations might act in concert to dysregulate specific signaling pathways that normally exert their functions on critical cell phenotypes, including the regulation of cellular metabolism, proliferation, differentiation, and survival. Targeted therapy against key components of altered signaling pathways has allowed an improvement in CRC treatment. However, a significant percentage of patients with CRC and metastatic CRC will not benefit from these targeted therapies and will be restricted to systemic chemotherapy. Mechanisms of resistance have been associated with specific gene alterations. To fully understand the nature and significance of the genetic and epigenetic defects in CRC that might favor a tumor evading a given therapy, much work remains. Therefore, a dynamic link between basic molecular research and preclinical studies, which ultimately constitute the prelude to standardized therapies, is very important to provide better and more effective treatments against CRC. We present an updated revision of the main molecular features of CRC and their associated therapies currently under study in clinical trials. Moreover, we performed an unsupervised classification of CRC clinical trials with the aim of obtaining an overview of the future perspectives of preclinical studies.

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Introduction

Colorectal cancer (CRC) is a molecular heterogeneous disease.[1] Several genomic alterations have been discovered in the past few years with the technological advances in the development of sequencing platforms. This has led to the integrative characterization of CRC molecular features, such as mutations, promoter methylation, and mRNA expression, which eventually uncovered several pathways important for CRC initiation and progression.[2-4]

The common affected pathways include Wnt signaling, receptor tyrosine kinase (RTK) signaling—with vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF1R), and MET as the main members—phosphoinositide 3-kinase (PI3K), transforming growth factor (TGF)-β, p53, and apoptotic signaling. Targeted therapy against the key components of these signaling pathways has allowed improvements in CRC treatment. However, a significant percentage of patients with advanced CRC will not benefit from these targeted therapies and will be restricted to systemic chemotherapy.

It has been shown that the mechanisms of resistance are directly connected to specific gene alterations, such as *KRAS*-mutated tumors that show resistance to anti-EGFR therapy.[5] Further insights into these mechanisms could enable a deeper understanding of tumor evasion to therapy and might identify specific potential targets that could stratify patients to receive the appropriate treatment. Therefore, a dynamic link between basic molecular research and preclinical studies, which ultimately constitute the prelude to standardized therapies, is very important to provide better and more effective treatments against CRC.

We present an updated revision of the main molecular features of CRC and their associated therapies currently under study in clinical trials. Moreover, we performed an unsupervised hierarchical clustering classification of 352 CRC clinical trials selected from the ClinicalTrials.gov database with the aim of obtaining an overview of the direction-pointing preclinical studies.

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Wnt Pathway

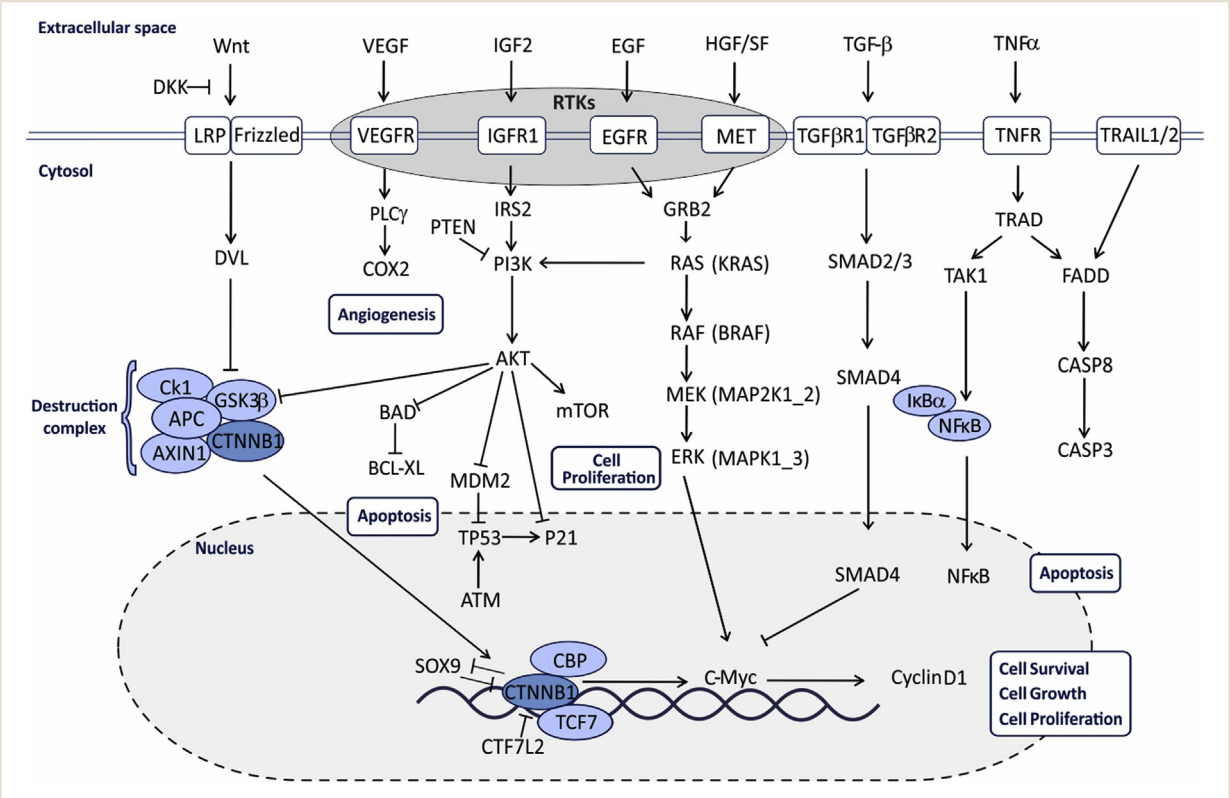
Wnt signaling is a highly conserved pathway involved in developmental processes, such as cell proliferation, differentiation, and polarity.[6] In the canonical Wnt pathway, the tumor suppressor adenomatous polyposis coli, axin, casein kinase 1, and glycogen synthase kinase 3 form the destruction complex that binds to β-catenin (CTNNB1), which is phosphorylated by glycogen synthase kinase 3 and subsequently ubiquitinated by being destroyed in the proteasome.[7] In contrast, when Wnt ligands bind to the lipoprotein receptor-related protein and the frizzled receptor, the cytosolic disheveled protein is activated, and it inhibits CTNNB1 phosphorylation and its consequent degradation. Thus, the protein accumulates in the cytosol and eventually translocates to the nucleus, where it binds to T-cell–specific transcription factor 7, and both participate in the activation of downstream target genes, such as *cMYC,* promoting cell proliferation (Figure 1).

Several components of Wnt signaling might contribute to tumorigenesis when they have been altered genomically.[8] According to the molecular characterization of CRC by The Cancer Genome Atlas group, 94% of the analyzed tumors showed the Wnt pathway was affected,[2] predominately (80%) with inactivating mutations of adenomatous polyposis coli and activating mutations of *CTNNB1*. They also found mutations in *SOX9*, mutations and deletions in T-cell–specific transcription factor 7-like 2 and DKK members (inhibitors of Wnt signaling), and overexpression of the frizzled receptor. Because these alterations could confer an advantage phenotype to malignant cells, targeting Wnt signaling has become one of the main focuses in the development of new targeted therapies for CRC.

Although no drugs targeting the Wnt pathway in CRC have yet been approved by the Food and Drug Administration (FDA), numerous small molecule inhibitors of this pathway have been developed and have been extensively reviewed by Song et al[9] in 2015. Some of them are currently being evaluated in clinical trials.

Because the vast majority of patients with CRC have the Wnt pathway affected in ≥ 1 components, hampering the stratification of patients into those with a good or bad response to therapy, one important challenge is to find the target that minimizes the side effects. A proposed strategy has been the development of inhibitors against molecules that do not constitute the central core of the pathway.[10,11] Inhibition of the interaction between CTNNB1 and Creb-binding protein by the small molecule ICG001, for instance, has shown a decrease in adenoma formation in mouse models of colon cancer.[12] This and similar agents have been considered in preclinical studies.[13-15] In a phase II clinical trial, the Creb-binding protein/CTNNB1 antagonist PRI-724 has been proposed for

Figure 1 Schematic Representation of the Main Pathways Affected in Colorectal Cancer. The Gene Symbols of the RAS-RAF-MEK-extracellular Signal-regulated Kinase (ERK) Signaling Cascade Are Indicated in Brackets



Abbreviations: APC = adenomatous polyposis coli; COX2 = cyclooxygenase 2; DVL = disheveled protein; EGF = epidermal growth factor; HGF = hepatocyte growth factor; IGF2 = insulin-like growth factor-2; LRP = lipoprotein receptor-related protein; TGF-β = transforming growth factor-β; TNF-α = tumor necrosis factor-α; TNFR = TNF receptor; TRAIL = TNF-related apoptosis-inducing ligand; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.