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Perspective

Pathway of Wnt Signaling in Colorectal Cancer

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DESCRIPTION

The WNT signaling pathway is a critical mediator of tissue homeostasis and repair, and frequently co-opted during tumor development. Almost all Colorectal Cancers (CRC) demonstrate hyper activation of the WNT pathway, which in many cases is believed to be the initiating and driving event. In this short review, we provide a focused overview of recent developments in our understanding of the WNT pathway in CRC, describe new research tools that are enabling a deeper understanding of WNT biology, and outline ongoing efforts to target this pathway therapeutically. Colorectal Cancer (CRC) is the second leading cause of cancer-related death in the world and accounts for almost 600,000 deaths annually. The majority of CRCs arise sporadically in patients with no family history of disease, and while colonoscopic removal of premalignant tumors has led to an overall reduction in morbidity, patients that progress to advanced disease have few effective treatment options and a dismal prognosis. In the age of rational drug design and precision medicine, CRC research and treatment is somewhat lagging.

The WNT family consists of 19 secreted, cysteine-rich glycoproteins that have been implicated in diverse biological processes, including cell fate specification, cell proliferation, cell migration, dorsal axis formation, and asymmetric cell division. The canonical, or β-catenin–dependent, signaling cascade is a multistep process that involves the relocalization, phosphorylation, and degradation of multiple proteins, culminating in a coordinated transcriptional response; detailed mechanistic models for Wnt signal transduction have been covered extensively elsewhere. Briefly, WNT ligands bind frizzled (FZD) and LRP receptor complexes, initiating membrane recruitment of key scaffold proteins (AXIN, DVL), and disruption of the β-catenin destruction complex (minimally composed of AXIN, APC, CK1, GSK3β). In the absence of this complex, β-catenin accumulates in the cytosol, and through poorly understood mechanisms, translocates into the nucleus where it associates with TCF family transcription factors and a host of co-activators to drive transcription of target genes. Wnt signaling is an essential factor in normal intestinal function, and in particular, for the maintenance and self-renewal of epithelial stem cells located at the base of intestinal crypts. WNTs emit glycoproteins that should go through a progression of adjustments before they are physiologically dynamic. In the Endoplasmic Reticulum (ER), the trans-membrane O-acyltransferase Porcupine (PORCN) catalyzes the lipidation (palmitoylation) of early WNT proteins at two unmistakable destinations. Then, lipid-bound WNTs are glycosylated in the ER prior to progressing to the Golgi, where they associate with a second trans-membrane protein, Wntless (WLS). WLS is fundamental for the conveyance and emission of WNT ligands at the cell surface and following discharge, WI protein is reused back to the Golgi, by means of retromer endosome transport. Repressing either the lipidation or transport of WNT by means of PORCN or WLS is adequate to totally obstruct WNT ligand emission, and in this manner, offers two possible remedial hubs for WNT-ligand driven sickness.

WNT signaling pathway disturbances in Colorectal Cancers (CRC)

Since the underlying distinguishing proof of APC modifications in human CRC, and the acknowledgment that the APC protein controls WNT action, obviously most of the colon tumor growths conveyed undeniable levels of WNT pathway action. Notwithstanding the WNT controllers depicted by the TCGA, a few examinations have since extended the scope of potential WNT-driving hereditary changes. In 2012, de Sauvage and associates distinguished the first intermittent genomic movements in CRC, including RSPO relatives (Rspo2 and Rspo3). Interesting, although generally few cases have been distinguished, in both their review and in follow-up work, RSPO movements were fundamentally unrelated with APC changes. Further work will be expected to decide if RSPO adjustments alone are adequate to drive cancer improvement in the digestive tract (intestines). In any case, there are numerous questions with respect to the solid determination for changes, specifically, WNT pathway qualities, and this may altogether affect our capacity to take advantage of such modifications for restorative addition.

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WNT signaling as therapeutic target

Notwithstanding the staggering proof that WNT pathway hyper-activation drives CRC, designated WNT treatments have not gained ground in the facility. While the Overall Survival (OS) for patients with CRC has dynamically stretched in the course of the most recent 30 years, it is to a great extent attributed to progresses in a medical procedure, chemotherapy, adenoma discovery and expulsion by colonoscopy, the utilization of headache medicine (aspirin) and NSAIDs for other clinical signs, and all the more as of late, improvement of specialists focusing on VEGF and EGFR flagging.

CONCLUSION

WNT signaling has emerged one of the most important biological pathways in development and disease. In CRC, WNT pathway hyper-activation is arguably the most critical cancer driver, and represents an exciting avenue for targeted therapy. As new technologies pave the way for a more refined understanding of WNT function in normal and transformed cells, we expect the identification and development of WNT-targeted therapeutics to accelerate, and hope that these efforts translate into a significant clinical benefit.