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Wnt/β-Catenin Signaling in Intestinal Cancers: Mechanisms, Therapeutic Targets, and Treatment Strategies

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Abstract: Intestinal cancers are always hazardous due to its high morbidity and mortality. Currently, it is known that an error in the Wnt/β-catenin pathway is an essential cause of intestinal cancers. After the inhibitors and markers involved in it are especially studied, targeted therapy has already been considered by the scientists. However, there is only overall understanding in Wnt/β-catenin pathway with many detailed mechanisms uncleared, thus no treatments can be put into practice. This article analyses proteins and factors which have the potential of being used as targets of targeted therapy. Besides, essential inhibitors, such as NEDD4 and E7386, of the Wnt/β-catenin pathway and how lack of them lead to oncogenesis are introduced. Furthermore, the possibility and examples of targeted medicine is discussed. This review offers a wider view of the entire mechanism of intestinal cancers spurred by Wnt/β-catenin pathways. The article encouraged further research in variable stages, and new breakthrough is purposed for therapy based on the Wnt/β-catenin pathway.

Keywords: Wnt/β-catenin pathway, colorectal cancer, crypt, intestine.

1. Introduction

The incidence of colorectal cancer (CRC) ranks third in the global cancer spectrum, below lung cancer and female breast cancer. The number of deaths ranks second in the global cancer death spectrum [1]. According to the estimation of ACS in 2023,there will be 152,810 diagnoses of colorectal cancer in 2024, in which 106,590 cases of colon cancer becomes dominant [2].

Wnt pathways, especially the typical one, involves widely in the microenvironment stability and tumor development in the small intestine and the colon, especially CRC.

The Wnt gene was first named to represent two genes with similar features in mouse breast cancer and the wingless gene of Drosophila, both of which take part in the regulation of embryonic development and are located on chromosome 12 [3].

There are three main types of Wnt signalling pathways. The most common one is Wnt/β-catenin pathway consisting of the extracellular signal, membrane segment, cytoplasmic segment and nuclear segment [4], which has a close connection to intestinal diseases [5].

All the ligands in typical Wnt/β-catenin pathway are secretory palmitoleate glycoproteins [6]. During the signal conduction of that typical pathway, palmitoleic acid attaches to the ligands and modified it in the endoplasmic reticulum(ER) [7]. After Wnt bounds to the Wntless protein on the ER, Golgi apparatus bud off, transport the Wnt ligands to the cell membrane then secrete the ligands through exocytosis.

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When Wnts are absent, the transmembrane receptors Frizzled(FZD) and Low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) remain unrecognized. The β-catenin degradation is activated when a destruction complex composed of multiple enzymes phosphorylates Casein Kinase 1 and Glycogen synthase kinase-3 [3].

Accumulation of β-catenin will result in the tumor formation. This situation occurs when Wnt/β-catenin signaling is initiated by binding the ligands with the Frizzled (FZD) receptors and the low-density lipoprotein receptor-related proteins 5/6 (LRP5/6) co-receptors on cells [8-10].

When FZD and LRP5/6 recognize Wnts, the destruction complex is recruited to the cell membrane thus unable to degrade β-catenin. The left β-catenin then translocates to the nucleus, interacts with TCF/LEF and gains the ability to take parts in transcription of target genes. From the process above, the cytoplasmic-nuclear shuttling of β-catenin is viewed as a significant characristic of Wnt/β-catenin pathway activation [11].

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On the one hand, the mutations in Wnt genes have already been proved to have a strong connection with tumors in the small intestine and in the colon. On the other hand, Stem cells with unlimited number of replications ensure the promptness and effectiveness of repairing damaged tissues, while the loss of repairing ability leads to more severe gastrointestinal disease. This report is going to study the mechanism behind the Wnt-pathway-related tumorigenesis and the stem cells, in order to provide insight targeting therapy and other ways of therapy.

2. Wnt/β-catenin Pathway and the Intestinal Diseases

2.1. To Prohibit the Cancer Cells Growing and Multiplying

2.1.1. NEDD4L

RNAScope ISH is used in detecting gene expressions on single cell level, specializing in observing cell differentiation and disease development. According to the image collected via RNAScope ISH, the difference between expression of NEDD4 in healthy mice’s small intestines and Apcmin is similar to the pattern in colorectal cancer tissues [12]: expression of NEDD4 is noticeably upregulated, while the expression level of NEDD4L shows an unchanged trend [13].

Researchers from Francis Crick Institute examined the intestinal activities in animals with a lack of NEDD4 or NEDD4L. They noticed that both stem cell markers in the small intestine and Wnt target genes were significantly upregulated. Besides, in the mutated organisms without NEDD4, organoid formation and proliferation became more efficient. Overall, the deficiency of NEDD4 and NEDD4L will prompt intestinal organoids to grow, as well as activate Wnt pathways [13].

On the other hand, NEDD4 and NEDD4L could have negative impact on Wnt signaling upstream by inhibiting the APC/β-catenin destruction complex at the surface receptor level, so the loss of them leads to more significant intestinal tumor phenotype [13]. That counteraction may suggest that NEDD4 can degrade DVL2 and LGR4/5 in order to change the Wnt signal strength [13].

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The results above showed that NEDD4 and NEDD4L are tumor suppressors which targets LGR4/5 and DVL2, resulting in the regulating function in maintaining ISC homeostasis as well as suppressing tumorigenesis in the intestine [13].

2.1.2. NEC Treatments

Apart from CRC, necrotizing enterocolitis (NEC) also has some new potential treatments. Agostino , et al. indicated that NEC is caused by the defection in Wnt signaling [14].

Amniotic fluid stem cells (AFSC) and the intestinal extracellular vesicles (EV) derived by AFSC are believed to have a positive impact on NEC intestinal injury recovery. Technically, ISC will mediate intestinal regeneration to protect the intestine from further damage [15], but NEC causes depletion of ISC [16].

Previous researchers showed that EV can reduce injury in NEC by acting as a kind of intercellular messengers [17]. A recent research discovered that in both the rat model [18,19] and the mouse model, AFSC injection reduced NEC-induced gut injury.

Porcn takes part in the process of making Wnt proteins mature and releasing them. Wnt-C59 and IWP2 are two inhibitors of AFSC. After being treated with the two chemicals, the Wnt activity would decrease. This outcome represents that exogenous Wnt signaling mediators can be produced by AFSC. Then, the researchers cocultured healthy mouse intestinal organoids together with the AFSC-deficient or Wnt-deficient ones. After seven days, only the organoids with AFSC showed an increase in the number as well as surface area, while the Wnt-deficient group had no change. Thus, AFSC could be artificially amplificated then induced to differentiate in order to repair damaged intestinal tissues, which suggested a possible method in tackling with inner injuries.

More importantly, AFSC-EV has the ability to rescue organoids when NEC injury has already occurred. Experiments indicated that adding Wnt and AFSC-EV in media leads to a larger size of intestinal organoids. Furthermore, the organoids in EV-rich media tended to maintain their round shapes more than those in the normal media, which are features of maintained pluripotency [14].

In addition, the timing of applying for the medicine including AFSC-EV is decisive. When administrating AFSC-EV before inducing NEC, IL-6 and TNFαwere expressed more, while Lgr5 and Ki67 were expressed less in the mice. However, the administration earlier than inducing NEC resulted in only rose epithelium proliferation but no change in the NEC severity score and the symptom of intestinal inflammation. Taken together, EV is involved in recovery from the damage attributed to NEC, but it cannot prevent NEC from occurring [14].

2.1.3. Lymphatic Endothelial Cells

Lymphatic endothelial cells were proved as another factor helping repair damaged intestines. Based on the fact that endothelial cells can secrete paracrine factors which are essential for organ regeneration [20], Ophir Klein and his colleagues explored the function of LECs in intestine repairance.

Combining whole-mount imaging with CUBIC clearing, there is a small distance between LECs and crypt cells.

After enriching LECs via fluorescence-activated cell sorting, the sample was identified as CDH5+ and PDPN+ cells, RNAscope was used to figure out the molecular composition of the researcher's object. The final result indicated that during homeostasis, R-Spondin 3 (Rspo3), an effective activator for classical Wnt pathway,, was specifically expressed by LECs adjacent to epithelial crypt cells.

Further experiments instantaneously uncovered the importance of Rspo3 in damaged intestinal recovery. Genetic models in which Rspo3 in LECs had been specifically deleted were utilized in observation of the proliferation of stem and progenitor cells. Using 5FU to cause injury in both the

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control group and Rspo3 knocked out mice, in the same time period, the knocked out mice had a decrease in the level of proliferation of stem cells in the crypt. However, LEC itself and the proportion of crypts proximate to LECs showed no change, reaching a conclusion that it was changed in lymphangiogrine signaling instead of the altered LEC structures which brought about the reduction in proliferation of stem cells. Similarly, other colitis suppressors like cyp4b1 have also been found in LTCs [21].

Under 5FU-induced damage, the expression level of Scl1 in mouse models lack of Rspo3 decreased. As a result, it ca be concluded that after being damaged, Sca1 plays a role in the transition to a fetal-like state. Conversely, Sca1 was expressed less in intestinal epithelial cells without lymphatic Rspo3, which was confirmed via flow cytometry. When applying qPCR analysis, anti-lymphangiogenic genes were shown to be expressed at higher level, which explained the previous phenomenon.

The disability in mucus secretion is related to colitis [22]. Violin plot demonstrated a loss in secretory progenitors, meanwhile the number of secretory lineage cells also fell.

Scientists have worked on targeted therapy related to Wnt pathways for intestinal cancers, and medicines could already show their effectivity in primary experiments. for cancer therapy.

2.1.4. E3786

E3786 is a synthetic orally active compound, which is believed to have a regulating effect in Wnt/β-catenin pathway by preventingβ-catenin and CSK-binding protein (CBP) from interacting [23] .

It is known that GSK3β can phosphorylate β-catenin in the pathway. Therefore, the researchers made the function of GSK3 loss by inhibiting its function via incubating HEK293 cells in 40mmol/L LiCl in order to activate the Wnt pathway. In cells treated with E3786, Coimmunoprecipitation of the activating factors of Wnt pathway from the whole-cell lysate was significantly downgraded, meaning that β-catenin and CBP were less likely to interact. Besides, the research group has proved that their medicine could play a role in combination treatment with anti-PD-1 antibody.

2.2. The Discovery of Targets Sparks Insights in Therapy of CRC

2.2.1. YTHDF1

By analyzing how m6A machinery is expressed in an activated Wnt pathway, indicated that Wnt3A remarkably induced YTHDF1 protein, whose distribution had remarkably increased.

Further studies uncovered how APC mutation regulated YTHDF1. When an overexpression of APC was created, the number of YTHDF1 dropped without any change in its mRNA level. The protein could also remain stable when exerting cycloheximide (CHX) on it, a chemical resulted in translation inhibition. Thus, it could be concluded that the alteration in YTHDF1 expression was not due to protein degradation [24].

2.2.2. Lats1/2

Lgr5-CreER mice had no defects in organ growth and differentiation, while in Lats1/2 intestine thar processes almost stopped, with no differentiation markers observed, indicating that the procedures were inhibited by Lats1/2.

Nevertheless, the influence of Lat1/2 could be essential. Via RNA-seq analysis, the YAP/TEAD genes already known such as CTGF and Amot could be upregulated by Lats1/2. To further putLat1/2 dysfunctional intestines under RNAscope analysis, both Lgr5 transcripts and Axin2 were nearly completely lost, which showed that without Lats 1/2 kinases, Wnt pathway in the crypt will no longer remain its normal activation.

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The researchers used to try to identify the impact of Lats 1/2 on Wnt ligands, but experiments showed negative results; when Lats1/2 KO intestine received tamoxifen injection, the cells experiencing Cre recombination tended to loss CD44, a marker of stem cell molecules in Wnt pathway. In conclusion, Wnt pathway can be inhibited when Lats1/2 is deleted.

It seems contradict that though there are Wnt targets such as Axin2 and Lgr5 inhibited in Lats1/2 KO, the proliferation of cells in crypts showed an overall rising tendency. To explain why crypt over-proliferation is triggered by Lats1/2 deletion, scientists made a hypothesis. Based on the knowledge that Myc, a basic downstream effector which mediates harmful growth in intestine, is simultaneously recognized as the YAP/TEAD target, they projected that the signal spur Myc expression to convert from Wnt/TCF to YAP/TEAD while expressing is Lat1/2 intestines [25].

2.2.3. Mll1

Mll1, the histone methyltransferase, is positively related to colon cancer. According to immunohistochemistry, an abnormally high level of Mll1 is detected expression in every tumor stages.

Lgr5+ stem cells are proved as the origin of colon cancer [26]. Under Wnthigh, the LGR5+ stem cells incline to produce more absorptive progenitors and secretory progenitors, which migrate to the villus compartment. At that position with adequate differentiation-inducing factors, they start to differentiate [27].

When utilizing immunofluorescence to uncover how Mll1 along the crypt-villus axis of the mouse is expressed, a gradient was found from Lgr5+ stem cells to Paneth cells, then enterocytes. The especially high expression in Lgr5+ stem cells could suggest that it is inevitable for stemness, while lost upon differentiation.

In mice models induced tamoxifen, the Mll1+/- group developed adenomas, meanwhile their islets showed high Mll1 expression. In comparison, proliferation was only existed in the crypt region, without any alternative in villus structure in the group of Mll1-/- mice. Thus, it could be conclude that Mll1-/- can prohibit stem cells growth in population, and Mll1 is a must-required in β-cateninGOF-induced intestinal tumorigenesis.

To explain its role deeper, FACs was applied to separate stem cells from distinct groups. Subsequently, RNA sequencing are used in the changes in transcriptome. The results demonstrated that goblet cell-specific genes expression is upregulated, meanwhile a part of the genes downregulated were Paneth cell markers. Overall, instead of Paneth cells, the β-catGOF was being restricted to differtiate to only to Paneth cells, thus the stemness was remained [28].

2.3. The Mechanism of Regulation in Wnt Pathways

There are already examples against that differentiation in villi cells is irreversible by finding out its spatial heterogeneity [29].

Under the zonation analysis of the small intestinal stroma, Lgr5 shows a high level of expression among all receptors in the tip stroma of the villis. To futher ensure this unexpected discovery, researchers used smFISH and observed a large quantity of Lgr5 transcripts together with villus tip ligands in PDGFRa+ telocytes. Telocytes surrounding the crypts had already been identified as secretors of Wnt morphogens, similarly, Rspo3 that had the same role in keeping the stemness of Lgr5+ epithelial stem cells located in crypts.

A certain type of telocyte, the villus tip telocytes (VTTs) expresses a relatively high level of Lgr5, which is approximately equal to that level in the epithelial crypt base columnar stem cells. When carrying out experiments of Lgr5-knock-in mice, all models had Lgr5 and expressed induced GFP. In summary, Lgr5 could be a marker of telocyte at villus tips and epithelial crypt stem cells.

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After Lgr5+ cells ablated, the villus tip epithelium will experience a reduction in enterocyte gene expression. The research group suggested that the previous condition was because Lgr5+ VTTs fail to release signals. 48 hours after DT administration (can lead to VTTs ablation), they sequenced the epithelial layer and figure out that enterocyte genes at villus tips. On the other hand, other transcription factors and genes with remarkable basal expression showed no change in visualization, representing the ablity of VTTs to instruct how epithelial genes express at the villus tip [30].

2.4. Therapy Based on Wnt/β-catenin Pathway

A mutation in Wnt signaling components will lead to over-accumulation ofβ-catenin, which is a main cause of intestinal cancer. As a result, potential treatments lie in inhibition of that pathway. Among all possible targets,β-catenin is the most direct and frequent-discussed one.

A research group had upgraded the PROTAC β-catenin degraders. Drawing from the finding that the α-helix structure of Axin's β-catenin interaction region can fit within the shallow cavity of β-catenin, they engineered stapled peptides aimed at β-catenin to regulate the Wnt pathway. Despite the close sequence resemblance between two peptides, SAHPA1 stimulates Wnt signaling, whereas xStAx suppresses it. Utilizing their specific binding affinity for β-catenin, these stapled peptides served as targets in the development of dual-action PROTAC β-catenin degraders.

Experiments on BALB/C nude mice proved the effectivity of xStAx-VHLL. Tumors found in the mice which were injected xStAx-VHLL were clearly smaller. Moreover, using immunoblotting analysis to study the extracts of the tumor, a significant difference between itsβ-catenin level and the β-catenin protein level of the control group representing thatβ-catenin degradation was successfully triggered.

APC mutation is a classical cause of tumors. 11 weeks old APCmin/+ model mice experiencing the injection of xStAx-VHLL showed a decline in tumor number. Additionally, situ β-galactosidase staining indicated that Axin2 expression could be blocked by the chemical.

It is true that an important aim of intestinal targeted therapy is to induceβ-catenin degradation, but that is not the only way in such therapy. Besides xStAx-VHLL, there are numerous inhibitors usable in inhibiting Wnt/β-catenin signaling. PRI-724 can impede the β-catenin-CBP interaction, and PNU-74654 can interfere the interaction between β-catenin and TCF [31].

3. Conclusion

The failure in β-catenin degradation and the resulting accumulation of β-catenin are parts of main factors leading to oncogenesis. To further explain, the translocation of β-catenin to the nucleus and its subsequent involvement in the transcription of target genes are pivotal to the activation of the Wnt/β-catenin pathway. This study has underscored the importance of understanding the cytoplasmic-nuclear shuttling of β-catenin as a key feature of pathway activation. Additionally, the role of stem cells in tissue repair, with their capacity for unlimited replications, is crucial for the rapid and effective healing of damaged tissues, while a loss of this ability can exacerbate gastrointestinal diseases. After studying the proteins and factors that hold the potential for targeted therapy applications, as well as key inhibitors of the Wnt/β-catenin pathway and the consequences of their absence on the onset of cancer, specific instances of targeted medicines are already in experiment stage. The insights gained from this research into the mechanisms of Wnt-pathway-related tumorigenesis and the behavior of stem cells aim to inform targeted therapeutic strategies and other treatment modalities.

However, this article has some limitations. When giving an overall picture of Wnt-pathway-related cancers, it only introduces scattered cells, proteins and other molecules as examples, but neither separates them based on their different nature nor gives an all-included picture. As a result,

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researchers may find it is hard to gain new insights from the single examples. Further researches are expected to focus on single sections of the known pathway, in order to reach a higher efficiency in inhibiting the abnormal functions of the Wnt/β-catenin pathway.

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