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Wnt/b-Catenin: The Main Culprit behind Cancer Chemoresistance

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There are nineteen secreted glycoproteins in Wnts family which regulate several functions and biological output in humans. It is increasingly confirmed that Wnt signalling is highly conserved signal transduction pathway which acts as intracellular switches and controlling cell proliferation, cell migration, cell polarity and organogenesis. Wnt signalling also affects the maintenance of cancer stem cells and metastasis. Through this we impart an overview on Wnt signalling impact in human cancer types and during chemoresistance.

The Wnt signalling by secreted glycolipoproteins is highly conserved signalling mechanism in metazoan animals that play a crucial role in several aspects of cell proliferation, cell migration, cell polarity and organogenesis during embryonic development [1]. To date major Wnt pathway studied is canonical Wnt signalling because of its potent role in cancer development. Wnt regulates transcriptional co-activator β-catenin in the cytosol, which controls the gene expression in the nucleus. β-catenin is degraded in the absence of Wnt ligands by Axin complex. In Axin complex, axin works as a scaffold protein having other proteins, the tumour suppressor adenomatous polyposis coli gene product (APC), casein kinase1 (CK1), and glycogen synthase kinase (GSK3). Both CK1 and GSK3 phosphorylate the β- catenin at amino terminal, which helps in recognition by β-Trcp leads to ubiquitination and proteasomal degradation of β-catenin [2]. β-catenin degradation prevents the entry of β- catenin into the nucleus thereby checked the binding of T cell factor/lymphoid enhancer factor (TCF/ LEF) family of proteins with target genes.

For activation of this pathway Wnt ligand is bind to Frizzled (Fz) receptor and co-receptor complex low-density lipoprotein receptor related protein 5/6 (LRP5/6). One most important fact is that stimulation of Wnt stabilizes Axin through de-phosphorylation, which leads to alleviating the cytoplasmic level of Axin. Wnt-Fz-LRP6 complex promotes scaffolding protein Dishevelled (Dsh) binding causes dual phosphorylation of LRP6 by CK1 and GSK3. This complex stabilizes β-catenin by preventing its Axin mediated phosphorylation. Stabilization of β- catenin causes their accumulation and transport towards nucleus where it mediates the Wnt target gene expression of TCF/LEF family.

Wnt signalling has a prominent role at the time of embryonic development and stemness as well as closely associated with most of the cancer type. Aberrant Wnt signalling has been observed in many cancer types. Despite the main role of Wnt signalling in the development of cancer still, its precise role in cancer drug resistance is not well established. For long term maintenance normal hematopoietic stem cells (HSC) depend on Wnt signalling in a fully controlled way whereas Wnt activity was overexpressed in leukaemia [3]. The contribution of canonical Wnt signalling is seen in melanoma development but the role in disease progression is yet to be discovered [4]. Clinical studies showed that decreased level of nuclear β-catenin levels significantly increases the overall survival of melanoma patients. Other study on breast cancer patients showed active Wnt signalling in more than 50% of patients and decreases their survival rate. Nuclear β-catenin was over expressed in many breast cancer subtypes [5] as well as canonical Wnt signalling has been involved in triple negative breast cancer development and progression [6].

Most of the cancers types are characterized that intrinsic resistance development for cytotoxic agents after few months of treatment. Apoptosis, angiogenesis, highly resistance cancer stem cells (CSCs) and deregulated cell cycle are the main factors responsible for cancer chemoresistance. It is very interesting to note that Wnt/β-catenin signalling have their prominent role in above these four aspects and cause cancer. However, researchers have proven that deregulated Wnt/β-catenin signalling is a culprit in cancer chemoresistance moreover there is no direct evidence. The β-catenin master component in Wnt signalling can modulate

the expression of a member of apoptosis protein inhibitor gene *Survivin*. It inhibits the apoptosis and increases the resistance in pancreatic cancer towards gemcitabine by upregulating the Survivin [7]. Another study shows that one of the target gene of Wnt/β-catenin, *MMP-7* promotes apoptosis on cancer cells by down regulating Fas receptor leads to chemoresistance [8]. Recent reports suggested that Wnt signalling promotes tumour angiogenesis through induction of endothelial cell proliferation and their survival [9]. According to one of the study, Wnt1 overexpression is related to *VEGF-A* and *MMP-7* expression involve in angiogenesis [10]. Wnt/β-catenin signalling plays important role normal stem cell regeneration while their aberrant activation may help in the maintenance of cancer stem cell. Cyclin D1 and c- Myc, the two constituents are upregulated by Wnt/β-catenin and involved in cell cycle progression at G1/S transition point [11]. In pancreatic cancer over expression of *cyclin D* is one of the main cause of poor prognosis and knockdown of *cyclin D* downregulate the expression of many chemoresistance genes and resensitize the drug sensitivity in pancreatic cancer [12].

In conclusion, targeting Wnt signalling can improve our better understanding related to molecular mechanisms of chemoresistance and help in drug resensitization against many human cancer types.

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