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# REGULATION OF NON-CANONICAL WNT SIGNALING PATHWAY IN STEM CELLS DEVELOPMENT AND CARCINOGENESIS

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**ABSTRACT:** Since 1982, Wnt1 (Wingless int-1) was first identified in mammary carcinoma. Further, Wnt signaling pathway was discovered. Wnt signals were involved in stem cells development, regeneration, cell cycle and repair mechanism. Finally abnormality Wnt signals were stimulated variety of cancers. Especially, non-canonical signaling pathways such as Wnt/PCP and Wnt/Ca2+ pathway were involved in development process. These pathways regulated stem cells and organ development such as cell polarity, adhesion, cell shape and cell movement. Despite, aberrant expression of non-canonical pathway induced tumorigenesis in development. In clinical studies, drugs were developed against cancer cells not in cancer stem cells. Drugs will synthesis against cancer stem cells based on the activation of abnormality of Wnt signaling.

**INTRODUCTION:** Organ development, stem cells have ability to self-renewal and proliferate normal to mature cell types. Stem cells have been developed adult organ from pluripotent stem cells. Many signals were involved in the development and carcinogenesis [1]. Wnt (Wingless int-1) gene was first identified as int-1 gene by activation of mouse mammary tumor virus (MMTV). Finally, full circulations of Wnt signaling pathways were developed in stem cells and cancer development [2, 3]. Wnt signals play crucial role in stem cells development and tumorigenesis. Wnt signals expressed both of stem cells and cancer stem cells (CSCs). Wnt signals classified as canonical and non-canonical pathway.

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Further non-canonical pathway consists of Wnt/Planer cell polarity (PCP) pathway and Wnt/$Ca^{2+}$ signaling pathway. PCP and $Ca^{2+}$ signals were regulated variety of stem cells and organ developments. Despite, abnormalities of non-canonical Wnt signals regulated many types of cancer development [4, 5].

## Non-canonical Wnt/PCP signaling pathway

The Wnt/PCP pathway was involved in stem cells development such as cell polarity, adhesion, and shape and cell movement. Regulation of PCP pathway not required β-catenin and it was first identified in *Drosophila*. This PCP pathway was inhibited nuclear activity of β-catenin and stimulation of PCP pathway not required low density lipoprotein receptor (LRP) as a co-receptor.

The complex of Wnt proteins and frizzed heterodimeric receptor (FZD) were triggered the regulation of Wnt/PCP signaling pathway. This complex Wnt-FZD recruits Dishevelled (Dsh) to enhanced signaling pathway. Activated Dsh bind

with Dishevelled-associated activator of morphogenesis 1 (DAMM1). Daam1 activated G-protein Rho through guanine exchange factor (GTP) then Rho stimulated Rho-associated kinase (ROCK). Dsh was also regulated Dsh-Rac1 and mediated profilin and actin complex.

This profilin and actin complex enhanced restructuring of the cytoskeleton and gastrulation. Rac1 also involved in the activation of JNK which lead to actin polymerization and also JNK stimulated gene transcription such as c-jun **(Figure1).** PCP pathway has crucial role in stem cells and development such as angiogenesis, bone morphogenesis, gastrulation [6, 7].

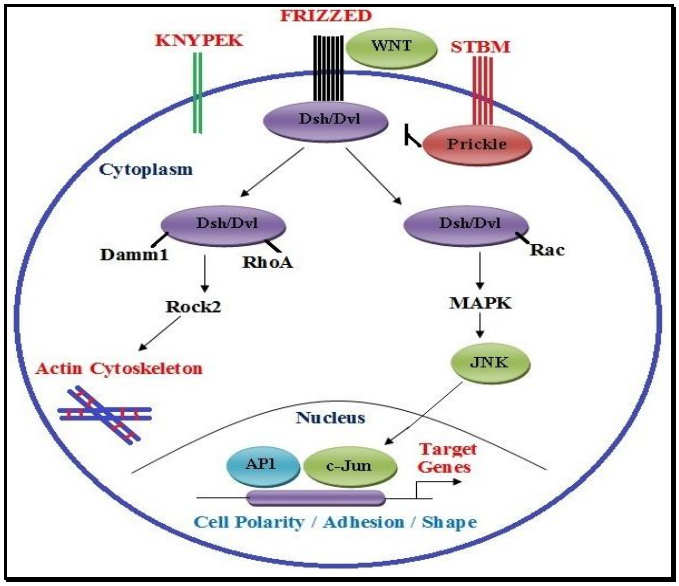


**FIGURE 1: NON-CANONICAL WNT/PLANER CELL POLARITY (PCP) SIGNALING PATHWAY IN DEVELOPMENT**

## Non-canonical Wnt/$Ca^{2+}$ signaling pathway

Wnt/$Ca^{2+}$ signaling pathway mostly induced by Wnt5a and Wnt5b proteins which mediated the synthesis of secondary messenger such as calcium. Finally, this secondary messenger signaling pathway described as Wnt/$Ca^{2+}$ signaling pathway. Wnt/$Ca^{2+}$ signal also not required β-catenin and calcium released from endoplasmic reticulum (ER) to control intracellular $Ca^{2+}$ levels. Wnt-FZD complex directly activated trimeric G-protein. Dsh and G-protein complex stimulated the activation of PIP2 and activated PIP2 was cleaved into DAG and inositol 1, 4, 5-trisphosphate (IP3). And another way inactivation of PKG or elevation of IP3 regulated calcium from ER [6, 7].

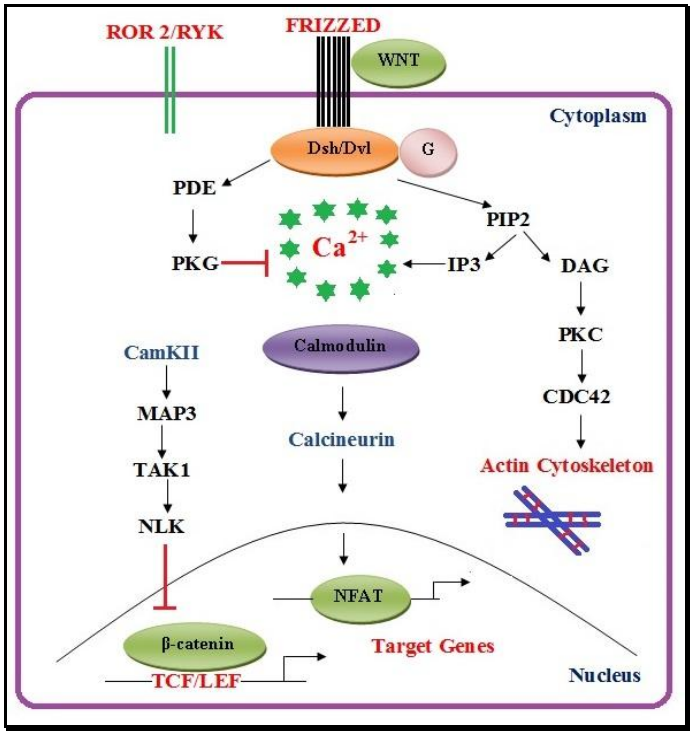


**FIGURE 2: NON-CANONICAL WNT/ $CA^{2+}$ SIGNALING PATHWAY IN DEVELOPMENT**

DAG was activated cdc42 which commonly regulated ventral patterning. High level of calcium ions stimulated calcineurin and CaMKII activation through calmodulin. Calcineurin also activated nuclear factor of activated T cells (NFAT), which regulated ventral patterning, cell adhesion, migration and tissues separation. CaMKII was activated MAPK signaling and it was also activated TGF-b-activated kinase (TAK1). NLK expression was induced by TAK1 and NLK act as an antagonist of Wnt/ β-catenin signaling pathway **(Figure 2)**. Despite, Inhibition of calcium release occurred from ER by activated PDE [6, 8].

## Non-canonical Wnt signaling in Stem cells and development

Wnt signals have crucial impact in organ development from non-vertebrates to vertebrates. Especially, non-canonical Wnt signaling have specialized function in stem cells and development such as cell fate, cell proliferation and differentiation, cell survival and apoptosis, cell behavior, cell adhesion, migration and tissues separation and ventral patterning [9].

Non-canonical signaling pathways also regulated self-renewal, differentiation and proliferation **(Table 1).** Both of Wnt/PCP pathway and

Wnt/$Ca^{2+}$ signaling pathway have specialized role in development **(Table 2).** Commonly, these pathways regulated variety of stem cells to development such as central nervous system development, Limb, facial, digestive tract, genitourinary, cardiogenesis and spermatogenesis and skeletogenesis [7].

**TABLE 1: NON-CANONICAL WNT/PCP SIGNALING PATHWAY IN STEM CELLS AND DEVELOPMENT**

| Wnt signaling | | Functions in development | References |
|---|---|---|---|
| Wnt/PCP | Over all | Central nervous system development, Limb, facial, digestive tract, genitourinary, tail and body wall, human embryonic stem cells self-renewal and proliferation, cell fate and embryonic patterning, hematolymphopoiesis, skeletogenesis, ovarian follicle development, satellite stem cells expansion, hair follicle stem cells regulation, early patterning of oral-pharyngeal ectoderm and mesendoderm, heart and pectoral fin bud morphogenesis. | 7, 11, 13, 14, 18, 19, 20 |
| | Knypek | Cell polarity control during gastrulation and cell movement. | 35 |
| | Prickle | Asymmetric division and regulation of tissue polarity, stem cells self renewal, cell movements and neuronal migration. | 36, 37 |
| | RhoA | Cell shape and migration, morphological and transcriptional changes during development, differentiation of mesenchymal stem cells and osteogenesis, cell proliferation, apoptosis, cell polarity, cell adhesion and plasticity of cell migration. | 38, 39, 50 |
| | JNK | Mesenchymal stem cells differentiation and cell fate determination, homeostasis. | 40, 41 |

**TABLE 2: NON-CANONICAL WNT/$CA^{2+}$ SIGNALING PATHWAY IN STEM CELLS AND DEVELOPMENT**

| Wnt signaling | | Functions in development | References |
|---|---|---|---|
| Wnt/$Ca^{2+}$ | Over all | Limb, facial and CNS development, digestive tract, genitourinary, cardiogenesis and spermatogenesis, osteogenic differentiation and bone formation, early patterning of oral-pharyngeal ectoderm and mesendoderm, heart and pectoral fin bud morphogenesis, odontoblast differentiation and tooth morphogenesis, | 7, 12, 15, 16, 19, 20, 21 |
| | Ror2 | osteoblastogenesis , mesenchymal stem cells differentiation, formation of chondrocytes, growth plate development | 42 |
| | PIP2 | Spermatid cell polarity, exocyst localization and cell proliferation. | 43 |
| | IP3 | Myoblast differentiation, embryonic stem cells differentiation, cardiomyogenesis, myelopoiesis | 44, 45 |
| | CDC40 | Hematopoietic stem cells regulation aging, rejuvenation, progenitor stem cells differentiation. | 46, 47 |
| | Calmodulin | Promote ventral cell fate, mesenchymal progenitor cells differentiation. | 48, 49 |

## Non-canonical Wnt signaling in carcinogenesis

Non-canonical Wnt signaling pathways also involved in cancer development. Abnormality of non-canonical Wnt signaling induced tumorigenesis in development process. Wnt1 was first identified ongogene in mammary carcinomas [2]. Many deregulation of Wnt signals stimulated unwanted vast cell growth and movement. Cancer was one of critical problem in human world. Aberrant expression of non-canonical Wnt signals were regulated various cancers such as mammary carcinogenesis, prostate cancer, colon carcinoma, pancreatic cancer, cervical and renal cell carcinoma, hepatocellular carcinoma, gastric and oral squamous cell carcinoma. These are few types of cancer regulated by deregulation of non-canonical Wnt signaling.

**TABLE 3: NON-CANONICAL WNT/PCP SIGNALING PATHWAY IN CARCINOGENESIS**

| Wnt signaling | | Types of Cancer | References |
|---|---|---|---|
| Wnt/PCP | Over all | Mammary carcinogenesis, prostate cancer, oral squamous cell carcinoma, colon carcinoma, hepatocellular carcinoma, gastric, cervical and renal cell carcinoma, oral squamous cell carcinoma, teratocarcinoma, pancreatic cancer. | 22-27 |
| | RhoA | Breast cancer, prostate cancer and ovarian cancer. | 51, 52 |
| | Rock2 | Non-small cell lung cancer, prostate cancer, bladder and fibrosarcoma, melanoma cancer and hepatocellular cancer, | 53 |
| | JNK | Hepatocellular carcinoma, breast cancer, prostate and skin cancer | 54-56 |
| | Ras | Breast cancer, colon cancer, prostate cancer, pancreatic cancer, brain tumors, ovarian and gastric cancer, head and neck squamous cell cancer, leukemias and non-small cell lung cancer. | 57 |

In Wnt/PCP signaling, Wnt5a and Wnt5b to regulated metastasis of melanoma, gastric and breast cancer by overexpression of Rac and JNK and also play critical role in metastasis of sarcoma. Clinical studies, Dsh1 and Dsh3 highly expressed in cancer metastasis, mainly in non-small cell lung cancer. Damm1, Rac, JNK, Rock and profilin were involved in the upregulation of cancer [9] **(Table 3).**

**TABLE 4: NON-CANONICAL WNT/$CA^{2+}$ SIGNALING PATHWAY IN CARCINOGENESIS**

| Wnt signaling | | Types of Cancer | References |
|---|---|---|---|
| Wnt/$Ca^{2+}$ | Over all | Breast cancer, prostate cancer, gastric carcinoma, endometrial carcinoma, Leukemia, melanoma, lung carcinogenesis, pancreatic adenocarcinoma, medulloblastoma, oral squamous cell carcinoma, colorectal adenocarcinoma, esophageal squamous cell carcinoma and Basal cell carcinoma. | 23,28-33 |
| | Ror2 | B-cell chronic lymphocytic leukemia, gastric carcinoma, non-small cell carcinoma cell lines, osteosarcoma, Renal Cell Carcinoma, neuroblastoma, acute lymphoblastic leukemia | 58 |
| | PIP2 | Breast cancer, cervical cancer, melanoma, colon cancer | 59 |
| | IP3 | Colorectal cancer, gastric cancer, non-small cell lung cancer, breast cancer | 60 |
| | PKC | Skin cancer, colon and gastric cancer, prostate cancer, ovarian cancer, breast and endometrial cancer, brain tumor, lung cancer, Multiple Myeloma, Leukemias, Lymphomas | 61 |
| | Calmodulin | Breast cancer and prostate cancer | 62, 63 |

In Wnt/$Ca^{2+}$ signal, Wnt5a and Wnt5b act as a proto-ongogene in breast cancer, pancreatic cancer, prostate cancer, melanoma and tumor suppressor gene in neuroblastoma, breast cancer, acute myeloid lymphoma, colon carcinoma, esophageal squamous cell carcinoma and thyroid carcinoma [8] **(Table 4).**

## Future research

Wnt signals plays important role in organogenesis and cancer development. Abnormalities of non-canonical Wnt signal majorly regulated various cancer. Many drugs were developed against cancer based on abnormality of Wnt signals. Cancer therapy was also inhibited or killed cancer cells but not in cancer stem cells. These Cancer stem cells were regulated vast cancer cell growth and proliferation. So new drugs are need to synthesis, especially to kill cancer stem cells. Herbal drugs were highly expressed and killed cancer cells without side effect. New drugs will develop against cancer stem cells based on deregulation of non-canonical Wnt signaling pathways.

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