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REGULATION OF WNT GENES IN STEM CELLS DEVELOPMENT AND ORGANOGENESIS

Rajendran Prakash

Department of Biotechnology, VMKV Engineering College, Vinayaka Missions University, Salem - 636308, Tamil Nadu, India.

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Correspondence to Author:
R. Prakash

Research Student,
Department of Biotechnology,
VMKV Engineering College,
Vinayaka Missions University,
Salem - 636308, Tamil Nadu, India.

E-mail: yokaprakash0007@gmail.com

ABSTRACT: Stem cell biology, many signals regulated stem cells and organ development. Wnt factors play a crucial role in stem cells development and induced signaling pathway in stem cells. Wnt signals classified as a canonical and non-canonical pathway. Wnt factors regulated both pathways for stem cells self-renewal, proliferation, and differentiation. Wnt canonical pathway induced by Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt6, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt10a and Wnt10b. Wnt non-canonical pathway regulated by Wnt factors such as Wnt1, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt9a, Wnt9b, Wnt10a, Wnt10b, Wnt11, and Wnt16. These all factors have a specialized role in stem cells and development. These factors also regulated wound healing mechanism and variety of organ regeneration. Finally, abnormality or aberrant expression of Wnt signals regulated a variety of cancers.

INTRODUCTION: More than 31 years ago, int-1 was identified as a proto-ongogene activated by mouse mammary tumor virus, and later it was renamed as Wnt1 gene [1]. Further development, 19 Wnt genes were discovered in our animal kingdom from hydra to human. These Wnt proteins are induced by three different pathways such as Wnt/β-catenin, Planer cell polarity (PCP) and Wnt/Ca^{2+} pathway. Wnt signaling pathways were mainly involved in stem cells development and carcinogenesis. In stem cells development, Wnt proteins have a crucial impact in the embryogenesis, adult tissue formation and regeneration.

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During development, Wnt molecules involved in many specifications, such as germ layer formation, body axis formation and patterning, cell fate specification, limb and facial development, adult organ development and finally regeneration [2].

Wnt Genes and Pathways: Wnt genes were regulated that specific Wnt signaling pathways and 19 Wnt genes were involved in the canonical and non-canonical pathway. In canonical pathway, Wnt/β-catenin signal was induced by Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt6, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt10a and Wnt10b [3].

Non-canonical pathway, Wnt/Planar cell polarity pathway was regulated by Wnt3a, Wnt4, Wnt5b, Wnt7a, Wnt7b, Wnt9a, Wnt9b, and Wnt11. Wnt/Ca^{2+} signaling pathways was also stimulated by Wnt1, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt9a, Wnt9b, Wnt10a, Wnt10b and Wnt16. Here, Wnt4, Wnt7a genes regulated both of canonical and non-canonical pathways. Finally, Wnt5b, Wnt9a,

Wnt9b, Wnt11, and Wnt16 genes were stimulated only Wnt non-canonical signaling pathways [4, 5].

Wnt Genes in Stem Cells and Development: In stem cells signaling, Wnt signals play a major crucial role in stem cells development and regeneration. Wnt signals expression was discovered from zygote to mature adult cells and also Wnt signals involved in the wound healing process and repair mechanism **Table 1**.

Embryonic Development: Wnt genes were involved embryonic development in a variety of organism, both of vertebrates and invertebrates **Fig. 1**. Wnt gene was first identified in Drosophila, and it was involved in segment polarity. Many Wnt genes were involved in the development process such as germ layer formation, cell fate determination, ectoderm, and mesoderm differentiation, limb and facial development, fetus formation, nervous system and spinal cord development [2, 6].

TABLE 1: WNT GENES IN STEM CELLS AND DEVELOPMENT

Wnt genes	Pathway	Function in organ developments	References
Wnt1	Wnt/β-catenin and Wnt/Ca^{2+}	Central nervous system (CNS) development, cell fate, and embryonic patterning, endothelial progenitor cells, neural crest progenitors, liver regeneration, epidermal stem cells differentiation, human embryonic stem cells self-renewal and proliferation.	12, 15, 19, 21-25
Wnt2	Wnt/β-catenin	Limb and facial development, otic vesicle, heart, lung and body wall development, foregut endoderm development, hematopoietic, endothelial and cardiac lineages.	12, 13, 26
Wnt2B	Wnt/β-catenin	Branchial arch, CNS development, otic vesicle, eye, lung and genitourinary, liver formation, retinal cell differentiation, lung progenitor in foregut and hepatopancreatic specification.	12, 27-30
Wnt3	Wnt/β-catenin	Ectoderm, facial and CNS development, heart and lung, head regeneration, hematopoietic differentiation.	12, 31, 32
Wnt3A	Wnt/β-catenin and planar cell polarity (PCP)	CNS development, digestive tract and tail formation, osteoblasts and fate differentiation, mesoderm formation and cardiomyogenesis, mesenchymal stem cells and hematopoietic, epidermal self-renewal and progenitors differentiation.	12, 33-36
Wnt4	Wnt/β-catenin, PCP and Wnt/Ca^{2+}	Limb, facial and CNS development, otic vesicle, digestive tract, genitourinary and ectoderm, muscle regeneration and osteogenesis, hematolymphopoiesis, skeletogenesis, ovarian follicle development.	12, 16, 20, 37, 38
Wnt5A	Wnt/β-catenin and Wnt/Ca^{2+}	Limb, facial and CNS development, lung, digestive tract, genitourinary, real line and head mesenchymal, osteogenic differentiation and bone formation, cardiogenesis and spermatogenesis, endothelial differentiation and regeneration.	12, 39-42
Wnt5B	PCP and Wnt/Ca^{2+}	Limb, facial and CNS development, otic vesicle, eye, digestive tract, genitourinary and tail, mesenchymal cell aggregation and chondrocyte differentiation.	12, 43
Wnt6	Wnt/β-catenin and Wnt/Ca^{2+}	Ectoderm, facial and CNS development, otic vesicle, genitourinary and real line, epidermis and epithelial development, extraembryonic endoderm formation, osteoblastogenesis, stromal cell proliferation	12, 44-47
Wnt7A	Wnt/β-catenin, PCP and Wnt/Ca^{2+}	Ectoderm, facial and CNS development, otic vesicle, eye and digestive tract, satellite stem cells expansion	12, 17
Wnt7B	Wnt/β-catenin, PCP	Ectoderm, facial and CNS development, otic vesicle, eye, lung, and digestive tract, hair follicle stem cells regulation and homeostasis, replication of epithelium and mesenchyme	12, 14, 48
Wnt8A	Wnt/β-catenin	Otic vesicle and eye development, axis and	12, 49, 50

		mesoderm development,	
Wnt8B	Wnt/β-catenin	CNS development, retinal progenitor formation	12, 51
Wnt9A	PCP and Wnt/Ca^{2+}	CNS and otic vesicle development, palate morphogenesis, early patterning of oral-pharyngeal ectoderm and mesendoderm, hepatic epithelial morphogenesis	12, 52-54
Wnt9B	PCP and Wnt/Ca^{2+}	Facial, genitourinary and surface ectoderm, early patterning of oral-pharyngeal ectoderm and mesendoderm, heart, and pectoral fin bud morphogenesis	12, 53, 55
Wnt10A	Wnt/β-catenin and Wnt/Ca^{2+}	Ectoderm, branchial arch and heart development, osteoblastogenesis, odontoblast differentiation, and tooth morphogenesis, apical ectodermal ridge and limb development, tooth, face, and skin development	12, 56-59
Wnt10B	Wnt/β-catenin, Wnt/Ca^{2+}	Ectoderm, facial and oral line, stimulates osteoblastogenesis, development of limbs, tooth, face and skin	12, 56, 59
Wnt11	PCP	Limb, facial, CNS and PNS development, otic vesicle, heart, oral line, tail and body wall	12
Wnt16	Wnt/Ca^{2+}	Head mesenchymal and CNS development, otic vesicle, heart, digestive tract and tail	12

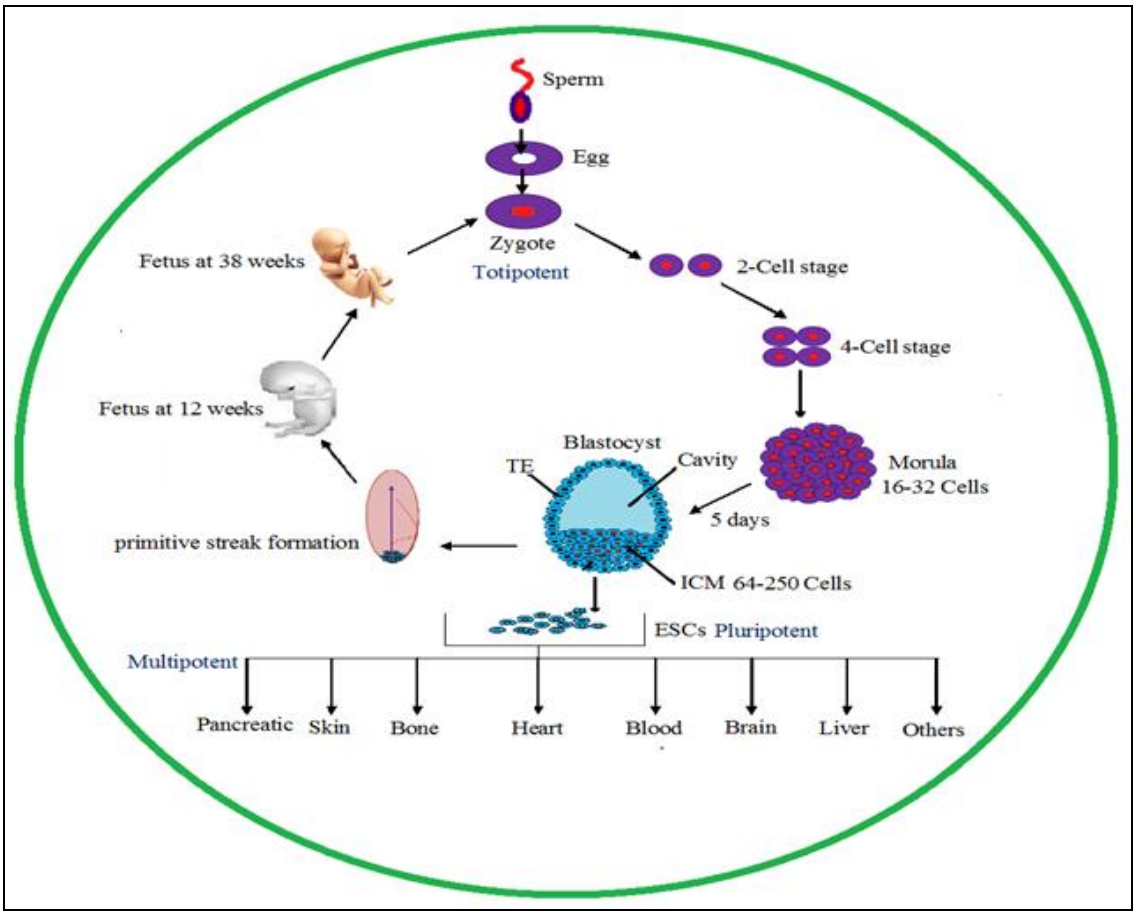

FIG. 1: ORGAN DEVELOPMENT CYCLE FROM ZYGOTE TO ADULT HUMAN

Wnt Genes in Axis Patterning and Cell Fate Determination: In embryonic development, body axis formation is critical steps and different axis including anteroposterior axis, dorsoventral axis, and right-left axis. Wnt genes were involved in the formation of the anteroposterior axis and dorsoventral axis [7]. Cell fate determination or cell differentiation, undifferentiated cells were specialized to mature null potent cells. Wnt1, Wnt3a, Wnt6, Wnt8a, Wnt9a, and Wnt9b genes were regulated endoderm and mesoderm differentiation [8]. Wnt1 gene was antagonized neural differentiation and

also an important regulator in self-renewal of neural stem cells. Other Wnt genes were involved in sex determination, neural crest cell differentiation, gut tissue specification, germ cell determination, hair follicle development, lung, nephron and ovary development **Fig. 2** [9].

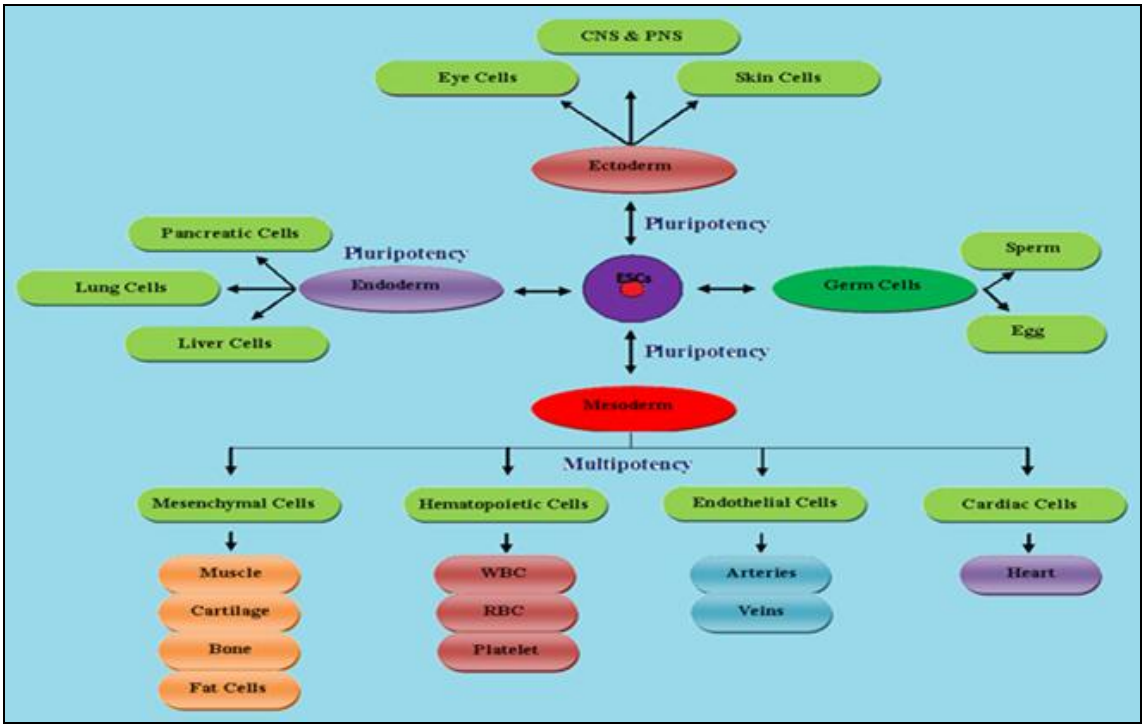

FIG. 2: SCHEMATIC REPRESENTATION OF STEM CELLS DIFFERENTIATION BASED ON THE INVOLVEMENT OF WNT SIGNALING PATHWAY

Cell Proliferation and Pluripotency: Undifferentiated cells were proliferated and migrated by Wnt signaling pathway. Wnt signals were induced differentiated and proliferated pluripotent stem cells to mesoderm and endoderm then proliferated to adult mature tissues type. Wnt3a was stimulated the proliferation of hematopoietic stem cells. Expression of several Wnt genes and Wnt pathway molecules in the blastocyst indicated the self-renewal and maintenance of pluripotency in the early embryo. Wnt3a was induced up-regulation of Wnt canonical pathway, and it was maintained self-renewal of human and mouse embryonic stem cells [10, 11].

Wnt Molecules in Organ Development and Regeneration: In organ development, hemato-poiesis or blood formation was done by stimulation of Wnt2, Wnt3, Wnt3a, and Wnt4. Development of cardiogenesis was stimulated by Wnt2, Wnt3, Wnt3a, Wnt5a, Wnt10a, Wnt11 and Wnt16 [12-14]. Wnt2, Wnt3, and Wnt5a were involved in the development of lung. Wnt2b, Wnt5b, Wnt7a, Wnt7b, and Wnt8 were induced in the development of eye formation. Wnt3a, Wnt4, Wnt5a, Wnt5b, and Wnt7b were stimulated digestive tract formation **Fig. 3**. Formation of the genitourinary system was induced by Wnt2b, Wnt4, Wnt5a, Wnt5b and Wnt6 [12].

Neuronal Development and Bone Formation: Wnt1, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt8b, Wnt9a, and Wnt16 proteins were involved in the formation of the central nervous system (CNS) by differentiation of mesoderm. Wnt11 was also stimulated both of CNS and peripheral nervous system (PNS) development. Wnt3a, Wnt4, Wnt5a, Wnt6, Wnt10a, and Wnt10b were induced in the development of bone formation [12].

Wnt1 was involved the most important function of human embryonic stem cells self-renewal and proliferation [15]. Wnt2, Wnt3, Wnt4, Wnt5a, Wnt5b, and Wnt11 were induced limb and facial development from germ layer differentiation [12]. Wnt 3a was also involved in epidermal and progenitor self-renewal and proliferation. Wnt4 especially stimulated ovarian follicle development, and over-expression was induced ovarian carcinogenesis [16].

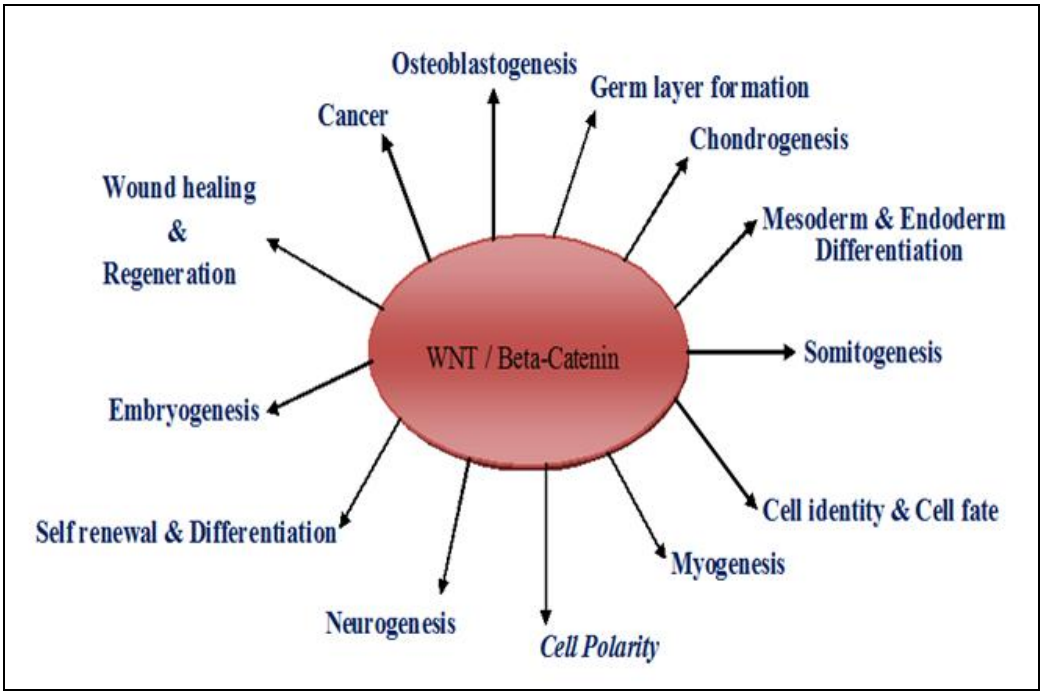

FIG. 3: FUNCTION OF WNT SIGNALING PATHWAY IN STEM CELLS DEVELOPMENT AND CARCINOGENESIS

Wnt5a also has specialized role information of spermatogenesis and Wnt7a involved expansion of satellite stem cells [17]. Wnt8b and Wnt9b were stimulated the development of retinal progenitor and bud morphogenesis [12, 18]. In regeneration, Wnt signaling factors were involved in wound healing and regeneration. Different Wnt factors were stimulated different organ regeneration, and Wnt has a specialized role in wound healing. Wnt1 involved in liver regeneration and Wnt3 in head regeneration [19]. Wnt4 and Wnt5a were induced muscle and endothelial regeneration and differentiation [12, 20].

CONCLUSION: Before 31 years ago, no one knows how Wnt signals were involved in stem cells and development. Nowadays, Wnt signaling pathways have a crucial role in stem cells development and carcinogenesis. Overexpression and mutations of Wnt factors were stimulated many varieties of cancer. In cancer treatment, few drugs only available against abnormality of Wnt signaling. In stem cell biology, Wnt signals play a crucial impact in stem cells maintenance, self-renewal proliferated and developed specialized organ. Wnt signals were also regulated wound healing and regeneration. Where and how Wnt signals are activated and which is the evolutionary origin. These all like unknown and well developed new specialized drug will identify when these are well known. Future work, identify and develop a new drug against cancer from an abnormality of Wnt signals.

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CONFLICT OF INTEREST: Nil

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