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CURRENT UNDERSTANDING IN THE ROLES OF WNT/RYK SIGNALING IN DEVELOPMENT AND HOMEOSTASIS

Pemahaman Terkini tentang Peran Pensinyalan Wnt/Ryk dalam Perkembangan dan Homeostasis

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ABSTRACT

Wnt/Ryk signaling represents a critical yet underexplored branch of the Wnt pathway, with significant roles in embryonic development and tissue homeostasis. While canonical Wnt/β-catenin signaling has been extensively studied, emerging research highlights Ryk as a key noncanonical Wnt co-receptor influencing processes such as convergent extension, organogenesis, stem cell regulation, and inflammation. Wnt/Ryk signaling mediates diverse cellular outcomes through interactions with ligands like Wnt5a and Wnt11 and exhibits complex crosstalk with canonical pathways. Its dysregulation has been linked to developmental disorders, neurodegenerative diseases, and cancer progression. This review summarizes current insights into Wnt/Ryk function during development and homeostasis, highlights its relevance in human health, and identifies open questions regarding its molecular mechanisms and therapeutic potential. A deeper understanding of this pathway may offer novel strategies for regenerative medicine and targeted treatments for Wnt-related diseases.

Keywords: *Embryonic development, Organ development, Ryk, Tissue homeostasis, Wnt signaling*

ABSTRAK

Pensinyalan Wnt/Ryk merupakan bagian dari jalur Wnt yang penting dalam perkembangan embrionik dan homeostasis jaringan namun belum dieksplorasi. Sementara pensinyalan Wnt/β-catenin kanonik telah dipelajari secara ekstensif, berbagai penelitian telah menyoroti Ryk sebagai ko-reseptor Wnt nonkanonik yang memengaruhi berbagai proses biologis seperti ekstensi konvergen, organogenesis, regulasi sel punca, dan inflamasi. Pensinyalan Wnt/Ryk memediasi hasil seluler yang beragam melalui interaksi dengan ligan seperti Wnt5a dan Wnt11 dan menunjukkan interaksi yang kompleks dengan jalur kanonik. Disregulasinya telah dikaitkan dengan gangguan perkembangan, penyakit neurodegeneratif, dan perkembangan kanker. Ulasan ini merangkum wawasan terkini tentang fungsi Wnt/Ryk dalam perkembangan dan homeostasis, menyoroti relevansinya dalam kesehatan manusia, dan mengidentifikasi pertanyaan mengenai mekanisme molekuler dan potensi terapeutiknya. Pemahaman yang lebih dalam tentang jalur ini dapat memberikan strategi baru untuk pengobatan regeneratif dan perawatan yang ditargetkan untuk penyakit terkait Wnt.

***Kata kunci**: Homeostasis jaringan, Perkembangan embrio, Perkembangan organ, Persinyalan Wnt, Ryk*

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INTRODUCTION

Wingless-related integration site (Wnt) signaling is an evolutionary conserved pathway that is crucial in some cellular functions, such as embryonic development, cell differentiation, cell migration, cell proliferation, and tissue homeostasis (Liu et al. 2022;Guo and Xing 2022). Wnt gene was discovered in 1982, derived from integrase-1 in mouse breast cancer and the wingless gene of *Drosophila*. Due to the similarities between these two genes and their functional proteins, researchers merged the terms as the Wnt gene (Nusse and Varmus 1982). Wnt proteins are secreted as cysteine-rich glycolipoproteins and comprise a large family of signalling molecules (Guo and Xing 2022).

Wnt signaling can be categorized as canonical and noncanonical pathways. The canonical pathway, known as β-catenin dependent pathway, involves the transport of β-catenin to the nucleus upon Wnt binding to the receptor Frizzled (Fzd) and the coreceptors LDL-receptor-related protein 5 or 6 (LRP5/6) (Liu et al. 2022). In the absence of Wnt, β-catenin is phosphorylated by the destruction complex, which composed of the AXIN protein, adenomatous polyposis coli (APC), glycogen synthase kinase 3 beta (GSK3β), and casein kinase 1 alpha (CK1α), leading to degradation. Without β-catenin, a repressive complex containing TCF/LEF and transducing-like enhancer protein (TLE/Groucho) recruits HDACs (histone deacetylases) to repress target genes. When Wnt is present, Wnt will bind to its core receptor complex and recruits cytosolic (Dvl) protein to the plasma membrane. DVL proteins then polymerize and become activated, leading to the inactivation of the β-catenin destruction complex. This results in accumulation of β-catenin in the cytoplasm which then translocate into the nucleus. In the nucleus, β-catenin forms a complex with TCF/LEF to induce the expression of Wnt target genes (Liu et al. 2022; Zhao et al. 2022). In contrast, the noncanonical Wnt pathway is known as β-catenin independent pathway, as it is independent of β-catenin-T cell factor/lymphoid enhancer-binding factor (TCF/LEF) (Liu et al. 2022). The noncanonical pathway comprises Wnt/planar cell polarity (PCP) pathway and the Wnt/calcium (Ca^{2+}) pathway (Qin et al. 2024).

Since Wnt signaling was identified, studies on Wnt signaling have been steadily growing, especially in developmental process and homeostasis. Wnt signaling is a major key player in development which control cell-fate specification, proliferation and differentiation, cell polarity, and morphogenesis (Hikasa and Sokol 2013). Knockout of Wnt may lead to developmental defects. A study by Takada et al. (1994)shows that Wnt3a knockout leads to defects in somite and tailbud formation of mouse embryo. Some studies also found the pivotal role of Wnt signaling in maintaining homeostatic balance in various tissues, such as in the bone (Hu et al. 2024), liver (Goel et al. 2022), and lung (Kim et al. 2019).

Wnt ligands can bind through other types of receptors besides Fzd, such as Ryk (related to receptor tyrosine kinase). The Ryk receptor is a member of the RTK (receptor tyrosine kinase) family (Green et al. 2014). Ryk protein is composed of an extracellular domain (ECD) similar to the secreted Wif-1 (Wnt inhibitory factor 1), a transmembrane (TM) domain, and a kinase-dead tyrosine kinase domain (Lin et al. 2010).

Ryk is known to be involved in development and homeostasis through Wnt-mediated signaling. Previous research showed that Wnt/Ryk signaling can regulate gastrulation movement in zebrafish, and Ryk knockdown in zebrafish leads to gastrulation defects (Lin et al. 2010). Another research also showed the importance of Wnt/Ryk signaling as an antiinflammatory modulator during lung development and homeostasis in mice (Kim et al. 2022). Therefore, Wnt/Ryk signaling has a prominent role in developmental process and maintaining homeostasis. Mutation in Wnt signaling components may cause dysregulation of the pathway, leading to genetic disease and cancer progression (McGowan et al. 2023). Elucidating this pathway and its role in development and homeostasis may provide insights into associated diseases and inform the development of targeted therapeutic strategies. However, studies of Wnt/Ryk signaling for developmental and homeostasis

are still limited and have not been widely explored.

Here, we systematically review the current understanding of WNT/Ryk signaling during development and homeostasis. We also highlight the insights from Wnt/Ryk signaling studies for human biology and future directions of Wnt/Ryk signaling studies.

Wnt/Ryk Signaling Pathway in Embryonic Development

ryk is expressed in a variety of tissues during developmental stages. In zebrafish, expression of *ryk* is found in maternal and zygotic stages. During the somite stages, *ryk* is mainly expressed in the forming somites and the central nervous system. By 30 hours postfertilization (hpf), *ryk* is strongly expressed in the brain, heart, eyes, and posterior tail. At 4 days postfertilization (dpf), *ryk* expression becomes enriched along the ventricular zone linings and in the notochord (Lin et al. 2010).

Wnt/Ryk signaling plays an important role since embryonic development, and its role has been investigated in various model organism. Some studies have highlighted its role during gastrulation. Gastrulation stage is critical as three embryonic germ layers (ectoderm, mesoderm and endoderm) are formed in this stage, therefore establishing the basis for the future body plan (Pinheiro and Heisenberg 2020). This stage involves convergent extension (CE) movements, by which cells polarize and elongate along the mediolateral axis and intercalate toward the midline (convergence), leading to extension of the anterior/posterior axis (Kim et al. 2008).

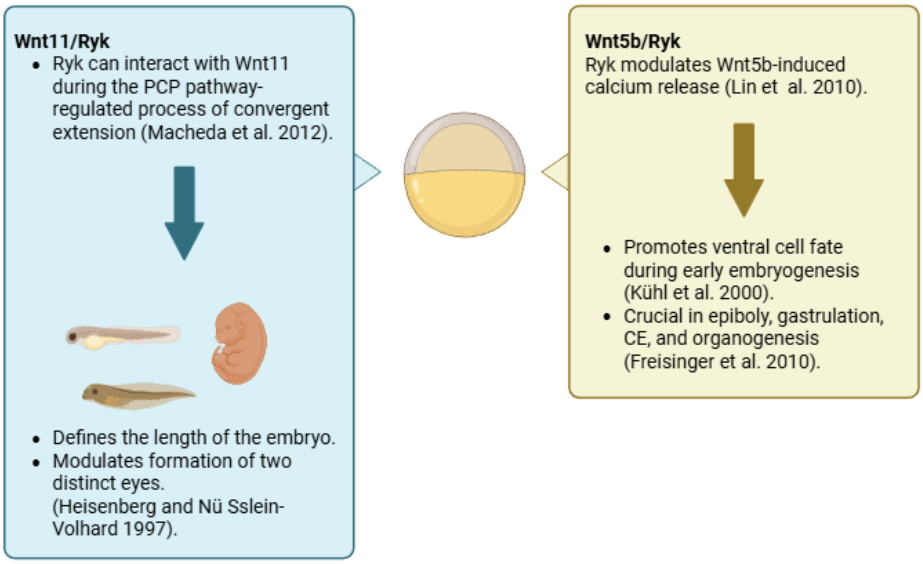

Figure 1. Role of Wnt/Ryk signaling in embryonic development, particularly during gastrulation period. Ryk may interact with Wnt11 or Wnt5b to modulate some cellular processes involved in gastrulation

In zebrafish, Wnt signaling directs CE movements during embryonic development, which defines the length of the embryo. In addition, the extension of the anterior axis divides the initial single eye field, resulting in the formation of two distinct eyes (Heisenberg and Nüsslein-Volhard 1997).

CE movements during gastrulation is driven by Wnt11. Absence of Wnt11 results in a shortened body axis along with significantly reduced interocular distances or cyclopia (Heisenberg et al. 2000). Ryk can interact with Wnt11 during the PCP pathway-regulated process of zebrafish embryo convergent extension. The knockdown of *ryk* also reduced the body length and displayed a mild eye phenotype (Macheda et al. 2012). Ryk also binds with Wnt5b to regulate gastrulation movements of zebrafish. Knockdown of *ryk* and Wnt5b causes defect to CE and retina structure. It was also found that Ryk is involved in modulating Wnt5b-induced calcium release (Lin et al. 2010). The Wnt/Ca^{2+} signaling pathway promotes

ventral cell fate during early embryogenesis (Kühl et al. 2000). Calcium release in zebrafish embryos is important in epiboly, gastrulation, CE, and organogenesis (Freisinger et al. 2010).

Another study showed that either *ryk* overexpression or depletion in *Xenopus* lead to disruption in CE movements, as the embryos failed to straighten the anteroposterior axis (Kim et al. 2008). In mice, Ryk control developmental processes in the nervous system and cochlea through the PCP pathway. Ryk deficiency resulted in disruption of orientation of the stereociliary bundles of cochlear hair cells. Besides that, Ryk deficient E18.5 embryos had craniorachischisis, a severe condition where the brain and spinal cord remain open during neural tube development (Macheda et al. 2012).

Wnt/Ryk Signaling in Organ Development

Various studies have elucidated the role of Wnt/Ryk signaling in various organ development. In the brain, McKenzie et al. (2019) found that Wnt/Ryk signaling may contribute to brain function by regulating interneuron cell-fate specification both in vivo and in vitro. Interneurons play a crucial role in maintaining inhibitory control and are essential for regulating cortical rhythmicity, attention states, and signal timing. Besides that, the Ryk receptor is essential for the Wnt3a-induced neurite outgrowth, a critical process in early neuronal development (Lu et al. 2004). Another study also showed that Ryk can interact with Wnt5a to guide the axons in establishment of the corpus callosum. In Ryk deficient mice, the cortical axons exhibit abnormal projections across the corpus callosum (Keeble et al. 2006). Ryk is also required for repulsive axon guidance by Wnt3, ensuring that axons are positioned correctly along the medial-lateral axis. Therefore, Wnt/Ryk signaling plays important role in guiding visual connections in the brain (Schmitt et al. 2006). Wnt/Ryk signaling also regulates the neuronal differentiation during cortical neurogenesis, which happens during embryogenesis (Lyu et al. 2008).

The role of Wnt/Ryk signaling for heart development has also been studied. (Kugathasan et al. (2018) found that Wnt/Ryk signaling is essential in cardiac structure morphogenesis. Loss of *ryk* in mice resulted in a variety of malformations of the heart and outflow tract, such as aortic arch defects and myocardium growth abnormalities. A study by Kim *et al*. (2022) found that Wnt/Ryk signaling is also crucial in lung development. Ryk plays a role in myofibroblast development, and its deficiency results in impaired lung vessel wall integrity. Disruption of *ryk* expression also causes lung mesenchymal cells death in the postnatal lung, therefore inducing lung inflammation.

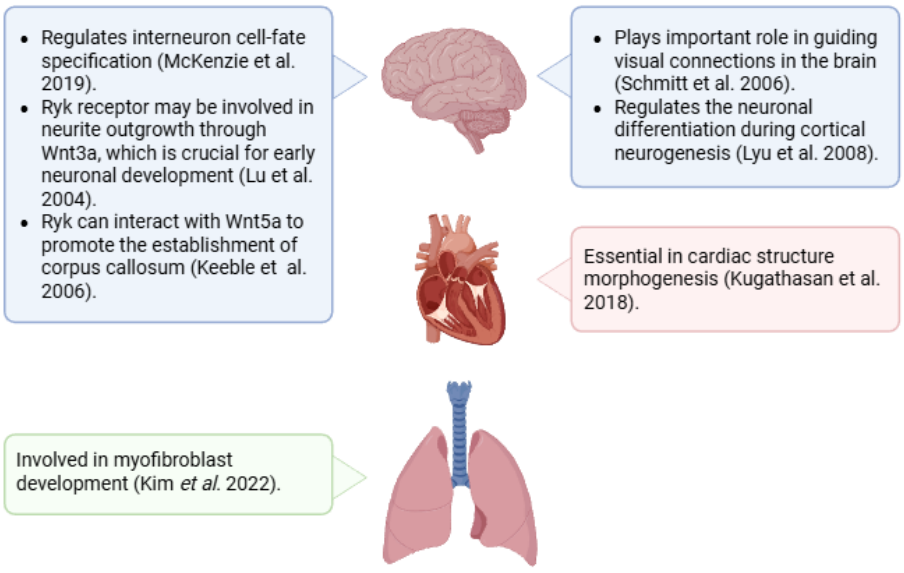

Figure 2. Role of Wnt/Ryk signaling in organ development. Some studies have found that Wnt/Ryk signaling plays a role in brain, heart, and lung development

Wnt/Ryk Signaling in Homeostasis

Various studies have investigated the role of Wnt/Ryk signaling pathway in maintaining homeostasis.In lung, Wnt/Ryk signaling is crucial for maintaining the balance of airway epithelial cell populations during repair processes as this signaling prevent goblet cell hyperplasia by repressing genes associated with it. Ryk deficiency causes goblet cell hyperplasia during lung regeneration, therefore it may contribute to the pathogenesis of human lung diseases (Kim *et al*. 2019). Another study found that Ryk is important in regulating Wnt signaling intensity in the bone marrow (BM) microenvironment, particularly in mesenchymal stromal cells (MSCs), to control hematopoiesis. Hematopoiesis depends on a carefully balanced BM microenvironment, and interaction between Ryk and Wnt may control self-renewal of hematopoietic progenitor cells (Jeong et al. 2020). Ryk is also important in hematopoietic stem cell repopulation. Knock out of *ryk* leads to proliferation-induced apoptosis and decreased self-renewal. This shows that Ryk plays important role in regulating apoptosis, therefore maintaining homeostasis (Famili et al. 2016). Wnt signalling also regulates the stem cell maintenance. Excessive Wnt signaling prevents differentiation in intestinal organoid cultures, highlighting the crucial role of balanced Wnt signaling in maintaining tissue homeostasis (Pond et al. 2020).

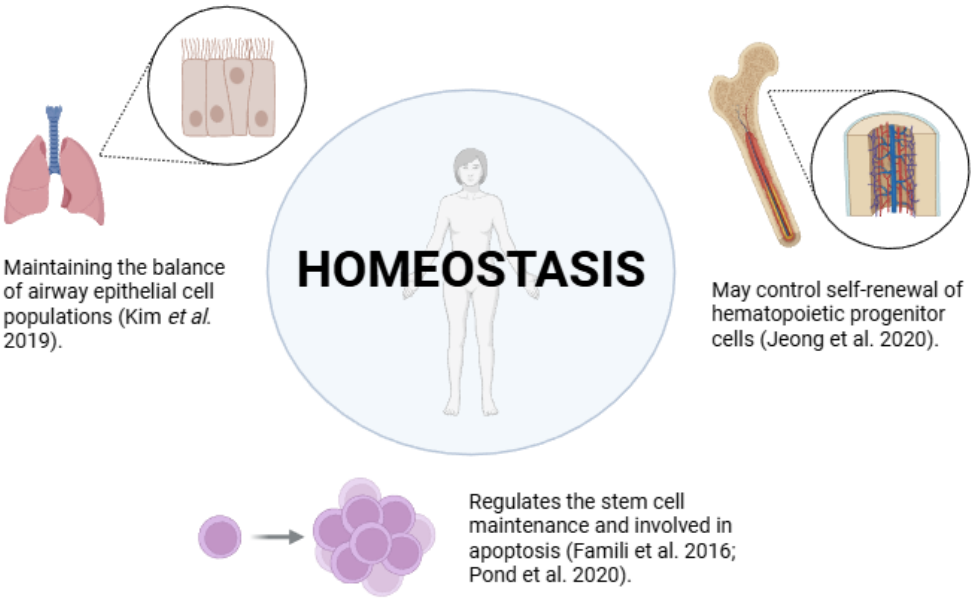

Figure 3. Role of Wnt/Ryk signaling in homeostasis. Previous studies have elucidated its role in various cellular processes, such as maintaining airway epithelial cell populations, hematopoietic progenitor cells' self-renewal, and stem cell

Crosstalk between Wnt/Ryk Signaling with Canonical Pathway

Previous studies have found that noncanonical Wnt pathway as inhibition role to the canonical pathway and the other way around. If one of noncanonical component's function is inhibited, then the binding between canonical Wnt ligands with the Fzd receptor may increase, leading to activation of canonical pathway. Therefore, as a noncanonical pathway, Ryk-mediated Wnt signaling may affect the regulation of canonical Wnt target genes involved in developmental and homeostasis (Urbanek et al. 2023). Previous research found that Wnt5a, which is important in embryonic morphogenesis and post-natal homeostasis, can bind to both Ryk and Fzd, activating both pathways (Kumawat and Gosens 2016; Thiele et al. 2018). Another study by (Adamo et al. 2017) found that Ryk plays a role in maintaining Glioma Stem Cells through canonical Wnt pathway.

Insights from Wnt/Ryk signaling studies for human

Wnt/Ryk signaling has emerged as a crucial pathway in various biological

processes, offering valuable insights into human development, tissue homeostasis, and disease mechanisms. One of the most promising areas of Wnt/Ryk research is its role in neural development and homeostasis. During embryonic development, this signaling pathway plays a key role in shaping the central nervous system by guiding axonal growth and neuronal positioning, ensuring proper neural circuit formation (Keeble *et al*. 2006). Disruptions in this process have been linked to neurodevelopmental disorders such as autism spectrum disorders (Caracci et al. 2021) and schizophrenia (Vallée 2022), both of which are associated with abnormal Wnt signaling. In addition, Wnt/Ryk signaling in tissue homeostasis may be linked to cancer progression. Dysregulation of this pathway is often linked to uncontrolled cell proliferation and tumor growth. A study by Thiele et al. (2018)found that Wnt5a/Ryk signaling is involved in mediating the pro-apoptotic and anti-proliferative effects of WNT5A in prostate cancer. Additionally, (Fu et al. 2020) discovered a strong correlation between Ryk and gastric cancer (GC) tumorigenesis, as well as its potential for liver metastasis. Specifically, Wnt has been found to modulate epithelial-mesenchymal transition (EMT), a key process in cancer metastasis (Patel et al. 2019).

Given its widespread influence in development and homeostasis, understanding the Wnt/Ryk signaling may help us to develop a promising target for therapeutic interventions. For instance, understanding how Wnt/Ryk signaling influences tumor behavior could lead to new therapeutic strategies, including small-molecule inhibitors or monoclonal antibodies that target Ryk-mediated pathways (Patel et al. 2019). In addition, Ryk acts as a major inhibitor of axon regeneration in spinal cord injuries. Blocking its function with antibodies or small-molecule inhibitors has been shown to enhance neural repair and improve functional recovery in preclinical models (Miyashita et al. 2009). The complex crosstalk between Wnt/Ryk Signaling with canonical pathway may also help us in developing targeted therapies for diseases where Wnt signaling is dysregulated.

Future Directions and Open Questions

Wnt signaling is a crucial pathway in various biological processes. Wnt signaling itself has been studied for a long time, but the discovery of Ryk is still relatively new so the role of Ryk as a Wnt co-receptor for developmental and homeostasis has not been widely explored. Wnt/Ryk signaling still has vast potential to be studied. For example, how does Ryk-mediated WNT signaling integrate with other pathways such as Notch, Hedgehog, or BMP during development and homeostasis? Additionally, the interaction of Ryk with other Wnt receptors such as Fzd and ROR to mediate distinct signaling outcomes is not yet fully understood.

Despite its significance, studying Wnt/Ryk signaling presents several challenges across developmental and homeostatic contexts. As part of a highly complex signaling network, the noncanonical Wnt pathway has inhibition role to the canonical pathway and the other way. A prior study conducted by (Flores-Hernández et al. 2020) demonstrated that Wnt ligands can activate both the canonical and noncanonical Wnt signaling pathways, leading to the formation of complex signaling networks that coordinate these pathways in colon cancer cells. Therefore, Wnt/Ryk signaling may involve both canonical and non-canonical pathways, leading to potential crosstalk that can complicate the interpretation of phenotypic outcomes. Additionally, expression of *ryk* has tight temporal regulation, requiring careful timing in experimental models to clearly identify its functional roles (Lin et al. 2010). Structural characterization of Ryk remains incomplete, with limited data on Wnt/Ryk binding interfaces, which hinders rational drug or inhibitor design for therapeutic applications. Furthermore, in vivo studies pose additional challenges, as Ryk plays a critical role in early development, and its knockout in animal models often results in embryonic lethality or severe developmental defects, making it difficult to study its postnatal functions.

The study of Wnt/Ryk signaling in development and homeostasis remains a complex but crucial field. Overcoming these challenges will require advanced genetic tools, improved structural insights, and refined model systems to dissect Ryk-specific

functions. A more in-depth exploration may unlock the full therapeutic potential of WNT/Ryk signaling in regenerative medicine and disease treatment. It is also important to selectively modulate Ryk signaling to achieve beneficial outcomes while minimizing side effects.

CONCLUSIONS

Wnt/Ryk signaling plays a vital role in development and homeostasis. This pathway is crucial from early embryonic stages, and its disruption can lead to developmental abnormalities. It is also involved in the development of several organs, including the brain, heart, and lungs. Given that Ryk is expressed in various tissues, further research is needed to explore its role in other organs. Additionally, Wnt/Ryk signaling is essential for maintaining homeostasis, contributing to processes such as apoptosis regulation and cancer metastasis. However, despite its critical role, our current understanding of this pathway remains limited due to its relatively recent discovery and associated challenges. Wnt/Ryk signaling is highly complex as it can interact with the canonical pathway as well. Further investigation is necessary to deepen our knowledge of Wnt/Ryk signaling in development and homeostasis. Overcoming these challenges could open new avenues for therapeutic interventions targeting Wnt/Ryk pathways in developmental disorders and regenerative medicine.

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