

R-Spondin 1 Regulates WNT Signaling Pathway by Antagonizing the Function of Dickkopf Homolog 1

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Short Communication

The R-Spondin (RSPO) family of secreted proteins are implicated as potent activators of the WNT signaling pathway. R-spondins (RSPOs) consisting of four members are a group of secreted proteins which could activate the canonical WNT/ β -catenin-dependent signaling pathways [1]. Dickkopf homolog 1 (DKK1) is another important player, which is a well-known inhibitor of the canonical WNT signaling pathway [2]. More and more evidences declare that RSPO1 regulates WNT signaling by antagonizing the function of DKK1.

The WNT family of secreted proteins play important roles in diverse biological processes, including development, proliferation, and differentiation, which regulate various diseases, such as prostate cancer, breast cancer, glioblastoma, type II diabetes and others. The WNT ligands could activate two major intracellular pathways: known as the canonical pathway which is β -catenin-dependent, and non-canonical pathway which is β -catenin-independent [3,4].

In the canonical WNT pathway, the WNT ligands could bind to their cell-surface receptors, which could lead to inactivation of Axin/GSK3/APC complex, resulting in stabilization of cytosolic β -catenin and subsequent nuclear translocation of β -catenin. In the nucleus, β -catenin could form a complex with T cell factor (TCF) to regulate target gene transcriptional activation. However, in the absence of WNT, cytosolic β -catenin is phosphorylated by the complex and targeted for rapid degradation by the proteasome [5].

It has been proved that RSPO1 involves in the WNT signaling pathway; however, the potential mechanisms by which they induce β -catenin still remains unknown. More and more evidences declare that RSPO1 regulates WNT signaling by inhibiting internalization of LRP6 via antagonizing the function of DKK1. DKK1 has the ability to form a complex between receptors to trigger LRP5/6 internalization [2]. It has been reported by Binnerts et al. that RSPO1 could rescue the inhibition triggered by DKK1 [6]. Yin et al. demonstrated that DKK1 repressed the effect of RSPO1 on the activation of hepatic stellate cells [7], which supported that RSPO1 and DKK1 form a signaling regulation network. Kim et al showed that RSPO1 could activate WNT signaling through LRP6 by antagonizing the function of DKK1 [8]. Lu et al. demonstrated that DKK1 could block the phosphorylation of LRP6 and stabilization of cytosolic β -catenin stabilization induced by RSPO1

and/or Wnt3A in C2C12 cells, suggesting that RSPO1 may play important roles in osteoblast differentiation [9]. Wei et al. found that DKK1 could inhibit RSPO1 induced phosphorylation and activation of LRP6 [10].

WNT signaling pathway was implicated in the development of breast, melanoma, prostate, lung, and other cancers, as well as Type II diabetes. It would be beneficial to declare the relationship between RSPO1, DKK1 and WNT signaling pathway.

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