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E-cadherin and β-catenin across the branches of hematopoiesis in evolution

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Publication date
2024

Link to publication

Citation for published version (APA):
Krimpenfort, R. A. (2024). *From solid roots to rustling leaves: E-cadherin and β-catenin across the branches of hematopoiesis in evolution*. [Thesis, fully internal, Universiteit van Amsterdam].

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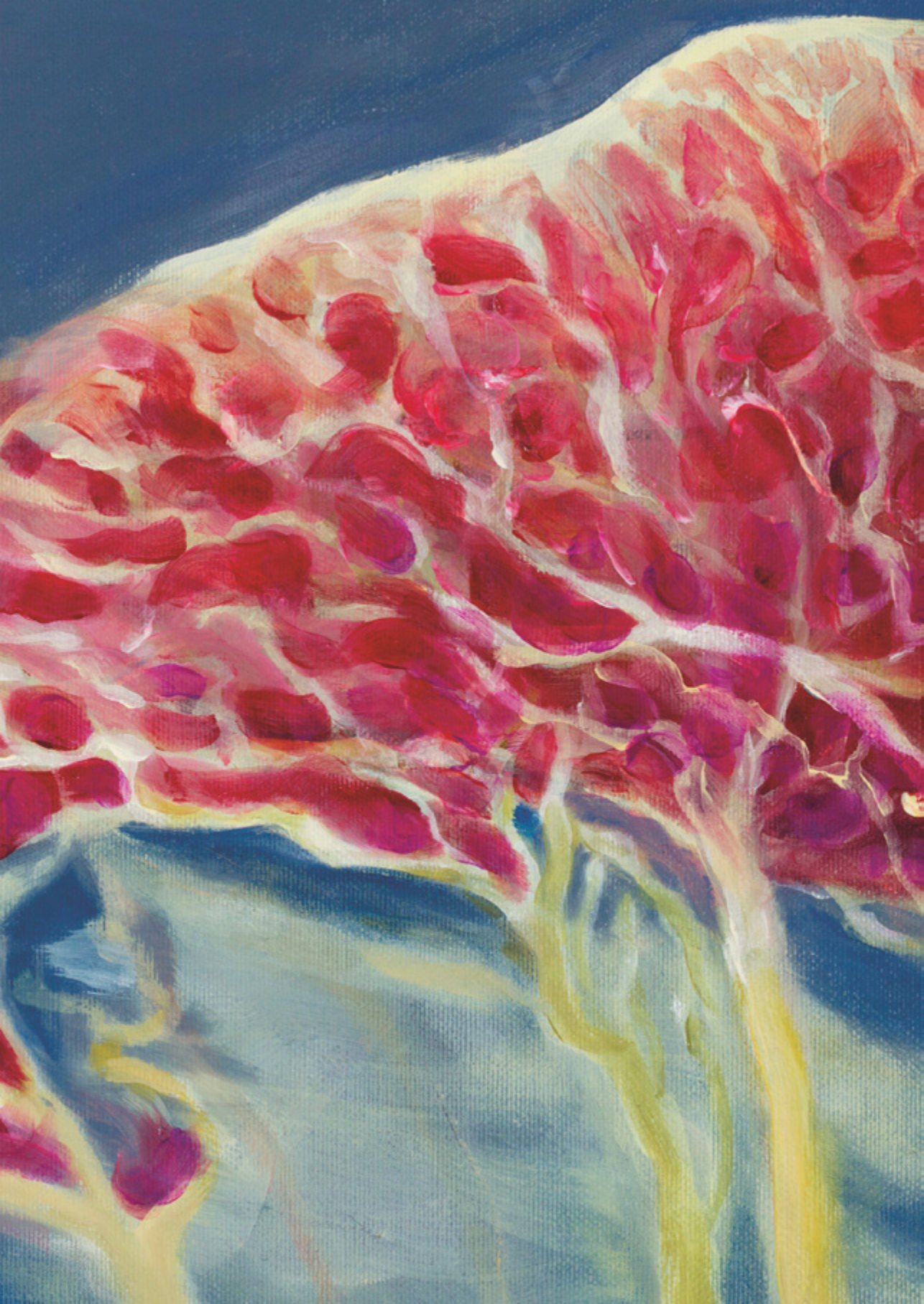

Chapter 4

Wnt/β-catenin Signaling Pathway Components in the Human Erythroid Lineage

Short Report

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Manuscript in preparation

Abstract

We previously identified β-catenin protein expression to mark erythropoiesis in humans. The Wnt pathway, known for its intricate regulation of stem cell differentiation and proliferation, relies on the key signaling molecule β-catenin. Dysregulation of this pathway is implicated in various cancers, including colorectal, breast, and hematopoietic malignancies.

Here, we explore the expression of Wnt receptors and regulatory components in healthy human bone marrow (BM) and cultured erythroblasts derived from hematopoietic stem and progenitor cells (HSPCs). This study thereby aims to understand the potential of Wnt to control erythropoiesis. In this study, we identify essential Wnt components, such as Wnt receptors and negative regulators to be expressed throughout erythropoiesis. .

Introduction

The Wnt/β-catenin signaling pathway is an evolutionary conserved pathway that is involved in the regulation of stem cell differentiation and proliferation (121–123). With a family of approximately 20 ligands and a multitude of receptors, co-factors, co-receptors, and intracellular inhibitors, the Wnt pathway is highly complex. Wnt/β-catenin signaling is a tightly regulated signaling cascade, that can be controlled on many levels. There are many excellent reviews on the Wnt pathway components and cellular outcomes for different tissues (124–127).

In a nutshell, the Wnt pathway is driven by the key signaling molecule β-catenin. In healthy tissue, β-catenin protein is ubiquitously produced. When the Wnt pathway is inactive, β-catenin is phosphorylated by GSK3β, a member of the β-catenin destruction complex and targeted for degradation by the proteasome. The signaling cascade is activated upon the binding of Wnt ligand and Rspondin co-factors to their respective receptors frizzled, LRP and LGR. Hereupon, the β-catenin destruction complex components Axin2 and GSK3β are recruited by Disheveled at the membrane by which the degradation complex is inactivated. B-catenin can now accumulate and transmigrate to the nucleus where it associates with and initiates transcriptional activation by transcription factors TCF/LEF (128–130).

Activation of TCF/LEF mediated transcription results in the expression of a broad gene expression signature with both general and cell specific target genes. The most widely accepted target genes are involved in proliferation and stem cell-ness and include Cyclin D1 and c-MYC (131–133). The Wnt pathway is crucial for embryonic and organ development, including the intestine and mammary gland, but also hematopoietic tissue (103,122,134–139).

Additionally, Wnt/β-catenin signaling mediates tissue homeostasis and regeneration upon injury. When improperly regulated, however, β-catenin signaling has a detrimental dark side: impaired regulation of the Wnt pathway results in hyperactive β-catenin signaling, resulting in uncontrolled proliferation and tumorigenesis. There are multiple ways in which a cell can bypass the regulation of Wnt signaling (140). Inactivating mutations of destruction complex members have been described for APC and Axin1 inducing β-catenin accumulation (141,142). Another way by which β-catenin can escape the destruction complex is through mutations in the destruction complex recognition site of the β-catenin (142). Alternatively, inadequate turnover of Wnt receptors results in increased sensitivity to Wnt ligands and cofactors (143,144). Deregulated Wnt/β-catenin signaling can contribute to numerous cancer types including colorectal cancer and breast cancer, but also the hematopoietic malignancies such as MDS and AML (142,145–149).

We previously identified β-catenin protein to be expressed in erythroid progenitors in humans. In this study, we investigate the potential of canonical Wnt signaling to control erythropoiesis at various erythroid stages, by data-mining public available RNA-seq libraries. We identified

Wnt receptors and critical regulators of canonical Wnt signaling to be expressed, which thereby highlights the potential of Wnt/β-catenin signaling to direct erythropoiesis.

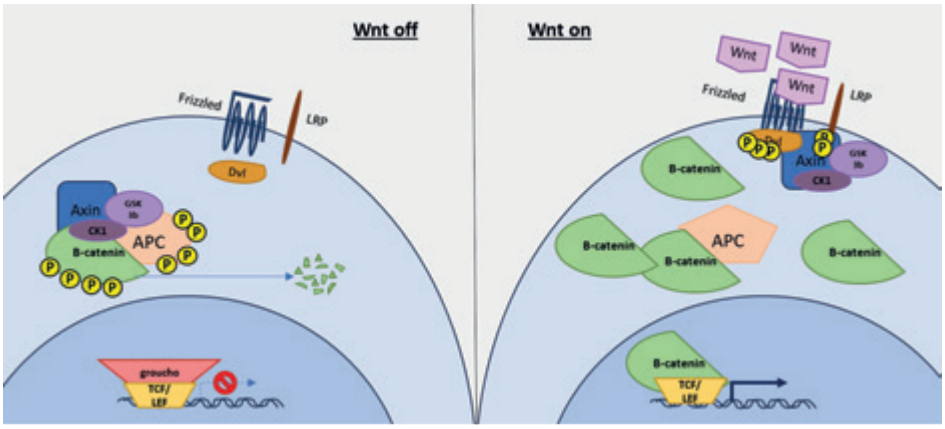

Figure 1. The main components of the Wnt/β-catenin signaling cascade. *When the Wnt signaling pathway is inactive (left panel), β-catenin is phosphorylated by the β-catenin destruction complex and targeted for degradation by the proteasome, while transcription of β-catenin target genes is inhibited. When the Wnt pathway is activated (right panel), the destruction complex is disassembled, and β-catenin accumulates and translocates into the nucleus, where it can bind and activate TCF/LEF1 for transcription of Wnt/β-catenin target genes.*

Methods

To investigate the expression of Wnt pathway components, we data-mined two different public available datasets. First, we conducted a query on a publicly accessible single-cell RNA sequencing dataset from healthy human BM subpopulations (150). Second, for our *in vitro* expression analysis, we extracted information from mRNA sequencing database published by our own department on cultured erythroblasts during differentiation (45). In short, erythroid cultures were conditioned to differentiate and sampled each day over 12 days. Sequencing libraries were created following the manufacturer's instructions, involving Trizol RNA isolation, complementary DNA amplification, and ribosomal RNA depletion with the HyperPrep Kit and RiboErase (KAPA Biosystems, Pleasanton, CA). The reads were then aligned to ChGR38.v85 and analyzed for differential expression analysis using EdgeR (151). For a more detailed description, we refer to Heshusius et al. (2019)(45).

Results

Single cell RNA-seq expression analysis of Wnt/β-catenin pathway components in the human hematopoietic cell lineage

To examine the potential control of canonical Wnt signaling on erythropoiesis we data-mined a public available single-cell RNA-seq dataset that has been obtained from BM of eight healthy

individuals (150). We started to explore the expression of the Wnt receptors; low-density lipoprotein receptor-related protein 5 or 6 (LRP5 and LRP6) (152–154). LRP5 and LRP6 expression mostly marks the CD34+ marked HSPC compartment and were barely expressed in the more mature hematopoietic cell lineage compartments (e.g; T- and B-cells, and monocytes and granulocytes) (Figure 2A). Intriguingly, within the erythroid lineage, early erythroblasts were found to express LRP5 and LRP6 at similar levels as displayed by HSPCs (Figure 2A).

LRP5/6 mediates Wnt ligand binding in conjunction with seven-pass transmembrane receptor Frizzled (FZD) family members (155,156). Frizzled family members were however barely detected. Yet low levels for FZD5 and FZD7 were detected of which FZD5 mostly seems to mark early and more mature erythroblasts (Figure 2A). LGR4 and LGR5 both potentiate Wnt signaling by binding of R-spondins (RSPO's) and thereby act as important WNT co-receptors (157–159). Whereas LGR5 expression was not detected, low levels for LGR4 were detected throughout the CD34+ marked HSPC compartments (Figure 2A). Intriguingly, among the hematopoietic cell lineage, erythroblasts expressed relatively high levels of LGR4 (Figure 2A). Dishevelled (DVL) relays Wnt signals from the Wnt receptors, to recruit and inactivate the β-catenin destruction complex (160,161). Whereas DVL1 and 3 expression was not detected, DVL2 expression was found to prominently mark both the HSPC compartment as also the erythroblast compartments (Figure 2B).

Whereas we previously revealed inhibition of GSK3β activity to stabilize β-catenin protein expression in cultured human erythroblasts, we subsequently examined the expression levels of key components of the destruction complex. Instead of Axin-2, we found Axin-1 to be expressed throughout the hematopoietic lineage as also seen for GSK3β (Figure 2B). Overall, these results indicate the potential of canonical Wnt to direct erythropoiesis *in vivo*.

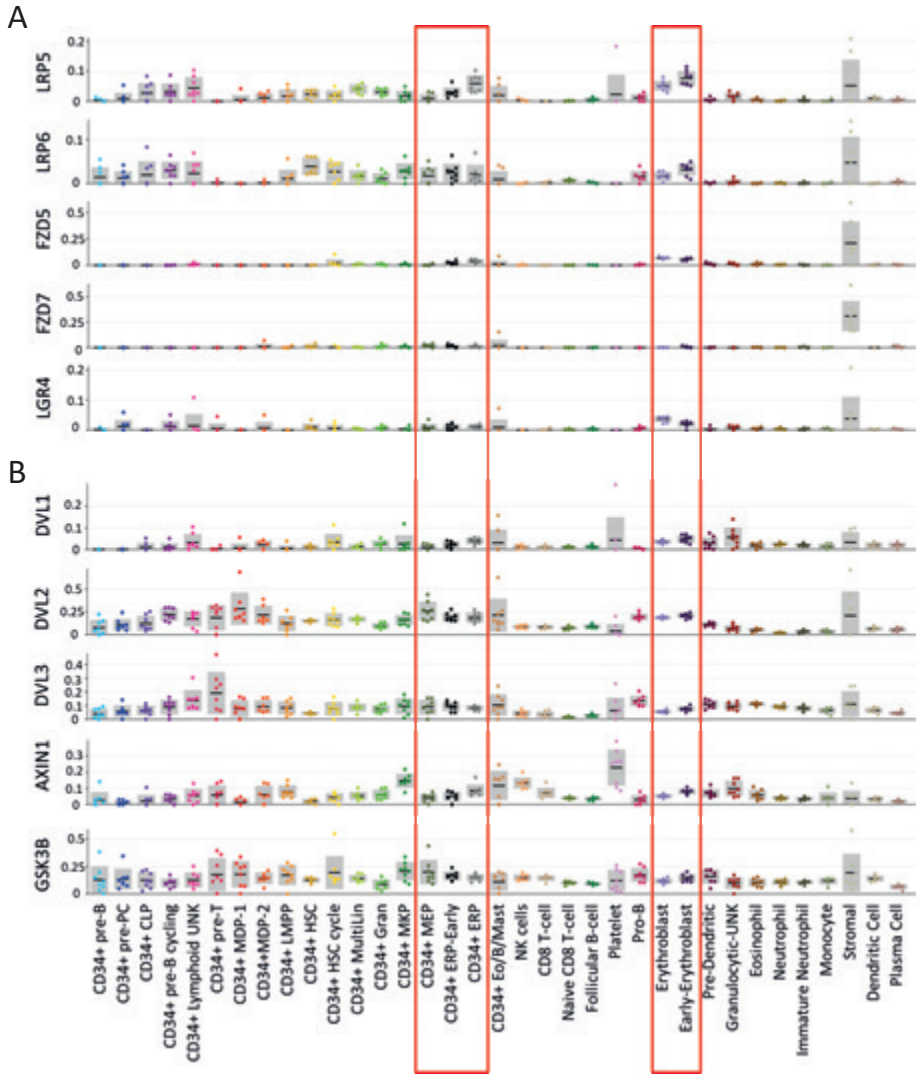

Figure 2. *mRNA expression of Wnt (co)receptors (A) and members of the destruction pathway (B) in healthy human BM populations in which each dot represents one human sample. Erythroid subpopulations are highlighted within the red boxes*

RNA-sequencing expression analysis of Wnt/β-catenin pathway components during erythroblasts differentiation

We next analyzed the expression levels of the identified Wnt (co)receptors and components during defined sequential stages of erythroblast maturation. We therefore examined a previously derived RNA-seq dataset that was established by our department from defined stages of cultured erythroblast maturation stages generated from HSPCs of 4 healthy donors (45).

Pro-erythroblasts, defined as CD71+CD235a- erythroblasts, were found to express both LRP5 (5.8 counts per million (CPM) and LRP6 (4 CPM), which both declined during erythroblasts differentiation (Figure 3). This is also in line with the obtained expression pattern in the hematopoietic cell lineage (Figure 2). FZD7 expression was not detected in pro-erythroblasts but, similarly as FDZ5, was found to peak during the formation of basophilic erythroblasts (CD71+CD235a-) (FZD5: 8 CPM and FZD7: 5 CPM (Figure 3). Erythroblast maturation also was associated with upregulation of LGR4 expression, as observed for FZD5 and 7, towards 4 CPM for basophilic erythroblasts (Figure 3). Destruction pathway components DVL-2, Axin1 and GSK3β were all strongly expressed during erythroblast differentiation (figure 3B). Overall these findings indicate the LRP5/6-FZD5/7 Wnt receptor complex to be transiently expressed during the transition of the pro-erythroblast to basophilic erythroblast cell stage.

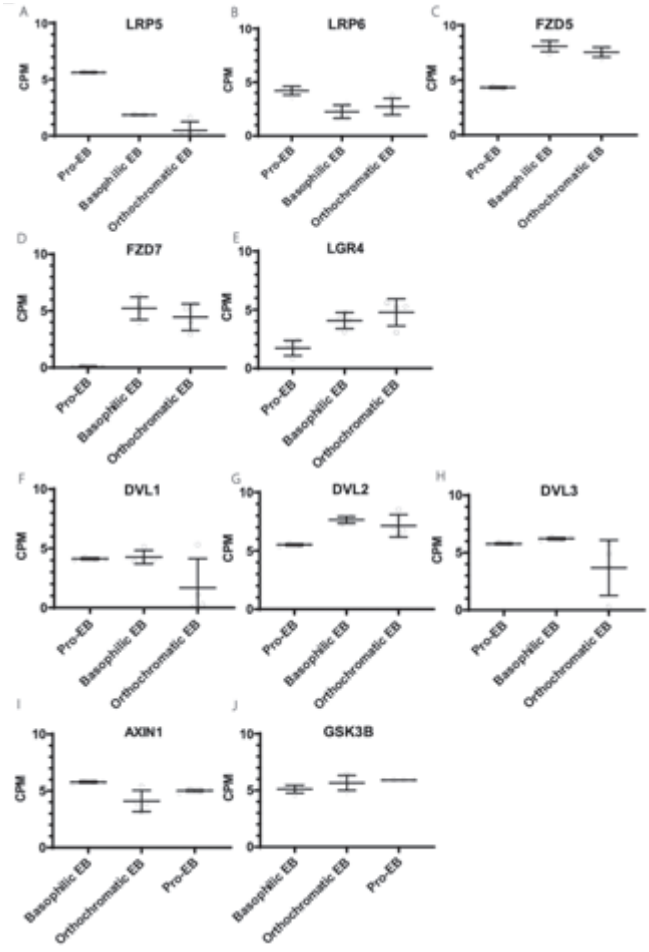

Figure 3. *Normalized mRNA expression depicted as counts per million (CPM) reads of Wnt (co) receptors (LRP5/6, FZD5/7 and LGR (A-D)) and members of the destruction complex (DVL1/2/3, Axin, GSK3B (F-J)) in the differentiation stages of cultured human erythroblasts.*

Discussion

In this study, we examined expression levels of Wnt (co)receptors and components of the β-catenin destruction complex that are expressed in erythropoiesis *in vivo* and *in vitro* in HSPC-derived erythroblast cell cultures. Single-cell RNA sequencing vs bulk RNA sequencing data are hard to compare due to different methodology, sequencing depth and analysis. However, both methodologies revealed (early) erythroblasts to display distinguished mRNA expression levels of the Wnt receptors LRP5/6 and FZD5/7. Bulk RNA sequencing analysis of the expression of these Wnt receptors suggests the transition from CD71+CD235a- towards CD71+CD235a+ to most optimally express both LRP5/6 as FZD5/7. However it remains to be defined to what degree the obtained mRNA expression correlates with subsequent protein levels.

Whereas Wnt ligands potentially may direct erythropoiesis, one should keep in mind that the presence of Wnt pathway components does not necessarily result in β-catenin-TCF/LEF1 mediated transcription as multiple non-canonical regulators of β-catenin have been described to be expressed in erythroid progenitors. For example, E-cadherin has been described to sequester β-catenin from both the destruction complex, but thereby prohibits its translocation into the nucleus (106,107,162–164). Additionally, the transcription factor of the Forkhead box O (FOXOs) is well-known to be highly important for erythroid differentiation, while in MDCK cells β-catenin interaction with FOXO proteins has been reported to enhance transcription of FOXO target genes at the cost of β-catenin-TCF mediated transcription (50–52,165). On the other hand, the lack of Wnt ligands or receptor protein expression does not rule out β-catenin-TCF/LEF1 mediated transcription, as β-catenin is also capable of nuclear translocation in response to other signals such as mechanical tension (166,167).

Overall, the erythroid lineage express all Wnt components to respond to Wnt ligands. Future studies are therefore needed to define if and in what context Wnt may direct erythropoiesis.

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