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From solid roots to rustling leaves

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

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Chapter 7

General Discussion

The research in this thesis addresses the role of E-cadherin in hematopoiesis. This highly conserved adhesion molecule and tumor suppressor is expressed in erythroid progenitors in human bone marrow (BM). However, the function of E-cadherin in erythropoiesis has not been elucidated. In this thesis, we investigate the molecular mechanisms through which E-cadherin may govern the behavior of erythroid cells in homeostatic and anemic conditions.

Erythroblast suspension cultures: challenges for studying intercellular adhesion and signaling

Studying E-cadherin in erythroid cell cultures comes with the necessary challenges. The most commonly used immortalized erythroid cell lines, such as BEL-A and HUDEP, for example, do not express E-cadherin. We identified the human erythroid cell line KU812 to express E-cadherin, but this cell line is also known for its basophilic traits (chapter 2). For the work in this thesis, we therefore predominantly used primary cells, derived from mobilized peripheral hematopoietic stem and progenitor cells. Primary erythroblast cell cultures have the beauty that there are no mutations introduced during their expansion but have the downside that they allow a limited time window to study E-cadherin expression and interactions before they spontaneously differentiate.

The erythroblast culture system used in our studies is highly optimized for the ultimate goal of generating transfusion units. Therefore, it does not necessarily fully recapitulate erythroid instructive signaling as occurs in steady-state conditions in human BM. The culture system, for example, contains an excess of growth factors and cytokines such as solubilized Stem cell factor (SCF), Erythropoietin (EPO), and dexamethasone, and on the other hand lacks serum. These conditions allow erythroblasts to undergo a maximum number of cell divisions by preventing them from spontaneous differentiation.

In vivo, EPO levels rarely reach these levels of growth factors and ample nutrients necessary for standard erythroid culture conditions. For example EPO levels within circulation typically range from 10 and 18 mU/ml, whereas 1 Unit/ml of EPO is used to optimally expand human (and mouse) erythroblasts *in vitro* (1). Moreover, glucocorticoid signaling in erythropoiesis, as induced with dexamethasone to stimulate the expansion of pro-erythroblasts, increases *in vivo* in response to anemia (2).

Besides these differences, primary erythroblast cell cultures do not require stromal cells and/or extracellular matrix proteins and typically grow and expand as suspension cultures. At first thought, the use of erythroblast suspension cultures seems an advantage for studying E-cadherin as its silencing with CRISPR/Cas9 would not disrupt the tissue/monolayer rigidity. In epithelial cells, this is almost inevitable, which makes it difficult to dissect direct from indirect effects of E-cadherin deficiency. However, cell-cell adhesion or even cell aggregation is hardly seen in erythroblast cell suspension cultures, even though these cells do express E-cadherin on their cell surface. Erythroid

cell suspension cultures therefore may not recapitulate the interactions that occur *in vivo* between erythroblasts in the erythroblastic islands. Future studies on the role of E-cadherin in erythropoiesis therefore need to be conducted in an adhesive environmental context. To study erythroblast behavior in a 2D model, it is possible to adhere them to a coating with recombinant VCAM-1, the main adhesion molecule expressed by nurse macrophages to bind erythroid progenitors and erythroblasts. Erythroblasts express α4β1 integrins, required to bind VCAM-1, up to the orthochromatic stage, largely within the same differentiation window as E-cadherin is expressed. Future experiments are therefore required to optimize erythroid cell adhesive culture conditions to study the control of cell adhesive signaling (such as E-cadherin) on erythropoiesis *in vitro*.

Evolutionary conservation of E-cadherin in hematopoietic lineages: a species analysis

In correspondence to recently published work by Wanet et al., (2021), we identified E-cadherin in mouse BM to selectively mark the basophil lineage (chapter 2). This revealed a discrepancy between mouse and human hematopoiesis as hematopoietic E-cadherin protein expression in human hematopoiesis is not detected in basophils, but in contrast, restricted to the erythroid lineage.

The divergence in expression of hematopoietic E-cadherin between humans and mice within the erythroid and basophil lineages is remarkable, particularly in the context of a recent study from the Socolovsky lab which implicated that the erythroid and basophil lineage are derived from a common pool of late hematopoietic progenitors (4). In this study the hierarchy of the traditional hematopoietic tree was revisited upon performing single-cell RNA-sequencing of mouse bone marrow-derived hematopoietic stem and progenitors (4). The classical view on hematopoiesis proposes hematopoietic progenitor cells to follow a hierarchical path before commitment to their definitive lineage. However, the hematopoietic trajectory that recently has been defined with single-cell RNA-seq looks more like a continuum with an undifferentiated core from where all hematopoietic paths emerge. Within the core there might be more space for plasticity as compared to the classic tree in tree in which cells could only change their differentiation fate under very specific conditions. Interestingly, the proposed hematopoietic hierarchy in this new model also deviates from the initial hematopoietic tree, as the basophil-mast cell fate is in fact more likely to derive from the megakaryocyte/erythrocyte path rather than from the GMP/Monocyte/Neutrophil path. Moreover, within the MEP trajectory, the basophil/mast cell fate lies between the erythroid and the megakaryocyte fate. The question remains however whether the basophil and erythroid trajectories are as closely related to one another in human hematopoiesis.

Single-cell hematopoietic landscapes as described by Socolovsky for mouse and the Wilson lab for human (4,5) are rarely oriented from the basophil/mast cell perspective, as these lineages are

relatively underrepresented in the BM as compared to other lineages. However, in both datasets, *CDH1* expression can be found at the common base of the erythroid and basophil/mast cell paths. Our data in chapter 3 and the study of Wanet and colleagues show that besides marking the basophil/mast cell lineage, a small fraction of E-cadherin-positive cells in fact seems to mark HPCs with a ery/megakaryocyte/basophil or even a basophil/erythrocyte potential. These findings therefore, beautifully correspond with the Socolovsky model in which basophil-fate derives from the MEP path.

Wanet and colleagues also found that *Cdh1* expression in mouse hematopoiesis is controlled by GATA2, but not GATA1, explaining why E-cadherin protein is just expressed in the basophil, but wears down in the erythroid lineage. Interestingly, we were unable to detect E-cadherin cell surface protein on human basophils. Nor is *CDH1* mRNA detected in either of the human basophil lineages represented in the single cell RNA databases that we datamined in chapter 3 and 4. However, GATA recognition motifs at the *CDH1* locus seem to be evolutionally conserved and have also been reported to regulate its expression in different organisms. In Drosophila, several GATA co-factors such as U-shaped, Serpent and Friend-of-GATA (FOG) are suggested to positively and negatively regulate E-cadherin expression in hematopoietic progenitors (6). In mice, *Cdh1* has been reported to respond to GATA2 in the basophil lineage (3). Also the human *CDH1* promoter has GATA like motifs as is shown in MCF7 and MDA-MB-231 breast cancer cells, in which E-cadherin protein is upregulated by GATA3 expression, and thereby prevents/reverses epithelial-to-mesenchymal transition and metastasis (7,8). As there is a discrepancy between species in the hematopoietic lineages where E-cadherin is expressed, namely in the mouse basophil lineage and in the human erythroid lineage, it remains to be determined how GATA transcription factors regulate *CDH1* expression. As GATA factors have been reported to be able to replace each other (9), it is likely that GATA transcription factors can activate *CDH1* independently in different species through differences in binding by specific coregulators. Whereas the Welner lab elegantly showed how E-cadherin expression is regulated in the mouse basophil/mast cell lineage, they discuss little about its function in these cells. We show that basophils can still be generated during steady-state hematopoiesis in BM of E-cadherin hematopoietic KO mice (chapter 3). Additionally, the erythroid lineage seems to be unaffected, as these mice display normal erythroblast counts and blood values in steady-state conditions. However, whether E-cadherin has a functional role during challenges of the basophilic lineage, for example upon helminth infection, has not been investigated and remains to be defined.

E-cadherin-driven regulation of β-catenin signaling

Another highly interesting question that remains, especially in the context of E-cadherin mediated regulation, is whether erythroblasts are capable of β-catenin mediated transcriptional activation in the absence of Wnt ligands, using the cadherin bound and stabilized β-catenin pool.

E-cadherin has been indicated to stimulate β-catenin nuclear localization and transcriptional regulation, independent of Wnt stimulation, through E-cadherin-driven endocytosis in response to mechanical stimulation (10,11). In response to mechanical tension, p120-catenin detaches from E-cadherin, thereby inducing endocytosis of the E-cadherin complex, and as a consequence stimulates β-catenin accumulation in the nucleus and transcriptional regulation. During stress erythropoiesis, the BM undergoes architectural changes, involving a decrease of adipocytes in favor of erythroid progenitors. As E-cadherin and β-catenin are both increased upon induction of anemia, it is not unthinkable that erythroblasts make use of one of these conserved pathways in which mechanic forces drive proliferation/differentiation through E-cadherin-β-catenin mediated signaling.

E-cadherin and β-catenin recently have been reported to form a membrane complex with Piezo1 in MDCK cells. Piezo1 is another mechano-transducer that has initially been reported to act as an important regulator of calcium influx in erythrocytes, which activates the Gardos channel (KCNN4) to export K+ and concomitantly drive H_2O efflux to allow deformability and passage through capillaries. More recently, Aglialoro et al. (2020) (12) defined that Piezo1 is also expressed in erythroblasts, whose mechanical or chemical activation results in activation of the Ca^{2+}-dependent Calcinurin-NFAT pathway. In MDCK cells, Piezo1 on its own has been reported to be able to induce a mechanically induced potential. This effect is potentiated by E-cadherin on its own, and even more with β-catenin in the complex. Interestingly, E-cadherin-mediated stimulation of Piezo1-mediated Ca^{2+} influx was reported to be driven independent of homophilic interactions. Whereas it remains to be defined whether E-cadherins' control on erythropoiesis is dependent on the formation of homophilic interactions, in their absence, E-cadherin-β-catenin signaling may still act in concert with PIEZO1 to stimulate erythropoiesis.

Wnt and erythropoiesis

We identified E-cadherin to stabilize β-catenin in human and rat erythroblasts. Stabilization of β-catenin by an inhibitor of the β-catenin destruction complex, CHIR, similarly enhanced β-catenin in CDH1 KO and wt erythroblasts. However, expression of β-catenin/TCF target genes in erythroblasts required a much higher dose CHIR as compared to HEK293 cells. Erythroblasts express Wnt Receptors and downstream signaling components, at least at the transcript level (chapter 4). Yet, our cultured erythroblasts did not stabilize β-catenin nor activated TCF/LEF signaling in response to the addition of Wnt ligands (recombinant Wnt3a or Wnt10b). This does not necessarily implicate that Wnt ligands cannot activate β-catenin signaling in EBs *in vivo*.

Interestingly, the Paulson group suggested stress erythroid progenitors respond to Wnt ligands in the mouse spleen in 2020. In this study, they demonstrate Wnt ligands are expressed by nurse macrophages and negatively regulated by EPO (13). Additionally, they show that β-catenin stabilization *in vitro* results in the proliferation of stress erythroid progenitors. They therefore

suggest that Wnt ligands directly control the proliferation of stress erythroid progenitors. However, the response *in vitro* was mimicked using inhibitors of the destruction complex, but not with Wnt ligands themselves. Technically, they hereby proved β-catenin responsiveness, but not the Wnt ligand responsiveness *in vitro*.

The single cell RNA sequencing database (14) shown in chapter 4 revealed essential canonical Wnt receptor complex and downstream signaling components to be expressed in the erythroid lineage in human BM. Several explanations can be indicated why our cultured human EBs are insensitive to Wnt ligands. First, culturing human erythroblasts comes with technical discrepancies with the *in vivo* setting as outlined above. One major example is that our erythroblasts are cultured in the absence of serum. Serum consists of many known and unknown compounds contributing to the net signalosome. Additionally, serum is known to be essential for the stability of synthetic Wnt ligands themselves, where Wnt ligands *in vivo* are highly insoluble and therefore to remain membrane-associated upon excretion (15–17).

Another difference that possibly affects the Wnt responsiveness is that the Paulson study uses the mouse as a model. As shown in chapter 2, mouse erythroblasts do not express E-cadherin. E-cadherin in turn has been suggested in epithelia to sequester β-catenin at the cell membrane and thereby inhibit β-catenin nuclear translocation. While human EBs express E-cadherin, perhaps mouse erythroblasts do respond to Wnt ligands because they lack expression of E-cadherin as a direct regulator of localization of β-catenin.

Lastly, there may be a difference in the presence of transcription factors affected by β-catenin in the nucleus; *in vitro* vs *in vivo*, or between mouse and human erythroblasts. As we show in chapter 6, cultured human erythroblasts barely express TCF and LEF, and only up to the pro-erythroblast stage, suggesting that upregulation of the canonical β-catenin target genes would be limited.

The interaction between β-catenin and FOXO3, and its conservation during erythropoiesis

In chapter 3, we find β-catenin to be upregulated in erythroid progenitors in response to acute anemia induction, while in chapter 6 we find that β-catenin signaling does not initiate its canonical transcription profile, as also TCF1/LEF are barely expressed. However, we also find in chapter 6 that rat erythroblasts, aside β-catenin, also upregulate FOXO3 expression, and FOXO transcriptional signature increases during stress erythropoiesis in rat erythroid progenitors.

The direct interaction between β-catenin and FOXO3 is technically challenging to define, but in literature, strong evidence exists that β-catenin and FOXO signaling regulate each other. While FOXO competes with TCF and thereby inhibits canonical β-catenin target genes, β-catenin has been described to enhance transcription of FOXO target genes (18,19). This regulation appears to

be crucial during oxidative stress and is conserved in many species from C. elegans and Drosophila to zebrafish and humans (18–22).

FOXO3 is well-known to be conserved in mouse and human terminal erythroid differentiation, and crucial during emergency erythropoiesis and oxidative stress (23–26). Also β-catenin has been described to be essential in early hematopoietic stem and progenitor cells for survival of oxidative stress and emergency hematopoietic regeneration upon irradiation in mice (27). However, we report that β-catenin protein is not expressed in steady state mouse erythroblasts (**chapter 3**). Does that imply mouse erythroblasts do not require β-catenin during stress erythropoiesis? Or do mouse erythroid progenitors upregulate β-catenin protein expression during stress erythropoiesis?

The Paulson group recently showed that mouse stress erythroid progenitors require Wnt/β-catenin signaling for proliferation, but upon EPO signaling during stress erythropoiesis, Wnt ligand expression by nurse macrophages is reduced and terminal differentiation is initiated. However, the role of β-catenin itself in mouse terminal differentiation during stress erythropoiesis, let alone its molecular interactions, remains unclear as it is not directly modeled in this study (13).

We suggest in chapter 6 that β-catenin/FOXO3 interaction also occurs in human and rat erythroid progenitors during stress erythropoiesis which may accelerate terminal differentiation by activating a FOXO3 transcriptional signature. However, the molecular mechanisms by β-catenin/FOXO3 affect erythroid cell behavior have not been elucidated.

Tenbaum and colleagues made interesting observations in colon cancer cells where FOXO3 signaling alone, induced by PI3K and AKT inhibitors causes apoptosis, but upregulation of β-catenin shifts the cell fate from apoptosis to cell proliferation (21). Additionally, only upon accumulation of both β-catenin and FOXO3, but not only β-catenin or FOXO3, transcription of IQGAP, CYR61 and/or CLDN1 is activated, all known to be involved cytoskeletal reorganization, tissue regeneration and epithelial to mesenchymal transition (28–36). Upon combined accumulation of β-catenin/FOXO3 they observed loss of epithelial phenotype as a consequence of E-cadherin internalization in subconfluent cell cultures and in vivo. It would be highly interesting to investigate if similar regulation of E-cadherin applies in erythroid progenitors in erythroblast islands in response to adipocyte decrease during stress erythropoiesis. This β-catenin/FOXO3 mediated internalization of E-cadherin would not be needed in mouse erythroblasts as they do not express E-cadherin, and they do not regulate stress erythropoiesis in BM.

Because of the technical challenges, future experiments will involve tools such as molecular tags to better visualize the interaction between β-catenin and FOXO3 in erythroid progenitors. Additionally, β-catenin KO experiments will be needed to prove that the FOXO3 mediated transcription in during stress erythropoiesis is indeed driven by β-catenin.

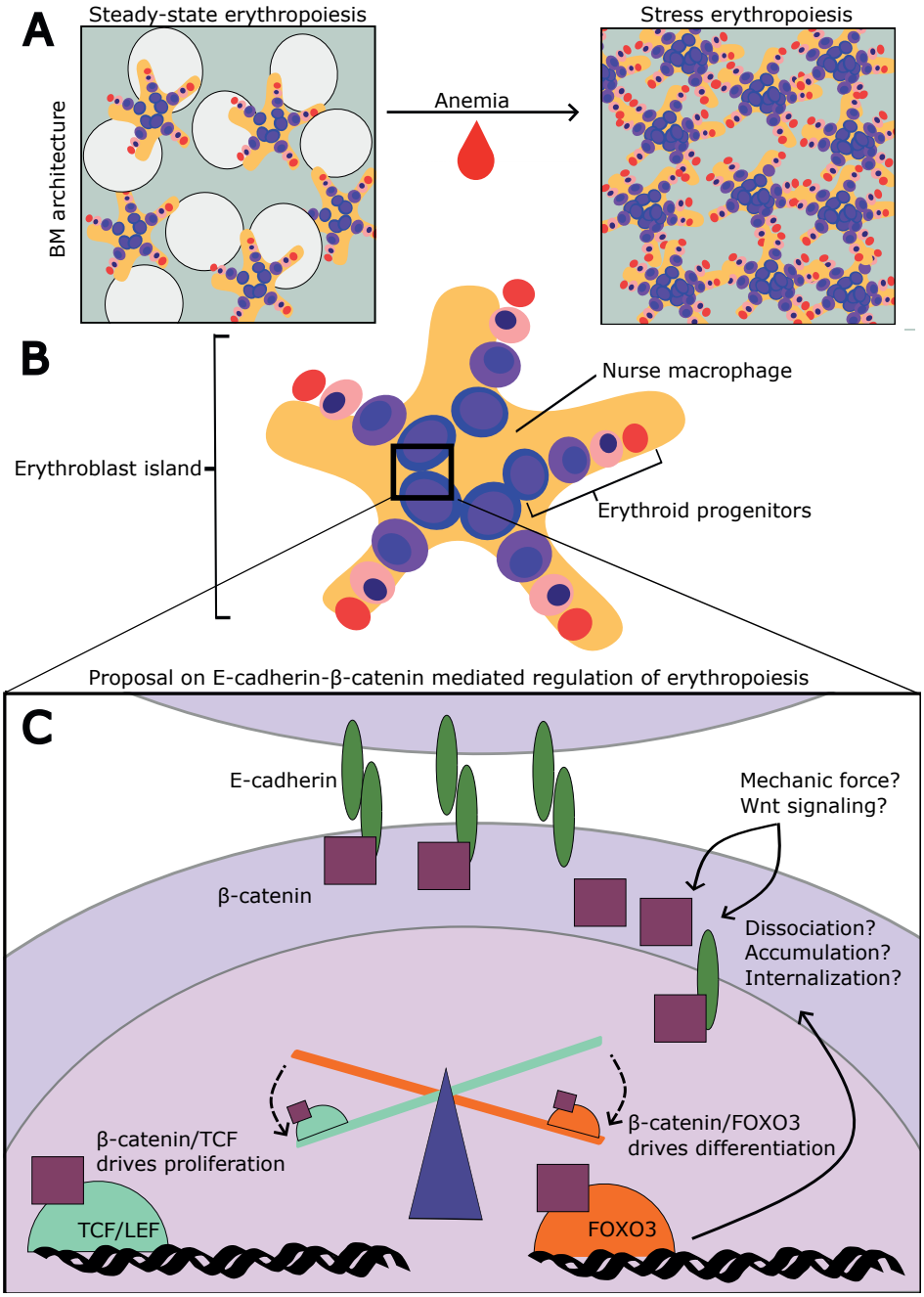

Figure 5. Schematic overview of proposed regulatory mechanism of E-cadherin/β-catenin on erythroid behavior. *(A) BM architectural change from steady-state adipocytic BM to hypercellular BM with increased amount of erythroblast islands to recover from anemia. (B) schematic illustration of erythroblast island consisting of a central macrophage and maturing erythroid progenitors. (C) proposed mechanisms of E-cadherin and β-catenin regulating erythropoiesis.*

The marriage of E-cadherin and β-catenin in erythropoiesis: a proposal

In this thesis, we reveal both E-cadherin and β-catenin protein expression in rat erythroblasts *in vivo* to be upregulated during stress erythropoiesis, suggesting a potential role for them in restoring red blood cell counts. Interestingly, corresponding with Zhang et al (2019) (37) we see a decrease of adipocytes in anemic BM. As a well-known transducer of mechanic forces, E-cadherin in erythroblasts would be the designated candidate to respond to this change in bone marrow structure. E-cadherin would facilitate erythroid progenitors to either proliferate in the Pro-erythroblast stage, or accelerate terminal differentiation in later stages. In Pro-erythroblast stage E-cadherin can sense mechanic forces created by the shrinking adipocytes that thereby decrease cell density of the hematopoietic compartment and thereby induce cell proliferation (similar to epithelial processes as shown by Tenbaum et al., or Donker et al., 2022 in MDCK cells (21,38)) or by β-catenin translocation upon E-cadherin relaxation or endocytosis in combination with Src activation, thereby inducing pro-erythroblast proliferation. From the basophilic erythroblast stage, FOXO expression increases. As β-catenin has the potential to associate with FOXO3 and enhance transcription of FOXO target genes, it would be interesting to investigate if β-catenin potentiates FOXO3 signaling during terminal differentiation, and if this association increases during stress erythropoiesis. Alternatively, during the decrease of the adipocytes, E-cadherin and β-catenin possibly facilitate PIEZO1-mediated Calcium influx, enhancing Stat5, ERK and P38 phosphorylation.

The mechanisms described above do not exclude one other but exist alongside each other to form a balance and likely act in a context-dependent fashion.

Clinical relevance of E-cadherin in hematopoietic malignancies

Little is known about the role of E-cadherin in hematopoietic malignancies. During the past decades, only a handful of seemingly contradictive data were published on both E-cadherin expression and suppression in malignant hematopoiesis. On the one hand, several other groups report that E-cadherin (together with CD117 and CD34) can be used a marker to distinguish erythroid from myeloid blasts within leukemic and myelodysplastic BM (39). Additionally, multiple research groups observe positive E-cadherin membrane staining in BM from of patients with pure erythroid leukemia (39–43). These results contrast with the findings of Acs and LiVolsi stating that E-cadherin is expressed only on cell membranes of healthy erythroid precursors, but not erythroid leukemic cells. Interestingly, both Acs and LiVolsi. (2001) (44) and Ohgami et al. (2014) (39) report E-cadherin staining the cytoplasm of erythroid leukemia cells. This observation was interpreted as incomplete processing or a higher protein turnover. Discrepancies between

E-cadherin mRNA and protein expression and localization were speculated to be caused by technical differences. However, they can additionally be explained by the expression of different E-cadherin isoforms, which have been reported to be involved in motility and signaling in other types of cancer (45–49).

Strikingly, the *CDH1* locus encoding E-cadherin has been reported to be frequently silenced by promoter hypermethylation in other subtypes of acute myeloid leukemia (AML) (50–52). Moreover, low *CDH1* expression and promoter hypermethylation in AML have been associated with poor prognosis, perhaps by acquirement of metastatic traits. However, mechanisms by which *CDH1* gene silencing may affect AML development and clinical outcome have not been investigated in these studies (53,54).

Interestingly, the publicly available database Bloodspot reveals an increased mRNA expression of *CDH1* in BM of myeloid dysplastic syndrome (MDS) patients as compared to healthy BM. However, they do not specifically analyze E-cadherin expression within hematopoietic lineages. Additionally, these data include all different types of MDS and AML in 1 category, while in the clinic, multiple subtypes can be defined. It would be interesting to investigate how *CDH1* expression is distributed in different subtypes of disease. Moreover, E-cadherin expression may be altered in response to hematopoietic malignant development due to immune adaptation, as can be induced by immunosuppressive interleukin 10 (IL10). Interestingly, IL10 has been reported to enhance the adhesive capacity of the AML cells to BM-derived mesenchymal stromal cells *in vitro*, in an E-cadherin-dependent fashion. E-cadherin expression was observed in a variety of primary monocytic AML cases and AML cell lines. Moreover, as a consequence of IL10 signaling, AML cells showed elevated adhesion and engraftment in mouse BM. Thereby they suggest that E-cadherin-mediated adhesion in the BM microenvironment is required for engraftment *in vivo* (55). Like in epithelial tumors, the studies listed here altogether do not provide an unambiguous overview of the exact role of E-cadherin in hematologic malignancies. However, they do demonstrate the complexity of the up-and-downstream regulation of E-cadherin and ultimately its control on hematopoiesis.

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