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Linking hematopoietic regeneration to developmental signaling pathways

A story of BMP and Wnt

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Following acute injuries to the blood system, such as chemotherapy, hematopoietic stem cells (HSCs) are activated to repair the damaged tissue.[1] Regeneration requires the rapid expansion of HSCs followed by differentiation of these cells into mature lineages. This process is mediated by crosstalk between cell intrinsic factors and external cues from the microenvironment. Developmental signal transduction pathways, such as BMP and Wnt, are often reactivated during regeneration. The ultimate effectors of BMP and Wnt signaling pathways are SMAD and TCF/LEF transcription factors, respectively.[2,3] The role of these pathways in hematopoietic regeneration and the underlying transcriptional mechanism for this function were explored.[4]

To test the hypothesis that the BMP and Wnt pathways are involved in blood regeneration, hematopoietic recovery following irradiation-induced injury in adult zebrafish was assessed. Stimulation of the pathways elevated the number of hematopoietic progenitors, whereas inhibition abrogated recovery. Induction of BMP or Wnt in zebrafish marrow cells after irradiation led to increased gene expression of key hematopoietic genes, suggesting that regulation of blood genes may be important for BMP and Wnt effects during regeneration.

These studies indicated that BMP and Wnt pathways influence transcription of blood genes but did not demonstrate if the effect is due to direct binding of BMP or Wnt transcription factors to these genes. To identify direct BMP and Wnt targets in hematopoietic cells, chromatin immunoprecipitation followed by sequencing (ChIP-Seq) for SMAD1, a BMP transcription factor, and TCF7L2, a Wnt transcription factor, in a human erythroleukemic cell line was performed in an erythroleukemia cell line. Surprisingly, most of the bound genes identified play a role in erythropoiesis. DNA motif analysis showed that SMAD- and TCF-bound regions were enriched in GATA motifs. GATA1 and GATA2 are master lineage regulators important for erythroid and progenitor cell fates. ChIP-seq for GATA1 and GATA2 confirmed that SMAD1 and TCF7L2 co-localize with these lineage-restricted transcription factors on blood cell-specific genes. Performing ChIP-Seq for SMAD1 and TCF7L2 in a different cellular environment tested the broader application of this mechanism. In a monocytic cell line, SMAD1 and TCF7L2 are mostly absent from red blood cell genes; instead, they are bound on white blood cell genes. The signaling factors bound adjacent to C/EBPα, a lineage regulator of the myeloid fate. These data show that signaling factors co-localize with different lineage factors in each hematopoietic cell type.

To determine the order of recruitment between the signaling or lineage transcription factors, the genomic localization of SMAD1 before and after induced expression of a lineage factor in two settings was evaluated. The first system is based on G1E Gata1-null cells, which are blocked at the proerythroblast stage. G1ER cells are derived from G1E cells containing an estradiol-inducible Gata1 that restores normal erythroid differentiation.[5] In erythroid progenitors, Gata2 is bound on progenitor and erythroid genes but is replaced by Gata1 on erythroid genes as the cells differentiate. In G1E cells, Smad1 localized with Gata2 on progenitor genes. Overexpression of Gata1 induced a loss of Smad1 binding on progenitor genes, while Smad1 is retained on erythroid genes with Gata1. Next, SMAD1 localization was assessed in an erythroid environment when a myeloid transcription factor (C/EBPα) was overexpressed.[6] SMAD1 still occupied many erythroid genes but now also bound myeloid targets together with C/EBPα. These results show that the dominantly expressed master regulator directs the genomic location of signaling factors to genes that maintain a cell's identity.

SMAD1 binding was also tested in a primary cell system for hematopoietic differentiation. Human $CD34^+$ hematopoietic progenitors can be expanded ex vivo and easily differentiated towards the erythroid fate. Similar to the G1E/G1ER results, SMAD1 bound progenitor genes with GATA2 in progenitor cells and erythroid genes with GATA1 in erythroid cells.

These data indicate that BMP- and Wnt-directed transcription factors selectively interact with a few master transcriptional regulators in each cell type and regulate cellular identity gene programs (**Fig. 1**). Recent genome-wide data for other signaling pathways, such as TGFβ,[10] Notch[7,8] and NFκB,[9] suggest that coordination of signaling and lineage regulators is a prevalent mechanism underlying many signal transduction cascades. Combined, these studies support a simple and universal model that explains how signaling pathways can have distinct effects in multiple cell types.

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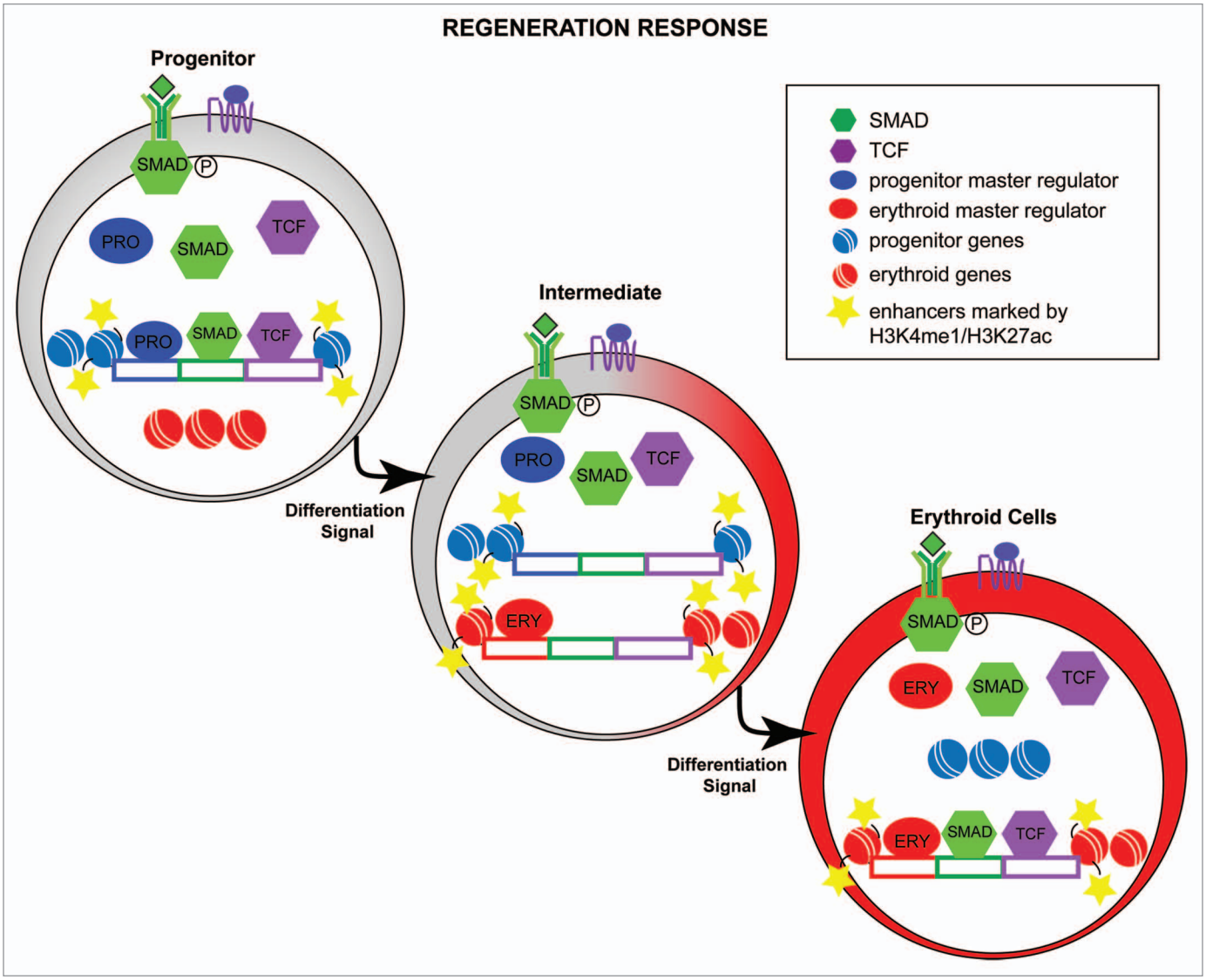

Figure 1. Regeneration response.

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