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Opposing Role, Depending on the Stage, of PU.1 during Erythroid Differentiation

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PU.1 is a member of the Ezb transformation-specific sequence family of transcription factors and is expressed mainly in granulocytic, monocytic and B-lymphoid cells [1]. The downregulation of PU.1 was reported to play a role in the pathogenesis of various hematological malignancies, including Acute Myeloid Leukemia (AML) [2], multiple myeloma [3] and Myelodysplastic Syndrome (MDS) [4]. PU.1 is also normally present in immature erythroid cells [5], and several reports have indicated that their downregulation is required for erythroid terminal differentiation [6-9].

Constitutive upregulation of PU.1 is believed to be the main cause for a blockade in the differentiation process of Murine Erythroleukemia (MEL) cells [6-9]. However, several findings [10-12] indicate a requirement for PU.1 expression for erythroid differentiation. Back et al. [10] have reported an important study. They produced a line of PU.1 deficient mice carrying a green fluorescent protein reporter at this locus. They revealed that, PU.1 deficient fetal erythroid progenitors lose their self-renewal capacity and undergo proliferation arrest, premature differentiation and apoptosis [10]. A recent study by Wantakal et al. [11] demonstrated that PU.1 regulates an extensive network of genes that constitute major pathways for controlling the growth and survival of immature erythroid cells. They further revealed that fetal liver erythroid progenitors, the earliest erythroid-committed cells, are dramatically reduced *in vivo* in mice with low PU.1 expression [11].

The use of DNA Methyltransferase (DNMT) inhibitors in MDS, AML, Chronic Myeloid Leukemia (CML) and sickle cell anemia is becoming an effective options for these diseases [12]. Recently, my research group examined whether the effects of DNMT inhibitor, 5-aza 2'-deoxycytidine (5-azadc), are correlated with PU.1 expression in PU.1-transgenic CML derived K562 cells [13]. We demonstrated that therapeutic concentrations of 5-azadc induce erythroid differentiation of these cells, that PU.1 expression is tightly related to the effect of the agent, and that sufficient PU.1 expression accelerates erythroid differentiation and apoptosis induced by 5-azadc [13].

These reports suggest that sufficient expression of PU.1 is necessary for erythroid differentiation. One possible explanation for this discrepancy, between those of employing MEL cells, is that K562 cells express the endogenous ε-globin and γ-globin genes, but not the adult stage-specific β-globin gene, and have therefore been considered as a model for the embryonic–fetal stages of erythroid development [14,15]. Wantakal's study [11], as well as Back's *study* [10], employed fetal liver erythroid progenitors from mice, which is also analyzing the embryonic-fetal stages. On the other hand, MEL cells are considered to be a model for fetal–adult development [15], which are employed in most of the previous studies analyzing the functions of PU.1 during erythroid differentiation [6-9].

Collectively, the roles of PU.1 differ during the erythroid differentiation stages. PU.1 expression inhibits erythroid differentiation in a certain stage, however, in the very immature stage, PU.1 expression is necessary for initiating erythroid differentiation. Therefore, PU.1 is a critical, versatile regulator in promoting or preventing erythroid differentiation.

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