Commentary

Stem Cell INVESTIGATION

Bringing light into gene regulation in hematopoietic stem cells by the Mediator complex

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Hematopoietic stem cells (HSCs) are the progeny of all hematopoietic cell lineages. They have on one hand the ability to self-renew and to maintain the HSC pool and on the other hand they can differentiate into all hematopoietic lineages. During lineage differentiation, they progressively lose their ability to self-renew (1). Cell intrinsic mechanisms, like precise transcription control and epigenetic modifications, have been shown to regulate the balance between self-renewal and differentiation (2). Several transcription factors (TFs) have been identified to regulate these stem cell features. However, how these TFs are regulated during development and maintenance is poorly understood yet.

The Mediator complex is a multi-protein complex that links enhancer bound TFs to specific promoter regions and thereby activates transcription.

In mammals, this complex consists of 26 subunits and this composition can change to alter its biological function. Furthermore, the specificity of the Mediator-complex is mediated by various domains that interact with different TFs (3).

One well described subunit of the Mediator complex is the cyclin-dependent kinase 8 module (CDK8 module) comprised of CDK8, CCNC, MED12 and MED13. As a kinase CDK8 has been proposed to generally regulate gene expression by phosphorylation of TFs and this has been described in several cases (4). Nevertheless, very few TF targets of CDK8 module have been identified. TF interactions in the CD8 module have been mainly linked to MED12, but how this specifically regulates transcription in particular in a cell type-specific way remains still unknown (3).

Aranda-Orgilles *et al*. investigated the role of the Mediator-complex in hematopoietic stem and progenitor cells (HSPCs) in different mouse models (5). They identified the MED12 subunit of the CDK8 Mediator complex as a key regulator of several HSC-specific genes and cell survival. The authors showed that loss of MED12 leads to rapid bone marrow aplasia due to massive reduction of HSPCs. Although MED12 is a member of the CDK8 Mediator complex, these effects appear independent from its function within the Mediator kinase module.

In addition, inactivating MED12 in hematopoietic cells leads to severe bone marrow failure and substantial loss of HSPCs and these animals die within 2 weeks after birth. This role of MED12 seems to be HSC-specific, since other cell types are not affected by MED12 inactivation. Interestingly, inactivation of MED12 in embryonic HSCs leads to reduced number of HSCs, but not as dramatic as observed in adult HSCs, pointing to a specific role of MED12 in adult HSCs. This is of particular interest, since there are several differences between fetal and adult HSCs, which need to be addressed in further studies to gain a deeper understanding of MED12 function in fetal HSC development and adult HSC maintenance (6). Furthermore,

by performing competitive transplantation assays with HSCs from different knockout strategies they showed that these effects are HS cell-intrinsic and that MED12-deficient progenitors fail completely to induce *de novo* haematopoiesis.

For example, different self-renewal potential and gene expression might, at least in part, be explained by specific regulation through the Mediator-complex. This is also reflected by the fact that in adult HSCs ablation of MED12 leads to a loss of the specific HSC gene expression signature. The majority of MED12 binding sites are located in enhancer elements and regulate transcriptional activation as well as repression. Deletion of MED12 leads to a severe change in H3K27Ac in enhancer elements.

Interestingly, MED12 directly interacts with the histone acetyl transferase (HAT) p300 and deletion of MED12 affects p300 recruitment and leads to a severe loss of H3K27Ac at enhancers of HSC genes.

The authors demonstrated that the Mediator-complex fulfils a specific function in HSCs, which is different from the function observed in other cell types and tissues. The authors convincingly demonstrate that MED12 is a key factor in regulation of HSC-specific gene expression in HSCs, which is facilitated by a recruitment of p300 to specific enhancer elements in HSCs. This is a unique feature of MED12, since deletion of other members of the CDK8-module does not have the same effect on HSC function. However, several open questions remain that need further investigation, e.g., it is not clear how MED12 affects more down-stream progenitors of the hematopoietic system and other cell types. It would also be of interest to identify molecular mechanisms that regulate the specific recruitment of MED12 to its enhancer elements in HSCs and other cell types. In this context, it might be also worth analysing how post-translational modifications might influence MED12 function. Uncovering molecular mechanisms underlying the recruitment of MED12 to enhancer elements in developing cells and under malignant conditions might also contribute to understand disease development. Another question is how this complex is involved in the regulation of gene expression after a challenge like DNA-damage or infection, since recent findings show that HSC can respond to stress by altered gene-expression (7,8).

These findings are of great interest in targeting the Mediator-complex in cancer therapy. Several gain-of-function mutations have been described that are associated with leukemias and lymphomas (9,10). To target the MED12 subunit and its interaction with p300 in leukemic stem cells might be a promising approach. Moreover, it might be interesting to down-regulate MED12 in leukemic stem cells and other tumour cells to gain information about the role of MED12 in malignant cells. Importantly, it has been demonstrated that down-regulation of MED12 has also been linked to chemotherapy resistance in several cancers and *MED12* loss induces an epithelial-mesenchymal transition (EMT)-like phenotype. Interestingly, inhibition of TGF-β signalling pathway has been shown to restore drug responsiveness in cells with down-regulated MED12 (11).

Taken together, the findings of Aranda-Orgilles and co-workers showed a key function of the Mediator-complex in HSCs. Furthermore, they discovered a very unique way how this is maintained by the CDK-module, independent of its kinase activity. MED12 recruits the histone acetyltransferase p300 to facilitate specific histone marks. This work strongly contributes to the understanding of tissue- and context-specific regulation of the Mediator-complex.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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