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POSTER 16: Translational control in Acute Myeloid Leukemia and monocytic differentiation

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Acute myeloid leukemia (AML) is characterized by a massive proliferation and accumulation of immature myeloid cells (or blasts). We have performed RNA sequencing from both healthy donors and patient blast samples to monitor the expression of mRNA translation initiation factors during normal and pathogenic haematopoiesis. Among them, the two factors eIF4E1 and eIF4E3 attracted our attention. They belong to the eIF4E (eukaryotic translation initiation factor 4E) family of translational initiation factors that regulate cap-dependent mRNA translation. eIF4E1, a well-known factor, plays a role in survival and proliferation in both normal and cancer cells while eIF4E3 is poorly described.

eIF4E1 has been recently described as required for proper erythrocytic differentiation. Based on our and on public datasets of sorted cells, we have indeed observed higher eIF4E1 expression accompanied by a lower eIF4E3 expression in cells of the erythroid lineage. In the other hand, eIF4E3 expression is high while that of eIF4E1 is low in cells of the monocytic lineage. We have then performed an *ex vivo* differentiation assay using cord blood CD34+ stem cells, showing that eIF4E3 expression goes up while that of eIF4E1 goes down during a myeloid differentiation toward the monocytic lineage. As compared to healthy donors, eIF4E3 expression in AML patients is lower, and its relative expression level is variable, the monocytic differentiation status of leukemic blasts being correlated with higher eIF4E3 expression. Also, when established leukemic cell lines (HL60 and U937) are engaged into monocyte differentiation, eIF4E3 expression is similarly increased. In addition, the down regulation of eIF4E3 in these two cell lines by stable shRNA transduction reduces their capacity to differentiate into monocytes. Finally, a functional cap binding assay performed during

monocytic differentiation revealed that the overexpressed eIF4E3 form does interact with the mRNA cap structure to the detriment of that of eIF4E1.

These results highlight a required switch from eIF4E1- to eIF4E3-dependent mRNA translation during monocyte differentiation, suggesting that eIF4E3 may play a specific role for proper monocytic differentiation. Characterization of the eIF4E1- and eIF4E3-specific translatomes will enable to identify the mRNA selectively targeted by these factors, and a better understanding of the regulatory mechanisms in normal and pathologic haematopoiesis.