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Identifying Critical Roles for the Lamin B Receptor and Additional Nuclear Envelope Proteins in Regulating the Proliferation and Differentiation of Myeloid Progenitors

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Et al.

Title: Identifying critical roles for the lamin B receptor and additional nuclear envelope proteins in regulating the proliferation and differentiation of myeloid progenitors

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Abstract:

Neutrophils are blood phagocytes that contain lobulated nuclei, development of which depend on the expression of an inner nuclear membrane (INM) protein called the lamin B receptor (LBR). Loss of LBR expression causes not only hypolobulation of neutrophil nuclei (Pelger-Huët anomaly) but also severe developmental defects in humans (HEM/Greenberg dysplasia) and mice (ichthyosis). LBR is considered a dual function protein: the N-terminal domain contains chromatin and lamin B binding sites, whereas the C-terminal domain anchors LBR to the INM and exhibits C14 sterol reductase activity. Despite our knowledge of these two structural features of LBR, which domain supports normal development is unclear. We recently addressed this issue with regards to myelopoiesis by expressing wild-type and mutant forms of mouse Lbr in myeloid cells derived from an ichthyosis mouse. We demonstrated that expression of the Lbr sterol reductase domain alone can support nuclear morphologic maturation and is critical to both cholesterol biosynthesis and lipid-stressed proliferative responses of myeloid progenitors. In contrast, myeloid progenitors that lack the homologous C14 sterol reductase Tm7sf2 displayed normal nuclear maturation, cholesterol biosynthesis and lipid-stressed proliferation. We have now generated ichthyosis myeloid cells that express forms of Lbr with missense mutations in the sterol reductase domain known to cause HEM/Greenberg dysplasia. Our preliminary results indicate that these sterol reductase missense mutations disrupt cholesterol biosynthesis and lipid-stressed proliferation, but do not appear to affect nuclear maturation. We are also analyzing the expression patterns of Lbr and two additional nuclear envelope (NE) proteins, Lamin A/C and Sun2, during neutrophil vs. macrophage differentiation using both cell line models and *ex vivo* differentiated mouse bone marrow, and examining how overexpression of either Lamin A/C or Sun2 affects myeloid differentiation. Our studies may reveal new insight into how different NE proteins regulate the complex functions of two professional phagocytes.