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A novel role of JDP2/miR-9 Axis in developmental megakaryocytopoiesis

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Background: Thrombocytopenia, defined as a platelet count <150 x 10^9/L is common among sick infants (20-35% of infants admitted to the Neonatal Intensive Care Unit). Neonates are affected by disorders of megakaryocytopoiesis that predominantly or exclusively present during this developmental stage, including a syndrome of megakaryocytic hyperproliferation known as transient myeloproliferative disorder (TMD) and the thrombocytopenia associated with the thrombocytopenia-absent radius (TAR) syndrome. It has been hypothesized that developmental differences between neonatal and adult megakaryocytes (MKs) contribute to the vulnerability of neonates to develop severe thrombocytopenia. The regulatory mechanisms underlying these developmental differences are unclear, but we hypothesize that epigenetics may play a critical role in the regulation of developmental megakaryocytopoiesis. Epigenetics is defined as heritable changes in gene expression, i.e. the presentation of a certain phenotype, without alterations to the genetic code. Recent advancements in the rapidly evolving field of epigenetics have shown extensive reprogramming of every component of the epigenetic machinery including DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs, specifically microRNA expression.

Objective: We hypothesized that miRNAs are differentially expressed in neonatal and adult megakaryocytes and, therefore, might contribute to their phenotypic differences.

Design/Methods: We cultured human cord blood (CB-) and peripheral blood (PB-) derived $CD34^+$ cells for 14 days in the presence of thrombopoietin. At day 14, >90% of cells were megakaryocytes ($CD41^+$) as measured by flow cytometry. miRNA was prepared using the miRNeasy mini kit (Qiagen) and expression analysis of 88 miRNAs was performed using a quantitative PCR-based array kit (SA Biosciences). Web-based computational approaches (TargetScan, PicTar and MiRanda) are used for putative target prediction.

Results: All samples (n=3 per group) expressed detectable amounts of all 88 screened miRNAs involved in stem cell development. Our studies revealed that miR-9 exhibited the largest developmental difference, being expressed at levels 22-fold higher in neonatal compared to adult MKs. To explain the potential roles of miR-9 in megakaryocyte development, we predicted the targets of miR-9 via the algorithms: TargetScan, PicTar, and miRanda and Jun dimerization protein 2 (JDP2) was found to be a predicted target by bioinformatic analysis. JDP2, a member of the AP-1 family of the basic leucine zipper transcription factors, is involved in cellular senescence, chromatin remodulation and proliferation. JDP2 is also involved in senescence, cell cycle arrest and cell differentiation processes, such as differentiation of skeletal muscle cells, osteoclasts and in stress response to ultraviolet irradiation. Various studies suggest that JDP2 has a dual role in malignant transformation. JDP2 is one of the candidate oncoproteins that collaborate in the oncogenesis associated with the loss of p27 as the result of insertional mutation. Serial analysis of gene expression identified increased levels of JDP2 in a number of cancers including prostate, kidney, liver and skeletal muscle. Our studies need further elucidation to prove the role of JDP2 in developmental megakaryocytopoiesis.

Conclusions: Our results indicate that neonatal and adult MKs has different miRNA expression profiles, which likely modulate critical regulators of MK development. JDP2 was found to be a predicted target by bioinformatics of miR-9 being upregulated-22 fold in neonates. This study suggests that JDP2 expression may play a critical role in megakaryocyte development by potentiating the compensatory proliferative response. The biological role of JDP2 in megakaryocytes, however, is unknown. We anticipate that JDP2 play major role in megakaryocyte development and differentiation. Characterizing miR-9/JDP2 will help in defining main pathways involved in developmental megakaryocytopoiesis and give a better understanding of neonatal MK disorders and enhance our understanding of MK biology as a whole. In addition, this may provide new mechanistic insights and therapeutic targets for adult hematopoietic disorders potentially associated with re-activation of fetal pathways (i.e. myeloproliferative disorders). This in turn will be useful in developing biomarker to use as a diagnostic tool.

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