St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Marta Derecka, PhD
Assistant Member
Experimental Hematology
MS 341, Room D3007A
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105-3678
marta.derecka@stjude.org
Phone: (901) 595-7232

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WES Leukemia Research Foundation Research Grant Final Report

I am very grateful to the When Everyone Survives (WES) Leukemia Research Foundation for its generous support provided to my laboratory for the project entitled "Targeting preleukemic onco-niche."

Crosstalk between hematopoietic cells and bone marrow (BM) microenvironment is crucial for the bone marrow homeostasis. However, in most blood malignancies neoplastic blood cells corrupt BM microenvironment creating an onco-niche, which confers a competitive advantage to the malignant clones, at the expense of healthy cells, and facilitates disease progression. Therefore, targeting the onco-niche represents a promising therapeutic strategy for blood malignancies. However, the mechanisms underlying onco-niche formation remain unexplored. Our project addresses this knowledge gap.

Myelofibrosis (MF) is a premalignant condition and one of the best examples of BM niche remodeling where mutant blood cells alter BM stromal cells and create highly inflamed and fibrotic onco-niche, which renders the BM a hostile environment for normal hematopoiesis. Consequently, patients suffer from fatal BM failure or transform to untreatable Acute Myeloid Leukemia (AML). Thus, new targets and therapeutic approaches are absolutely required. Our studies identified the transcription factor EBF1 and its target gene ITGB8 as key regulators of BM niche function during myelofibrosis. Animals with BM niche lacking EBF1 show reduced MF development. Moreover, the mice transplanted with MF causing MPL^{W515L} mutant cells and treated with ITGB8 neutralizing antibodies showed significantly decreased BM fibrosis and reduced expansion of mutant cells in the BM, peripheral blood and spleen compared to the controls. ITGB8 inhibition results also in decreased level of multiple pro-inflammatory cytokines that are normally upregulated in MF patients and mouse models. To confirm that the therapeutic benefits observed using ITGB8 neutralizing antibodies are due to targeting the onco-niche, we generated mice that lack ITGB8 only in their BM stromal cells. Indeed, similarly to animals treated with ITGB8 neutralizing antibodies, the animals with niche-specific Itgb8 deletion transplanted with MPL^{W515L} mutant cells exhibited reduced BM fibrosis and significantly decreased frequency of mutant cells in the BM and peripheral blood. Furthermore, we performed the co-cultures of human BM stromal cells with hematopoietic progenitors from MF patients in the presence of ITGB8 neutralizing antibodies and confirmed decreased expression of fibrotic markers by the stroma cells validating the results obtained from mouse models. In summary, our studies uncovered new mechanisms underlying fibrotic remodeling of BM in premalignant conditions and identified EBF1-ITGB8 axis as novel therapeutic target in myelofibrosis.

The support from WES Foundation allowed us to obtain critical preliminary results that were an important part of the NIH R01 application submitted recently. We hope that our work on preleukemic BM niche will advance treatments in blood malignancies in the future.

Sincerely,

Derecka

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