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Epigenetically Altered Diabetic Wound Plasmacytoid Dendritic Cells Direct Wound CD4 T-cells toward a Th17 Phenotype

Christopher O. Audu,1 Sonya Wolf,2 William Melvin,3 Frank Davis,4 Sriganesh Sharma,1 Kevin Mangum,1 Emily Barrett,1 Amrita Joshi,1 Andrea T. Obi,1 Katherine A. Gallagher,1 University of Michigan, Ann Arbor, MI; 2University of Michigan, Northville, MI

Background: Plasmacytoid dendritic cells (pDCs) are first responders to tissue damage and interact with wound CD4 T cells to orchestrate tissue repair. In diabetes, the role of pDCs and their subsequent influence on wound CD4 T cells and inflammation during tissue repair is unknown.

Methods: Using human diabetic wound single cell sequencing, we identified that human wound CD4 T cells are primarily the Th17 phenotype. Thus, we hypothesized that pDCs in the wounds may regulate this inflammatory T-cell phenotype, contributing to chronic inflammation. Although pDCs exist in low numbers in the wounds, we isolated wound pDCs from diabetic and control mice and examined them for inflammatory cytokine expression.

Results: We found that diabetic pDC produced significantly more IL6 (among other inflammatory cytokines) compared with controls. This is important as interleukin (IL)6 has been shown to skew CD4 T cells toward a Th17 phenotype in tissues. Upon co-culture of diabetic pDCs with naive CD4 T-cells, a significant increase in Th17 cells was observed by intracellular flow cytometry analysis. To examine the increased IL6 from diabetic pDCs, we isolated diabetic and control pDCs and performed an epigenetic superarray. We identified that histone demethylase Jarid1C was significantly decreased in diabetic pDCs compared with controls. We then isolated diabetic pDCs and performed a chromatin immunoprecipitation analysis on the IL6 nuclear factor-κB binding sites in the promoter and identified an increase in trimethylated lysine 4 on histone 3, a marker regulated by Jarid1C and consistent with increased transcription of IL6.

Conclusions: Taken together, these data suggest that, in diabetes, pDCs are epigenetically altered to produce increased IL6 and contribute to increased Th17 and inflammation in diabetic wounds.


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Periadventitial Lysyl Oxidase Inhibition Using Electrospun Nanofibers Improves Arteriovenous Fistula Maturation

Brandon C. Applewhite,1 Yuntao Wei,1 Fotios M. Andreopoulos.2 Laisel Martinez, Roberto J. Vazquez-Padron.2 University of Miami, Miami, FL; 2University of Miami, Coral Cables, FL

Background: Arteriovenous fistula (AVF) nonmaturation is associated with postoperative fibrosis and an increase in lysyl oxidase expression. The purpose of this study was to determine whether unidirectional periadventitial delivery of β-amino-prionitrile (BAPN) using bilayer poly lactic-co-glycolic acid nanofiber scaffolds is a feasible approach to reduce AVF fibrosis and encourage adaptive vascular remodeling.

Methods: AVFs were created in 30 Sprague Dawley rats (200-350 g) of both sexes by an end-to-side anastomosis of the epigastric vein to the femoral artery. BAPN-loaded (b-BAPN) (n = 10) or vehicle (b-BEH) (n = 10) scaffolds (5 mm x 5 mm) were wrapped around the juxta-anastomotic zone of the epigastric vein immediately after anastomosis. AVFs without treatment were used as an additional control (n = 10). Changes in lumen diameter were followed-up weekly using ultrasound examinations. Flow was calculated using the pulse wave velocity and lumen diameter. AVFs were collected at 21 days for histomorphometric analysis and to assess fibrosis.

Results: b-BAPN significantly increased dilation of AVFs at day 14 (185.9%) compared with b-BEH (135.8%; P = .0006) and control AVFs (115.6%; P < .0001). The treatment (214.2%) had a significant difference compared with b-BEH (155.8%; P < .0001) and AVF controls (122.8%; P < .0001) at day 21 as well. In addition, blood flow was significantly enhanced in the treatment group (38.13 mL/min versus b-BEH [9.43 mL/min; P = .0002] and AVF controls [16.11 mL/min; P < .0001]). Histomorphometric analysis confirmed the ultrasound findings. Treatment with b-BAPN significantly increased lumen area compared with control AVFs (354.12 mm² vs 95.580 mm²; P = .0048). While there was no difference in intimal growth (P = .5460), b-BAPN significantly reduced luminal occlusion with respect to control AVFs (0.061 vs 0.2067; P = .0002). Finally, b-BAPN (43.44%) significantly reduced the fibrosis percent area compared with b-BEH (72.14%; P = .016) and control AVFs (74.5%; P = .0007).

Conclusions: Periadventitial lysyl oxidase inhibition prevents AVF postoperative fibrosis and promotes adaptive vascular remodeling.