NOVEL THERAPEUTIC APPROACH TO PREVENT MATURATION FAILURE OF ARTERIOVENOUS FISTULA

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An autologous arteriovenous fistula (AVF) is the preferred vascular access in hemodialysis; however, a high rate of maturation failure that is characterized by inadequate dilation and inadequate blood flow in the outflow vein renders the fistula not useful for hemodialysis after initial adequate blood flow after AVF creation. Inflammation, neointimal hyperplasia and failure of outward remodeling are the major causes of AVF maturation failure accounting for 60% of all the newly created AVF. Proliferation, migration, and phenotypic changes of vascular smooth muscle cells and extracellular remodeling due to increased matrix metalloproteinases play a crucial role in the pathogenesis. In this study, AVF was created in Yucatan miniswine by anastomosis of femoral artery and femoral vein. TLR-4-mediated inflammation was examined using its inhibitor, TAK-242, to investigate the effect on vessel remodeling and AVF maturation. The expression level of several proteins, vein outward remodeling, artery and vein diameter, blood flow through the fistula and femoral artery and vein, and vessel thickness involved in AVF were assessed by ultrasound, angiography, optical coherence tomography, immunohistochemistry, and histomorphometry. The TLR-4 inhibition with TAK-242 attenuated inflammation, decreased neointimal hyperplasia, and favored femoral artery and vein remodeling; the features favoring AVF maturation. The bulk RNA sequencing and the Ingenuity Pathway Analysis revealed changes in many transcription factors and microRNAs that are involved in angiogenesis, vascular smooth muscle cell proliferation, migration, and phenotypic changes, endothelial cell proliferation and function, oxidative stress, vessel remodeling, immune responses, and inflammation. These findings suggest that not only the luminal factors but also the mediators from surrounding structures like muscles mediate vascular cuffing contributing to vessel thrombosis and AVF maturation failure via early thrombosis. Therefore, targeting the key regulatory sites, including TLR4, may have therapeutic potential.

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