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Dietary Interventions Modulate Immune Metabolism and Fibroblast-to-Myofibroblast Conversion to Attenuate Kidney Fibrosis

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Objectives : Kidney fibrosis, a hallmark of chronic kidney disease (CKD), is driven by the activation of fibroblasts into myofibroblasts, leading to excessive extracellular matrix deposition and organ dysfunction. Immune cells, particularly T cells, play a critical role in this process through their influence on the microenvironment and cellular metabolism. This study investigates the impact of dietary interventions on immune metabolism, fibroblast-to-myofibroblast conversion, and the development of kidney fibrosis.
Methods : A murine model of renal fibrosis was established using unilateral ureteral obstruction (UUO). Mice were assigned to either a control diet (n=6) or a diet incorporating specific dietary interventions (n=6), including calorie restriction (CR) and a high-fiber diet, for four weeks. Renal tissues were collected and analyzed for fibrosis using Masson's trichrome staining. The metabolic profile of infiltrating immune cells was assessed using Seahorse XF analysis, while the activation and differentiation of fibroblasts into myofibroblasts were evaluated by Real Time-PCR (COL6A1, COL4A1, COL1A1, COL8A1, COL3A1, ITGA, HSPG2, ACTA2, CTGF ,FN1, TGFB1, MMP 9, MMP 10, MMP2, TIMP1), Immunohistochemistry and Immunoblotting for α-SMA, type I collagen, , α-SMA and fibronectin.
Results : Mice subjected to dietary interventions, particularly CR and high-fiber diets, exhibited a significant reduction in renal fibrosis compared to controls ($p<0.001$), with decreased collagen deposition ($p<0.001$) and reduced expression of myofibroblast markers ($p<0.001$). These interventions led to a shift in immune cell metabolism, characterized by reduced glycolysis and increased oxidative phosphorylation (87% vs 29%, $P<0.0001$), which correlated with a decrease in pro-inflammatory cytokine production (IFN gamma, IL-17A, $p<0.001$). Additionally, dietary interventions inhibited the conversion of fibroblasts to myofibroblasts, depicted by down regulation of evidenced by lower α-SMA expression ($p<0.001$).
Conclusions : These findings suggest that targeting metabolic pathways through dietary strategies could serve as a novel, non-pharmacological approach to preventing or treating renal fibrosis in CKD.