The Role of Gut Microbiota in Neointimal Hyperplasia After Vascular Injury

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Introduction: There is increasing evidence that the gut microbiome regulates susceptibility to certain diseases through systemic effects of microbe-derived metabolites. Sodium butyrate is a short chain fatty acid that is produced by microbial fermentation of dietary fiber and has known anti-proliferative and anti-migratory effects on vascular smooth muscle cells (VSMC). We hypothesized that perturbation of the gut microbiome with antibiotics would alter systemic serum butyrate concentration and impact neointimal hyperplasia after vascular injury.

Methods: 10-wk-old male Lewis Inbred rats were treated with vancomycin (“vanco”) in the drinking water (0.5mg/mL) ± sodium butyrate (“buty”, 0.5mg/mL) for 4 wks prior to undergoing left carotid angioplasty. Serum butyrate concentration was assessed by gas chromatography. Gut microbial composition was assessed by 16S rRNA gene surveys of fecal samples. VSMC were treated with butyrate (0-5mM) and assessed for cell proliferation using cell counting, cell migration using a transwell assay, and cell cycle progression using FACS.

Results: Post-angioplasty carotid arteries from vanco-treated rats developed 38% more neointima than controls (0.032±0.004mm2 vs. 0.044±0.003 mm2, P=0.02), but vanco+buty treatment prevented this increase in intimal area (0.035±0.004 mm2, P=.62 vs. control). Analysis of gut microbial communities revealed unique shifts in bacterial clustering by treatment group, which correlated with changes in serum butyrate levels, with the lowest butyrate level detected in vanco-treated rats (0.54±0.1 μmol/mL control, 0.017±0.1 μmol/mL vanco, 0.45±0.1 μmol/mL vanco+buty, P=.008). In vitro, butyrate treatment inhibited VSMC proliferation at 24-48 hrs in a dose-dependent manner, which correlated with induction of G0/G1 cell cycle arrest (P=.001) and a reduction in chemotaxis (P=.03).

Conclusions: Oral vancomycin treatment induced a shift in the gut microbial community that was associated with decreased serum butyrate levels and increased neointimal hyperplasia, both of which were reversed by oral butyrate supplementation. These data demonstrate proof-of-concept that there is a correlation between gut microbial dysbiosis and susceptibility to neointimal hyperplasia.

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