Results: The myocyte fusion index in PAD (n = 8, proximal and distal) MuSC was one-half that of controls ($P < .03$; n = 4, analysis of variance). Pressure indices confirmed a perfusion gradient along the limb. The number of differentially expressed genes among PAD and controls are shown (Fig). MuSC in PAD vs controls had significant differences in canonical pathway expression including mitotic roles of polo-like kinase (z score = 7.5 distal, 13.5 proximal), and G2/M DNA damage checkpoint regulation (z score = 6.5 distal, 9.0 proximal). Genetic expression did not differ within PAD muscle as a function of perfusion.

Conclusions: Compared with controls, MuSC in PAD have significant differences in gene expression, even in better perfused muscle. Pathways affected included those essential to mitosis and DNA damage repair, both critical to cell survival and differentiation. These findings suggest perfusion-independent PAD effects on muscle that persist despite optimization. Adjunctive treatments beyond reperfusion may be required to mitigate muscle damage from arterial insufficiency.

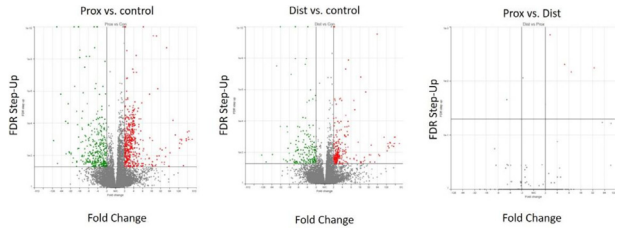

Fig. Differential gene expression among groups is shown. *Red*, Upregulate; *green*, downregulated; *gray*, no change.

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Fluvastatin and Vascular Endothelial Growth Factor-Containing Resins Promote Angiogenesis and Arteriogenesis

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Background: Select patients with critical limb ischemia who are not candidates for surgical revascularization rely on angiogenesis to ameliorate symptoms. Statin drugs and vascular endothelial growth factor (VEGF) stimulate angiogenesis. We studied whether resins used for local statin delivery to the ischemic bed would increase angiogenesis and be augmented by dual delivery with VEGF.

Methods: Functionalized hydrogel resins were loaded with fluvastatin or VEGF-165A. Matrigel or proliferation assays were performed on endothelial cells (ECs) treated with free drug, resin, or resin bound with drugs. Free or bound resins, or a combination of both resins were injected into male rat hindlimbs after femoral artery ligation. Doppler flow was measured preoperatively and on postoperative days 1, 3, 7 and 14 and compared with the contralateral uninjured leg. On day 14, the ischemic vastus and gastrocnemius muscles were stained with alpha smooth muscle actin (arteriogenesis) and CD34 (angiogenesis).

Results: In vitro, the statin release rate from resin was 10% per 24 hours; unloaded resin no EC toxicity and tubule formation was unaffected; both free and resin statin or VEGF promoted tubule formation ($P < .05$); tubule formation was the same for free statin and resin statin; resin VEGF or VEGF plus resin statin had less tubule formation compared with its respective free form ($P < .05$); and free and resin statin and VEGF equally increased EC proliferation. Doppler blood flow studies (day 14) showed that untreated control and empty resin had an 80% blood flow recovery; resin statin returned flow to preoperative levels ($P < .001$); the combination group increased blood flow more than statin alone ($P < .001$); and resin VEGF had the greatest effect increasing flow above preoperative levels ($P < .05$). Resin statin, resin VEGF, or both increased angiogenesis and arteriogenesis ($P < .05$); however, the empty resin had no effect.

Conclusions: In vitro, free fluvastatin and free VEGF were more effective than the respective resin, likely owing to slow release of the drugs from the resin. Both angiogenesis and arteriogenesis improved with VEGF or fluvastatin bound resins. Resin VEGF alone was strongest in vivo. Single dosing of resin VEGF effectively promoted angiogenesis, which may make this revascularization method more feasible clinically.

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Increased Interleukin-8 Expression in Regions of High Intraluminal Thrombus Deposition in Human Abdominal Aortic Aneurysms

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Background: Abdominal aortic aneurysms (AAA) have previously been shown to rupture at sites of high intraluminal thrombus (ILT) deposition. Neutrophil and macrophage activity have also been associated with AAA development, but their precise roles are not known. The purpose of this study was to evaluate the possible differential expression of macrophage chemoattractant protein 1 (MCP1), macrophage-derived protease (CD68), neutrophil chemoattractant factor (IL8), and neutrophil collagenase (MMP8) in regions of human AAA with high and low ILT deposition. We hypothesized that higher ILT deposition would be associated with increased MCP1, CD68, IL8, and MMP8 levels compared with low ILT deposition and control aorta.

Methods: Full-thickness AAA samples were collected from 15 participants using a systematic map. For each case, samples were taken from regions with low or high ILT. Infrarenal aortic control tissue was harvested from six participants undergoing aortobifemoral bypass. A cytokine array assay was performed to measure MMP-8, IL8, and MCP1. CD68 immunohistochemistry was also performed.

Results: AAA tissue had significantly higher levels of IL8 (145 pg/mg protein vs 64 pg/mg protein; $P = .044$), MMP8 (42,566 pg/mg protein vs 3740 pg/mg protein; $P = .015$), MCP1 (473 pg/mg protein vs 64 pg/mg protein; $P = .003$), and CD68 (1.770% vs 0.246%, $P < .001$) compared with control tissue (Fig). In AAA patients, the presence of ILT was associated with significantly higher levels of IL8 (185 pg/mg protein vs 99 pg/mg protein; $P = .035$), but not MMP8, MCP1, or CD68.

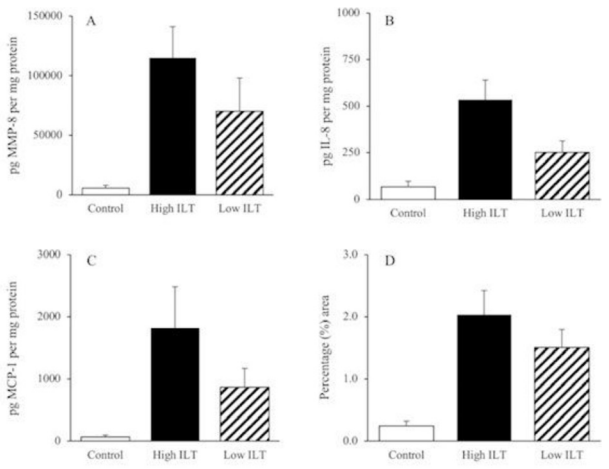

Fig. Levels of neutrophil collagenase (MMP8) **(A)**, neutrophil chemoattractant factor (IL8) **(B)**, macrophage chemoattractant protein 1 (MCP1) **(C)**, and macrophage-derived protease (CD68) **(D)** in control aortic tissue versus abdominal aortic aneurysm (AAA) tissue from arease of high intraluminal thrombus (ILT) versus areas of low ILT.