Published in final edited form as:
J Vasc Surg. 2007 June ; 45(Suppl A): A92–A98.

Cytokines and the Early Vein Graft—Strategies to Enhance Durability

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Surgical bypass via autologous vein remains an evidence-based treatment of choice for selected patients with infra-inguinal lower extremity or coronary occlusive disease. However, contemporary data shows that almost 40% of lower extremity vein bypass grafts develop occlusive lesions or fail within a year(1), and almost half of cardiac bypass patients will lose (> or = 75% stenosis) a vein graft within a year(2). Since many technical avenues for improved patency have been exhausted, the future of enhancing the durability of these reconstructions lies in a better knowledge of and interventions based on the biology of the vein graft wall.

This article will briefly review vein graft failure research to date, and then focus on the pro-inflammatory cytokine TNF-α and the early vein graft. Finally, the current status of the field will be outlined in the context of cytokine based research, and challenges and opportunities for the future discussed. Certainly a multitude of biochemicals (growth factors, cell cycle regulators, etc.) have been linked to mechanisms of vein graft failure, and the following is in no means comprehensive.

Evolution of Current Vein Graft Concepts

Vein grafts undergo a defined sequence of anatomic adaptations after placement, though not all favor long-term patency. The principal cause of failure is traditionally cited as development of neointimal hyperplasia which leads to an obliterative stenosis(3-7). Early work in the vein graft research field focused on mechanical factors(3-5;8). Like arteries, vein graft wall structure adapts to the hemodynamic environment(9;10), though there may be some subtle wall differences(5). Intimal hyperplasia has been noted to occur at vein graft areas of low flow(3), probably areas of low wall shear stress(4;8). Conversely, high flow appears to have protective effects(6;11), in association with decreased wall inflammation(12). The early 1990's also brought a recognition of the importance of circumferential wall tension on the adapting vein graft (5;13).

The 1990's saw increased recognition in vascular biology of the interplay between the inflammatory and cardiovascular systems. The arterial wall response to injury was associated with early inflammatory events including monocyte and T cell adhesion to vascular endothelial cells(14-16). Platelet activation and mural thrombus formation were also implicated in this cascade, as well as cytokine and growth factor elaboration, all leading to subsequent vascular remodeling(17) through cellular migration, proliferation, and matrix deposition(14-16;18;19). In the mid- 1990's, these paradigms began to transfer to the vein graft arena(20). Works

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specifically examined the role of inflammatory mediators in vein graft failure(10;21-24). For instance, the macrophage was identified as a pivotal cellular mediator of vein graft neointimal hyperplasia, with macrophage depletion suppressesing this process(22).

However, despite incremental progress over these decades, specific cause/effect links between hemodynamic factors → inflammatory biochemical mediators → cellular effectors → vein wall adaptations remain lacking. Thus, not surprisingly, few therapeutic agents to improve vein graft durability have been identified. Anti-platelet and anticoagulant approaches show only a modest benefit under specific circumstances (25;26). Recent trials testing edifoligide (an oligonucleotide decoy that binds to and inhibits E2F transcription factors) failed to yield substantial clinical benefit(1;2).

Pro-inflammatory Cytokines and Vein Graft Failure

Pro-inflammatory cytokines (e.g. TNF-α and IL-1β) were implicated in vein graft intimal hyperplasia almost a decade ago(10;23), though the initiating factors for their expression and the biologic implications of these inflammatory mediators in vein wall adaptations remained largely unknown. Expanding knowledge in cytokine-driven inflammatory pathways in other organ systems has led to effective methods for treating pathologies such as rheumatoid arthritis and inflammatory bowel disease(27-35), and several anti-inflammatory cytokine based pharmacologic compounds have emerged(36-38). While anti-inflammatory cytokine therapies have received recent attention as a means to abrogate primary arterial occlusive disease (39), cytokine manipulation strategies remain relatively unexplored with regards to vein graft failure.

TNF-α is a pleiotropic pro-inflammatory cytokine(40;41). Its expression is controlled at the level of both gene transcription and translation, and it can be synthesized by several cell lines relevant to vascular biology, including macrophages, T-cells, endothelial cells, fibroblasts, and smooth muscle cells(42;43). This potent pro-inflammatory cytokine is initially synthesized and processed to a transmembrane form(44). TNF-α-converting enzyme (TACE), a member of the matrix metalloproteinase superfamily, releases TNF-α from the cell surface(45;46), and as a homotrimer, the soluble TNF-α elicits responses in distal target cells(43). Since its description over three decades ago, several related ligands have been described and are grouped in a TNF superfamily of genes(47).

The tissue response to TNF-α is mediated through two distinct receptors, p55 (type 1 TNF receptor) and p75 (type 2 TNF receptor)(40;48). These receptors belong to a large TNF receptor superfamily which also includes NGFR, CD95, and Apo2(47;49;50). Most cell types co-express both TNF receptors, though expression of the two receptors appears to be differentially regulated and show tissue-specific prevalence. More importantly, the two receptors differ markedly in their intracellular structure and signaling pathways(40;43). The majority of the pro-inflammatory responses classically attributed to TNF-α appear to be mediated by p55 signaling. Studies have shown that administration of TNF-α muteins with specificity for the p55 receptor are pro-inflammatory and shock inducing, whereas p75 muteins lack any pro-inflammatory properties(51;52).

The theory for a pivotal role for TNF-α in vein graft neointima formation and the related pathologic process of atherogenesis is founded on *in vitro* cell culture studies, pathologic observations, and a limited number of *in vivo* studies. In cell culture, TNF-α augments expression of intercellular adhesion molecules in human vascular endothelial cells(53) and vascular smooth muscle cells(54), thus increasing the possibility of interactions between mononuclear cells, endothelial cells, and smooth muscle cells in neointimal lesions and atherosclerotic plaques. Additionally, TNF-α induces prostanoid synthesis, corticosteroids, and other cytokines(41), and stimulates smooth muscle cell migration(55) and proliferation after vascular injury(42). Via receptors, TNF-α signaling activates caspases leading to

apoptosis, MAP kinases and NF-kappaB(40)—intracellular mediators linked to numerous fundamental vascular processes.

Few studies have extended these *in vitro* cell culture and pathologic studies into the more complex *in vivo* vascular setting. Pathologically, TNF-α co-localizes to areas of occlusive lesions in human arteries(56) and arterialized vein grafts(23). In a rabbit heterotopic cardiac transplantation model, *in vivo* blockade of TNF-α by way of TNF soluble receptor suppressed the acute development of neointima formation by selectively reducing the vascular inflammatory reaction and accumulation of fibronectin(57). Nonetheless, the mechanisms of transplant atherosclerosis may be quite different from those of vein graft neointimal hyperplasia. Another set of *in vivo* experiments demonstrated that exogenous TNF-α causes coronary arteriosclerosis-like cellular changes in a porcine model(58).

Recent Research

For the last decade, our group has probed the role of cytokines in vascular biology. Initially, we were interested in the role of TNF-α in low shear stress induced arterial intimal hyperplasia. Using murine models and molecular approaches, we documented induction of TNF-α by acute lowering of arterial wall shear stress(59). We have also probed the role of cytokine signaling in the arterial wall response to high shear stress. It had been shown that TNF-α co-localizes to areas of active positive remodeling in response to increased wall shear stress(60). Working with collaborators, we completed experiments utilizing a novel murine model of arteriogenesis, a clinically relevant form of outward arterial remodeling in response to increased wall shear stress. The results showed that TNF-α positively modulates arteriogenesis, probably signaling via the p55 receptor(61). Recent experiments demonstrate that this process is blocked with the administration of TNF-α inhibitors(62).

Based on the above findings linking vascular wall adaptations to changes in hemodynamic environment via pro- and anti-inflammatory cytokine signaling, we hypothesized similar mechanisms in the vein graft. The vein graft is essentially an extreme example of acute hemodynamic change, coupled with a local injury response, leading to morphologic adaptations within the vascular wall. We developed and validated a bilateral jugular vein into carotid artery vein graft model with clinically relevant differential hemodynamic environments (6;63-65). In this model, unilateral reduction in carotid artery (and thus vein graft) flow is accomplished via placement of 8-0 silk suture ligatures to completely occlude the internal carotid and three of the four primary branches of the external carotid artery. Distal branch ligation results in an immediate 90% flow reduction ($p<0.001$) in the vein graft on the ligated side and 36% flow augmentation ($p=0.01$) in the contralateral vein graft. The vein grafts develop physiologically relevant levels of wall shear, and neointimal hyperplasia volume that is inversely proportional to wall shear.

To initiate studies into molecular mediators of these vein graft adaptations, quantitative real-time two-step polymerase chain reaction (RT-PCR) was performed for TNF -α, IL-1β and IL-10 on the paired high and low wall shear vein grafts in this rabbit model longitudinally. The results revealed several shear and time dependent cytokine expression signatures (Figure 1) (66;67). TNF-α induction was maximal at day one and gradually decreased over time, but was persistently elevated even four-weeks later ($p<0.001$). Low shear (associated with increased neointimal hyperplasia) resulted in significantly higher TNF-α mRNA expression ($p=0.03$). TNF-α was induced 198 and 110 fold in low and high shear vein grafts respectively by the first post-arterialization day. This elevation gradually decreased over time but was persistently elevated from baseline even four weeks later ($p<0.001$). Over the course of the study, low shear resulted in significantly higher TNF -α mRNA ($p<0.003$) vein graft wall expression.

While the general expression pattern of IL-1β expression mirrored that of TNF -α, several notable differences exist. IL-1β was induced a striking 1188- and 366- fold in low and high shear vein grafts respectively at day 1, but the return toward baseline was more rapid. Flow impacted IL-1β expression overall ($p<0.001$), though the differential was greatest at the 1 ($p=0.002$) and 3 ($p<0.0001$) day time points. Consistent with the theory that pro-inflammatory cytokine mechanisms drive downstream vein graft adaptations, these early quantitative TNF-α and IL-1β mRNA level changes were temporally distinct from the time course of later morphologic and cellular changes in the vein graft wall. High pro-inflammatory cytokine levels (as in the low flow setting) correlated positively with greater intimal hyperplasia. Via immunohistochemistry, TNF-α and IL-1β protein localize to the vein intima in the first three days after graft placement.

Finally, vein graft arterialization more slowly and modestly induced IL-10 mRNA expression. Overall this occurred independent of shear ($p=0.152$), though there was a statistically significant higher expression for high shear grafts at the 14-day time point ($p<0.001$). IL-10 is an immunosuppressive and anti-inflammatory cytokine produced by T-cells, B-cells, natural killer cells, and monocyte/macrophage cell lines(12;68). It has been shown to suppress the production of numerous inflammatory cytokines, including TNF-α(41). Conversely, TNF-α is a principal inducer of IL-10 biosynthesis(69). This acts in a negative feedback loop to suppress TNF-α production and processing.

IL-10 is believed to exert its anti-inflammatory effects on the vascular system through inhibition of leukocyte-endothelial cell interactions and inhibition of pro-inflammatory cytokine and chemokine production(12;68). In support of the hypothesis that the anti-inflammatory cytokine IL-10 downregulates vein graft neointimal hyperplasia, researchers have demonstrated an effect of IL-10 on vascular smooth muscle cell proliferation. Physiologic doses of IL-10 inhibited TNF-α and bFGF-stimulated DNA synthesis and cell proliferation (70), suggesting that endogenous IL-10 not only suppresses pro-inflammatory cytokine expression, but also may antagonize pathologic vascular remodeling induced by cytokines such as TNF-α(70).

These results(66;67) in the context of the medical literature (10;23;71-75) led our group to formulate the general hypothesis outlined in Figure 2. As an initial step to test this hypothesis, we utilized a pharmacologic approach to abrogate TNF-α signaling in the early vein graft of our validated rabbit model(66). Animals received pegylated soluble TNF-α Type I receptor (PEG sTNF-RI; Amgen) or vehicle via either short or long-term dosing. PEG sTNF-RI is a 20 kd molecule containing a homodimer of human p55 covalently linked to a polyethylene glycerol backbone(76). Molecular modification of these pegylated receptors through deletion of 1.4 intracellular domains reduces immunogenicity while having no impact on ligand binding (77). Due to a conserved sequence homology, the compound has been demonstrated to abrogate the adaptive immune response across a range of species, including rabbits(76;78). After 14-28 days, grafts were analyzed. PEG-sTNF-R1 was found in high concentrations in the serum, and localized to neointimal hyperplasia microscopically. Both high and low flow vein grafts from treated animals demonstrated similar volumes of neointimal hyperplasia compared to controls. PEG-sTNF-R1 had minimal impact on vascular wall cell turnover, as reflected by TUNEL and anti-Ki-67 assays(66).

Thus, while placement of a vein into the arterial circulation acutely upregulates TNF-α(23; 66;75) (whose expression level correlates with the degree of subsequent neointimal hyperplasia), pharmacologic interruption of this signaling pathway has no significant impact on neointimal hyperplasia or smooth muscle cell proliferation/apoptosis(66). These data suggest that early vein graft adaptations can proceed via TNF-α independent mechanisms. Recent work by other investigators, however, supports a differing conclusion. Using p55

receptor knockout animals, functional TNF-α inhibition has been shown to attenuate vein graft neointimal hyperplasia(71). Further investigation is required to elucidate these apparently contrasting observations.

Interesting comparisons can be drawn with observed challenges in application of anti-inflammatory approaches in other pathologies. Early anti-TNF-α clinical trials in acute inflammatory processes, such as sepsis, have had disappointing results(79-82) and may be attributed to an over-simplistic view of these disease processes and TNF-α mediated cytotoxicity(41). A similar situation arose in the setting of anti-TNF-α trials for heart failure (83). These experiences may have lessons for work with the vein graft. We have recently completed microarray analyses of vein graft wall in both mice and rabbits (both high and low flow)(84). The results reveal a large number of gene perturbations across multiple families of mediators. These results show that the overwhelming determinant of the wall's transcriptome is the temporal relationship to the operative graft placement—that is, the trauma of the operation itself, rather than the details (neointimal volume, etc.) of the wall adaption. Thus, it may be naive to believe that abrogation of a single mediator would have substantial lasting impact on the final morphology of the wall. Perhaps strategies that block central signaling molecules that control numerous genes for various cytokines and adhesion molecules will be effective (e.g. NF-kappaB)(85), though targets such as TNF-α seem to meet this criteria.

Future Considerations and Directions

To date several lessons have become apparent, and some considerations for future progress are summarized:

- *Single- vs Multi-agent Strategies* Narrowly focused molecular targets hold the appeal of limited unwanted side effects. However, in view of the large number of mediators implicated in the vein graft wall adaptation, pertubation of several pathways may be necessary to consistently achieve substantial and durable effect. For example, multimodality approaches stand as a mainstay of anti-neoplastic therapies. The multitude of processes involved in vein graft failure support use of such strategies, yet the rationale and safety of each component must be confirmed, and substantial investigative work will be required to define the composition of this “synergistic” cocktail.
- *Understanding the Interplay of Systems (e.g. Inflammatory, Thrombotic), including Genetic Factors* Large amounts of information (e.g. biologic and genetic) can now be rapidly acquired and analyzed via high throughput experimental and statistical techniques. Vascular biologist must embrace contemporary information management and modeling approaches to understand the interplay of these factors in vein graft failure.
- *Broadening Focus to the Entire Conduit Wall* Vein graft researchers must broaden their observations to the behavior of the entire conduit wall, not just the neointima. Adventitial events leading to fibrosis probably contribute substantially to vein graft failure(86).
- *Consideration of the Injured Host Patient* Simple harvest dramatically changes the vein wall cellular phenotype(87). Furthermore, surgical trauma globally impacts the phenotype of pivotal cells such as the leukocyte(88;89), and these effects may all biologically modulate local processes such as vein graft wall adaptations.
- *Delivery Strategies—local vs systemic* While vein grafts offer the unique situation of ability to treat the conduit wall(1;85;90), more systemic approaches may be needed in view of the extra-wall mediators (e.g. circulating cells) that participate in occlusive adaptations(91).

- *Optimization of Trial Design to Insure Gain of New Knowledge Regardless of Outcome* Animal models of vein graft disease hold substantial biologic relevance limitations, and clinical trials are expensive. While certainly breaking new ground, as designed, the PREVENT Trials(1;2) failed to generate substantial new biologic insights despite substantial work and fiscal investments. Thoughtful addition of mechanistic endpoints when feasible will insure some progress independent of human trial outcome.
- *Translation into other Arterial Occlusive Adaptations (Primary Atherosclerosis, Angioplasty Restenosis, etc)* Emerging endovascular approaches bring into question the relevance of vein graft research. However, contemporary evidence based guidelines confirm that a substantial portion of our aging population will require vein conduits for arterial revascularization. Additionally, basic biologic mechanisms delineated in the vein graft field hold a strong likelihood of relevance for other vascular responses to injury.

Summary

Understanding the cytokine mediated molecular mechanisms of vein graft arterialization may suggest clinical interventions that will alter the conduit's natural history. The field appears especially ripe for transfer of knowledge and therapeutic approaches that have evolved in the arterial system, and inflammatory mediated processes such as inflammatory bowel disease and arthritis. However, more robust research approaches such as broadening of the scope beyond focus on single mediators and neointimal hyperplasia will be necessary to reach translatable strategies to prolong human vein graft durability.

Acknowledgment

The author gratefully acknowledges the editorial assistance of Dr. Scott A. Berceli and Dr. Zhihua Jiang.

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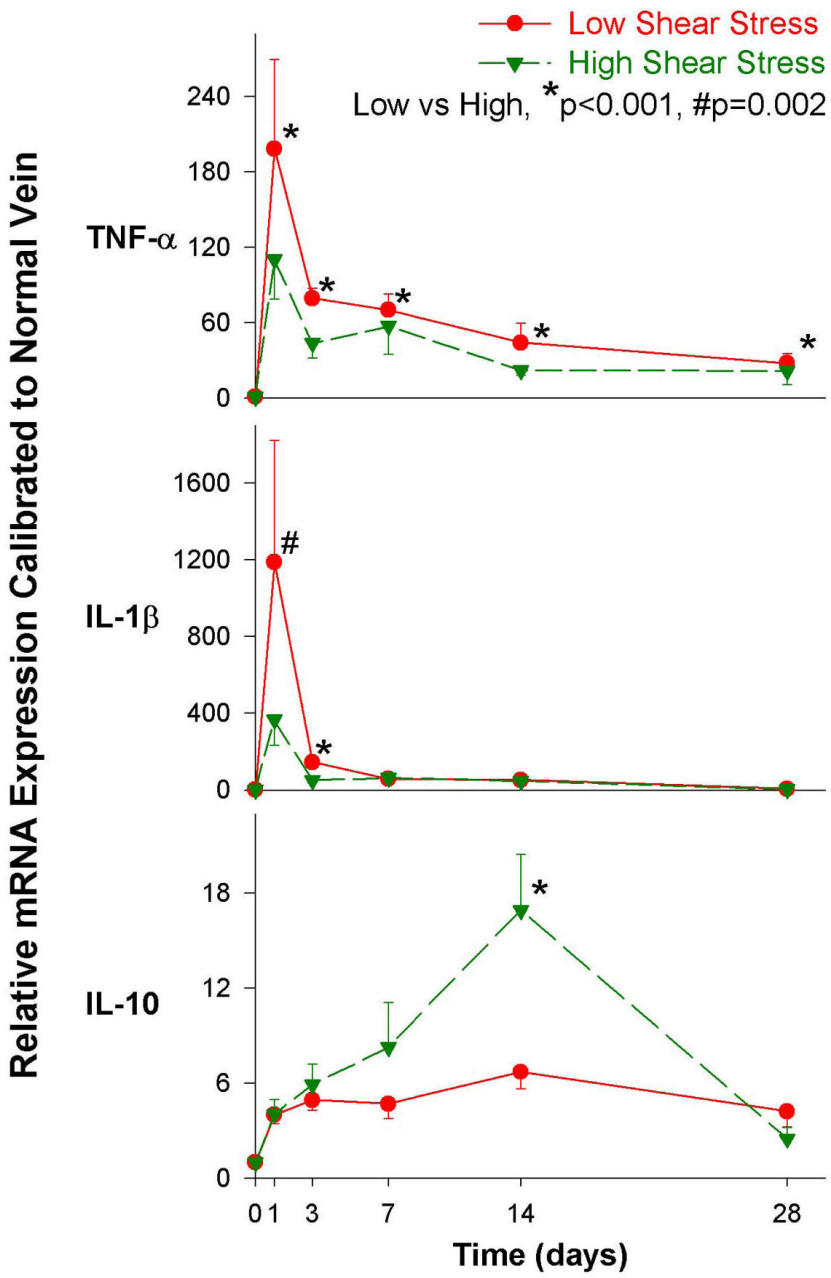

Figure 1.
Time course of cytokine mRNA expression in a rabbit bilateral vein graft model with differential shear. Data is combined from two prior *J Vasc Surg* reports(66;67).

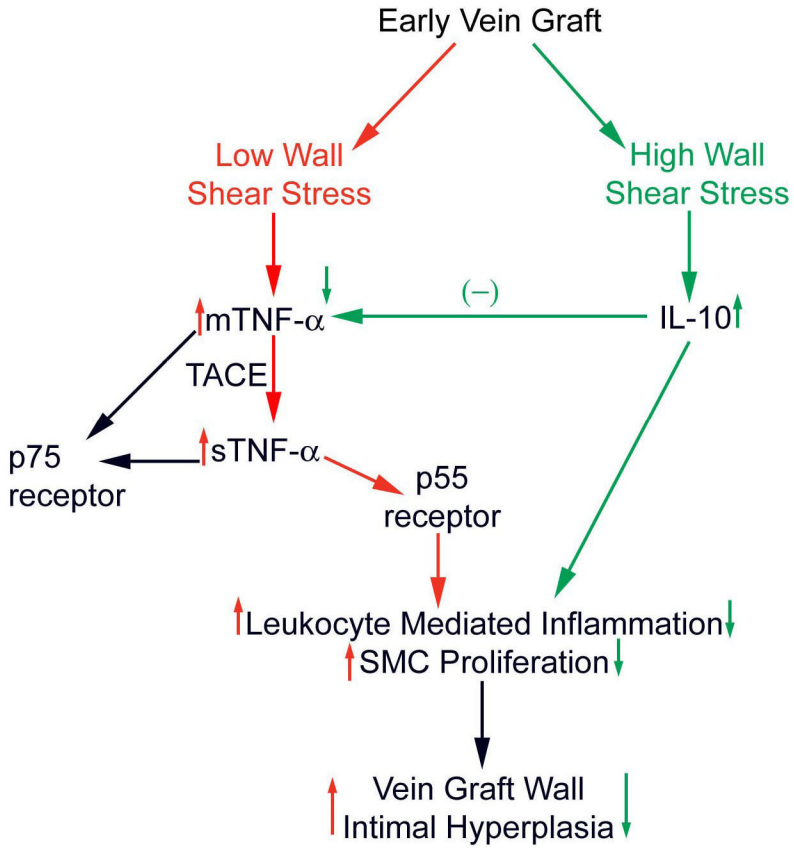

Figure 2.
Hypothetical mechanisms by which pro- and anti-inflammatory cytokines may interplay with wall shear to modulate vein graft wall adaptations.