



2009 Research Grant Program Winning Abstract

Atherosclerosis and Collagen V

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Atherosclerosis is the most prevalent pathological process leading to cardiovascular disease, including myocardial infarction and stroke, the number one killers in the Western hemisphere. Despite advances in diagnosis of risk factors associated with atherosclerosis development, sudden death due to an acute event is often the first sign of cardiovascular disease, most of which are thought to be the result of rupture of unstable atherosclerotic plaques. Unfortunately, accurate diagnosis of plaque stability and therefore a more accurate assessment of plaque rupture risk is lacking. A major shift in the understanding of atherosclerosis has directed research toward the inflammatory and autoimmune aspects of the disease. Therefore, a better understanding of the self-antigens and mechanisms involved that result in plaque destabilization and rupture could have a major impact on morbidity and mortality, allowing for earlier diagnosis and treatment.

Here we propose testing the hypothesis that autoimmunity to collagen type V [col(V)] is integral for atherosclerosis progression and particularly for destabilization of atherosclerotic plaques. This hypothesis emerges from earlier findings that the col(V) α 1 chain is specifically up-regulated in atherosclerotic plaques, and two of our recent findings that patients with severe coronary artery disease and atherosclerosis-susceptible mice have T cell responses to col(V). We predict that in some patients, the host immune response to col(V) will be T regulatory cell dominant, resulting in a more stable plaque formation with little inflammation. Conversely, we predict that other patients will have a col(V) specific T effector cell dominated (Th17 and/orTh1) response that will escape the T regulatory control and once this col(V)-driven inflammation is superimposed upon the process of plaque formation, plaque instability will be further exacerbated ultimately resulting in plaque destabilization. To test this hypothesis we will analyze blood samples and plaques from patients undergoing carotid endarterectomy, a surgical removal of plaque from the carotid artery, in two specific aims:

1. Determine if patients with varying degrees and types of carotid atherosclerosis have T cell responses to col(V). T cell responses and cytokine profile (Th1, Th2, Th17, Tr1, and Th3) for col(V) immune responses will be measured with a trans-vivo delayed type hypersensitivity assay (TV-DTH) of peripheral blood, which we have shown to be a reliable measure of T cell responses to many antigens including col(V).
2. Determine if the degree and type of T cell response to col(V) correlates with the type of plaque (stable versus unstable) as determined morphologically by histology of excised plaques [including plaque size, macrophage/foam cell area, presence and type of collagen, type of cellular infiltration, type of local cytokine production], flow cytometric analysis on plaque infiltrating cells, and plaque characteristics determined by observation during surgery [including whether plaque is smooth, calcified, granular, ulcerated, contains fresh thrombus, etc].



We anticipate that the analyses proposed here we will be able to determine if the response to col(V) is associated with plaque development or specifically with unstable versus stable plaques. Identifying an abnormality in the form of col(V) autoimmunity that effectively predicts plaque instability and is potentially measurable with a simple blood test would represent a significant advance in the treatment of carotid disease and perhaps other vascular conditions for which plaque instability plays an important role. Having such a tool would allow for determination of which patients would benefit from surgical intervention and avoid the risks of intervention for those with a low likelihood of stroke. Furthermore, the data obtained from this study will lead to new approaches in the prevention, early detection/monitoring, and therapy of atherosclerosis.

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