CMAJ Specialty Spotlight
Inflammatory disease

Harvesting viral proteins

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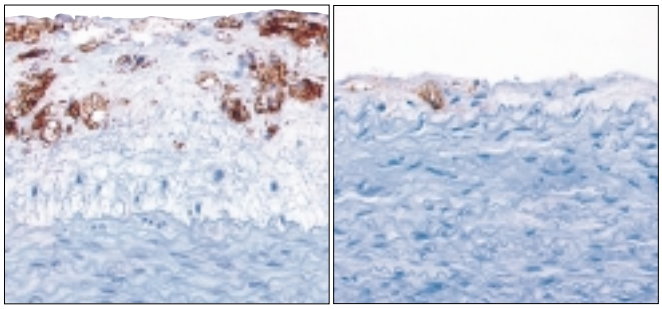
Technology: Viral immunomodulatory proteins
Use: Immune- and inflammation-mediated diseases, such as arthritis, asthma, dermatitis and inflammatory bowel disease, are difficult to treat. The large and complex DNA viruses, such as herpesviruses and poxviruses, have developed highly effective mechanisms for blocking and evading host immune responses to cellular invasion, often by secreting proteins that modulate pivotal points in inflammatory and immune responses.[1,2] The viral immunomodulatory proteins discovered to date include complement and growth factor regulators, cytokine and cytokine receptor mimics, and serine proteinase inhibitors (serpins). We are exploiting the capability of these secreted proteins, even in the absence of virus infection, to develop new therapeutic agents designed to inhibit excessive immune and inflammatory activity.
History: Our 2 laboratories have collaborated to create an innovative technology designed to assess purified, secreted viral proteins as novel anti-inflammatory reagents.[3] After the discovery of multiple myxoma virus virulence factors that protect the virus from clearance by inflammatory cells,[4] a serpin, designated SERP-1, was tested in a rabbit model of angioplasty-mediated injury.[3] Atherosclerotic plaque development was markedly reduced after a single injection of picogram to nanogram doses of SERP-1 given immediately after surgery (Figure).[3] This correlated with reduced counts of monocytes and macrophages invading the damaged arterial wall within the first 2 days after angioplasty.[3] In subsequent pilot studies SERP-1 was also effective in significantly reducing joint erosion in rabbit and rat models of collagen-induced arthritis[5,6] and plaque development in a rat aortic allograft model of transplant vasculopathy.[7,8]

SERP-1 binds to the plasminogen activators and plasmin, thrombolytic enzymes known to act in the early stages of monocyte responses to local injury by enhancing cellular adhesion and migration and by activating growth factors, cytokines and connective-tissue–degrading enzymes. We have postulated that infusion of potent viral proteins at the time of initial injury will suppress the first steps in the inflammatory response that trigger the cascade of events leading to subsequent excess scar formation and local tissue damage.
Promise: These potent viral proteins may prove highly effective in the treatment of inflammation-based diseases that are currently difficult to treat. Together with the John P. Robarts Research Institute, the University of Western Ontario, the London Health Sciences Center and a group of private investors, a new company, VIRON Therapeutics, has been established to discover new viral immunomodulatory proteins and to test their efficacy in animal models of angioplasty injury, allograft transplantation, arthritis, reactive airways disease, dermatitis, lupus nephritis and other inflammation-based disorders.



Cross sections of rabbit abdominal aorta after cholesterol feeding and angioplasty-mediated injury. Left: A large area of plaque with invading macrophages is evident at 4 weeks' follow-up in control group. Right: 30 ng of SERP-1, a viral immunomodulatory protein, markedly reduced plaque growth and macrophage invasion into the intimal layer. (Staining with mouse anti-RAM-11 antibody specific to rabbit macrophage and counterstaining with hematoxylin; original magnification × 400, reduced by 50%).

Problems: Immune or inflammatory reactions to the proteins themselves are possible, as are unforeseen adverse effects. There is also the scepticism attendant upon the use of any new technology that has not been clinically tested. In all of the animal models tested in our laboratories and in collaborating laboratories, however, no evidence of adverse immune or inflammatory responses to these proteins has been detected.
Prospects: These unique viral immunomodulatory proteins may provide both a new source of anti-inflammatory drugs and entirely new insights into the mechanisms of inflammation-based diseases and approaches to their treatment.

Competing interests: The authors have received grants for conducting research in this area. They are the founding scientists of VIRON Therapeutics.

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