Atherosclerosis, the underlying cause of heart attack and stroke, appears to be an inflammatory disease driven by retention of modified lipoproteins in the artery wall. Markers of inflammation, such as high sensitivity C-reactive protein, are independent predictors of cardiovascular (CV) events. If atherosclerosis truly is an inflammatory disease, then shouldn’t we be able to identify antiinflammatory or immunosuppressive medications that are effective in preventing this disease and reducing its clinical expression? The complexity behind this simple supposition was made clear by reports of an association between use of selective cyclooxygenase-2 inhibitors or nonselective cyclooxygenase inhibitors and increased risk of CV events. On the other hand, statins can be considered antiinflammatory drugs, because they lower high sensitivity C-reactive protein levels and display a variety of antiinflammatory effects in vitro and as such, provide plenty of data to support this hypothesis, including the results of the JUPITER trial, where subjects with low levels of low-density lipoprotein and slightly elevated high sensitivity C-reactive protein greatly benefited from statin treatment in terms of CV rate in less than 2 years. The proliferation signal inhibitors, sirolimus and everolimus, have been used in drug-eluting stents to prevent restenosis, but the processes of neointimal and smooth muscle cell proliferation involved in restenosis are not as prominent in the pathogenesis of atherosclerosis. A number of conditions that require treatment with antiinflammatory and immunosuppressive medications are associated with increased risk for atherosclerosis and CV events. Despite the impressive progress in defining the cellular and molecular basis of inflammation and the immune response in atherosclerosis, our understanding of the impact of antiinflammatory drugs on the development of atherosclerosis and subsequent CV events remains surprisingly incomplete. It is in this context that studies by Pols et al on the impact of 6-mercaptopurine (6-MP), a metabolite of the immunosuppressive drug azathioprine (AZA), on macrophage recruitment and apoptosis in atherosclerosis are of interest.

See accompanying article on page 1591

AZA and its metabolite, 6-MP, belong to the class of drugs known as thiopurines. AZA has been used as an antiproliferative agent in immunosuppressive regimens for organ transplantation for 5 decades and in the treatment of several autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. The main mechanisms of action are believed to include incorporation into DNA, inhibition of purine synthesis, and induction of CD4+ T cell apoptosis through inhibition of Rac1 activation. In the current study, Pols et al have turned their attention to the impact of 6-MP on monocyte functions in atherogenesis. In a series of in vitro studies using THP-1 human monocytes, they show that 6-MP decreases expression of the vascular adhesion molecules PECAM-1 and VLA-4 and reduces monocyte adherence to gel- or fibronectin-coated surfaces. In addition, expression of monocyte chemotactic protein-1 (MCP-1) is dramatically reduced when 6-MP is incubated with macrophages activated by lipopolysaccharide. Furthermore, they report that 6-MP induces apoptosis of THP-1 monocytes, which also show decreased expression of the intrinsic antiapoptotic factors Bcl-xL and Bcl-2. Using the apolipoprotein E-3 Leiden transgenic murine model of atherosclerosis, the authors found that local application of 6-MP by a femoral artery cuff reduced atherogenesis in vivo without affecting serum cholesterol levels. Furthermore, they found evidence for reduced expression of MCP-1, increased apoptosis, and reduced macrophage numbers in the atherosclerotic lesions. Based on these results, the authors conclude that their results support novel and previously unrecognized atheroprotective actions of 6-MP. Although the studies are important as a proof-of-principle that 6-MP influences monocyte functions and atherosclerosis development, several caveats are worth considering. The apolipoprotein E Leiden mutation is a rare cause of type III hyperlipoproteinemia and an extremely rare cause of atherosclerosis in humans. It would be important to determine whether these results are generalizable to other established murine models of atherosclerosis. Additionally, little is known about dyslipidemia-induced femoral atherosclerosis in the mouse, and lesions in this study were very small, uncomplicated, and relatively acellular. Although local administration by a cuff suggests the potential for a therapeutic benefit from delivery by a drug-eluting stent, this type of local approach may be more applicable for prevention of restenosis rather than prevention of atherosclerosis. Indeed, the authors have previously reported that 6-MP protects against neointimal and smooth muscle cell proliferation by enhancing activity of the nuclear receptor Nur77 in a murine model of cuff-induced neointima formation. In contrast to the current study, locally applied 6-MP did not affect inflammatory responses or apoptosis but inhibited expression of proliferating cell nuclear antigen and enhanced protein...
levels of the cell-cycle inhibitor p27Kip1 in the vessel wall.\textsuperscript{11} A recent report indicates that 6-MP affects dendritic cell function, reducing expression of the chemokine receptor CCR7.\textsuperscript{12} Given the importance of dendritic cells in atherosclerosis regression,\textsuperscript{13} this could represent another mechanism by which AZA/6-MP influences atherosclerosis. The authors speculate that the beneficial effects of AZA/6-MP in autoimmune disorders may relate to changes in monocyte macrophage function, including the reduction of MCP-1 expression. This raises the obvious question of whether AZA/6-MP is a modulator of atherosclerosis in individuals with autoimmune disease or organ transplantation. To gain some insight into this hypothesis, it would be interesting to examine the impact of systemic administration of 6-MP on the development of atherosclerosis in murine models of atherosclerosis and autoimmune disease.\textsuperscript{14}

A major question is how these results might translate to human atherosclerosis. The impact of AZA/6-MP on atherosclerosis and CV events is difficult to assess given that the underlying autoimmune processes are associated with increased risk for coronary artery disease. Furthermore, several immunosuppressive agents have been implicated in promoting coronary artery disease rather than preventing it.\textsuperscript{15} It has been suggested that AZA and another antiproliferative agent, myophenolate mofetil, have profiles that are more benign with regard to CV toxicity, because, unlike agents such as calcineurin inhibitors and steroids, they do not cause hypertension, dyslipidemia, or diabetes.\textsuperscript{16} However, AZA intake has been associated with increased risk for coronary heart disease in patients with systemic lupus erythematosus,\textsuperscript{17} and CV events in renal transplant patients\textsuperscript{18} and in patients with rheumatoid arthritis.\textsuperscript{19} It is possible that this may reflect disease severity rather than a proatherogenic effect, but it suggests that AZA/6-MP is no panacea for atherosclerosis in these patients. In heart transplant patients, myophenolate mofetil has shown superiority to AZA in terms of improved survival and reduced progression of coronary intimal thickening by intravascular ultrasound at 1 year,\textsuperscript{19} whereas sirolimus and everolimus are more effective in reducing coronary artery vasculopathy.\textsuperscript{20} However, this may not be a fair assessment of the antiatherogenic effects of AZA/6-MP, given that coronary artery vasculopathy is more of an autoimmune process, characterized by greater lymphocyte invasion than is seen in native atherosclerosis.

Can we assume that the 6-MP induction of macrophage apoptosis described by Pols et al is atheroprotective in humans? There has been tremendous interest in the mechanisms of macrophage apoptosis and the role of macrophage cell death on atherosclerosis.\textsuperscript{21} A current paradigm suggests that macrophage apoptosis in early lesion formation may reduce atherosclerotic lesion formation, because macrophage-derived foam cells are the dominant cell type in early lesions. However, increased macrophage cell death in more advanced lesions may actually contribute to increased lesion necrosis, which is a feature of unstable plaques. Thus, it is possible that 6-MP-induced macrophage apoptosis could actually promote plaque rupture in humans.\textsuperscript{21} Given the widespread use of immunosuppressive drugs in clinical practice, it is critical that we learn more about their effects on atherosclerosis in animal models and on CV events in humans.

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References


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6-Mercaptopurine, Monocytes, and Atherosclerosis
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The online version has been corrected.

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Correction

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