Myriocin as an atherosclerosis inhibitor

‘It appears quite possible that detailed investigations of the antiatherogenic actions of myriocin will reveal therapeutic targets that can be more selectively regulated in the future.’

Targeting the sphingolipid pathway to treat atherosclerosis

Atherosclerosis is a major cause of cardiovascular disease and accounts for approximately 50% of all deaths in westernized countries [1]. Atherosclerosis develops as a consequence of multiple pathways that involve dysregulated cellular proliferation, lipid accumulation and inflammation [2,3]. Hypercholesterolemia is a major risk factor for atherosclerosis and it is clear that HMG-CoA reductase inhibitors (statins) effectively lower serum total and LDL-cholesterol (LDL-C), and reduce cardiovascular morbidity and mortality [4]. However, it is well known that a significant number of patients are either resistant to or intolerant to statins and, with recent guidelines for LDL-C levels to be reduced below 2 mM, it has been reported that fewer than 50% of patients treated with statins achieve their targets [5]. In order to address this problem, statin combination therapies are under investigation, for example, using the cholesterol-absorption inhibitor ezetimibe [5]. As an adjunct to statin therapy, strategies targeting proatherogenic pathways that are not primarily aimed at reducing cholesterol synthesis or absorption would be predicted to result in a two-pronged approach to treat atherosclerosis. As a case in point, therapeutic targeting of the sphingolipid biosynthetic pathway may represent a feasible approach to treat atherosclerosis [6,7].

Ceramide-1-phosphate & atherosclerosis

Myriocin could potentially regulate the synthesis of additional sphingolipids such as C1P. C1P is generated by ceramide phosphorylation catalyzed by ceramide kinase (Figure 1). It is
established that C1P is a potent activator of cytosolic phospholipase A2α and, thus, a key regulator of macrophage cytokine-induced eicosanoid metabolism [14–18]. Macrophage foam cells present in atherosclerotic lesions secrete proinflammatory molecules that accelerate disease progression [2]. The products of macrophage eicosanoid metabolism, which include prostaglandins, leukotrienes and platelet-activating factors, are particularly important proinflammatory mediators (Figure 1). Identification of the major upstream regulators of macrophage eicosanoid metabolism and the design of drugs that inhibit such pathways is already recognized as a new avenue to treat atherosclerosis [19]. It remains possible that reductions in C1P generation achieved by myriocin could result in anti-inflammatory actions that inhibit the development of atherosclerosis in Apoe<sup>−/−</sup> mice. However, direct evidence for this has so far not been provided.

Sphingosine-1-phosphate & atherosclerosis

In contrast to C1P, which has not been studied in vivo as a therapeutic target for atherosclerosis, several studies have focused on the potential for the S1P analogue FTY720 to modulate atherosclerosis in both Apoe<sup>−/−</sup> and Ldlr<sup>−/−</sup> mice [20–23]. Two of the studies reported that FTY720 potently suppressed atherosclerosis in both the Apoe<sup>−/−</sup> and Ldlr<sup>−/−</sup> mouse models [20,21]; however, the third study indicated that atherosclerosis was not inhibited in Apoe<sup>−/−</sup> mice treated with FTY720 and (in contrast to the other two studies) a marked hypercholesterolemia was reported in the drug-treated animals [22]. The reasons for this discrepancy are unclear, but it is worth noting that lesion data were reported only for the aortic root in the latter study and this site has been shown to be refractory to treatment in other work [9].

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It is thought that FTY720 is phosphorylated in vivo and exerts most of its antiatherogenic effects via interaction with S1P receptors (most likely S1P1 and S1P3), which results in an anti-inflammatory action [23]. At present, it is not clear how FTY720 inhibited lesion development in the two positive mouse studies. There were no consistent changes in either macrophage or CD3<sup>+</sup> lymphocyte levels in lesions when the two studies were compared. Paradoxically, the potent...

![Figure 1. Sphingolipid pathway and inhibitor targets.](image-url)
Myriocin has, however, provided an important tool that has allowed us to begin to investigate which specific members of the sphingolipid family may be selectively targeted to treat atherosclerosis. It appears quite possible that detailed investigations of the antiatherogenic actions of myriocin will reveal therapeutic targets that can be more selectively regulated in the future.

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Myriocin as a new therapeutic for the treatment of atherosclerosis?
At present, it appears unlikely that myriocin will be useful clinically. There are several reasons for this. As already noted, myriocin inhibits SPT, which blocks the first step in sphingolipid synthesis, and this is likely to impact on many members of the sphingolipid family that have important roles in signaling and regulation of cell growth, differentiation, apoptosis and proliferation [27]. In addition, myriocin is an immunosuppressant (some data indicate it to be up to 100-fold more potent than cyclosporin [28]), which would preclude its long-term use as a treatment for cardiovascular disease in humans.

‘At present, it appears unlikely that myriocin will be useful clinically.’

Bibliography


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