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mTOR inhibition & cardiovascular diseases: Dyslipidemia and Atherosclerosis

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Disclosure

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Abbreviations

AKT, protein kinase B; protein; LDL, low-density lipoprotein; mTOR, mechanistic target of rapamycin
Abstract

Inhibitors of the mechanistic target of rapamycin (mTOR) have unique anti-atherosclerotic effects such as depletion of plaque macrophages, induction of autophagy and activation of cholesterol efflux. However, a common side effect of their use is dyslipidemia, a well-known risk factor for atherosclerosis. Indeed, mTOR inhibitors prevent lipid storage, increase LDL cholesterol levels and activate lipolysis. Statins and/or PCSK9 inhibitors can be used to manage these adverse effects.
Introduction

Since the discovery of the natural product rapamycin in the 1970s, interest in its therapeutic value has shifted from a macrolide with antifungal potential to an invaluable extension of immunosuppressant therapy following organ transplantation. Rapamycin binds to the intracellular immunophilin 12-kDa FK-506 binding protein (FKBP12), which results in a complex that physically interacts with the mechanistic target of rapamycin (mTOR). Correspondingly, the association of mTOR with other proteins is disturbed and mTOR function is inhibited. Following the discovery of this mechanism, the anti-proliferative effects of rapamycin and its semi-derivatives (known as rapalogs) were quickly utilized in anti-tumor therapy and interventional cardiology. The benefit of rapalog-mediated mTOR inhibition in the treatment of atherosclerosis has been highlighted by numerous groups. However, inhibition of mTOR is also known to induce dyslipidemia both in humans and in animal models. Here, we will discuss the effects of mTOR inhibition by rapalogs on lipid metabolism and atherosclerosis in an attempt to shed some light on their contradictory relationship.

mTOR

mTOR is a serine/threonine kinase highly conserved in all eukaryotes. This master regulator of cellular growth and metabolism is found in the cell as part of two multiprotein complexes (mTOR complex 1 [mTORC1] and mTORC2), each with different cellular functions. Under basal conditions, the thoroughly studied mTORC1 is highly sensitive to anabolic stimuli such as the availability of nutrients and growth factors. It responds to intracellular conditions by regulating the phosphorylation of its downstream targets, most notably S6 kinase 1 (S6K1) and 4e-binding
protein-1 (4eBP-1). As a result, mTORC1 is implicated in protein synthesis and lipid metabolism as well as in cellular growth and proliferation. Moreover, stimulation of mTORC1 blocks autophagy, a critical catabolic mechanism aimed at restoring cellular energy levels in times of nutrient deprivation and cellular stress. The second complex (mTORC2) is responsible for cell survival and cytoskeleton organization through activation of several kinases (e.g. protein kinase B [AKT], serum/glucocorticoid-regulated kinase 1 [SGK1]). Rapalogs are mainly inhibitors of mTORC1 though some reports indicate that prolonged treatment could inhibit mTORC2 activity as well.

**mTOR inhibition and dyslipidemia**

Dyslipidemia is a pronounced side effect of rapalogs affecting 40-75% of all patients receiving these drugs. The mTORC1 pathway stimulates lipogenesis as it controls the sterol regulatory element-binding proteins 1 and 2 (SREBP1/2), important transcription factors for fatty acid and sterol biosynthesis.\(^2,3\) Surprisingly, continuous activation of mTORC1 in vivo does not lead to lipid accumulation owing to strong inhibition of AKT as part of an mTORC1 feedback mechanism.\(^2\) Moreover, given that mTORC2 activates AKT, mTORC2 is also involved in the process of lipogenesis (Fig. 1).\(^2,5\)

Apart from lipogenesis, mTORC1 coordinates lipid storage in white adipose tissue by controlling adipogenesis, the process by which adipocytes are created (Fig. 1). Indeed, treatment with rapamycin or genetic approaches that lead to mTORC1 inhibition result in significantly less accumulation of adipose tissue via inhibition of proliferator-activated receptor γ (PPARγ), a nuclear receptor capable of initiating the adipogenic process.\(^2,5\)
Moreover, blocking mTORC1 signaling also actively increases low density lipoprotein (LDL) cholesterol levels by downregulating the expression of hepatic LDL receptors, causing less clearance from the blood. Along these lines, inhibition of mTORC1 directly causes hyperlipidemia by stimulating lipophagy, a specialized form of autophagy aimed at breaking down lipid droplets to release stored lipids, and by activating both hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) to facilitate lipolysis (Fig. 1). Genetic deletion of mTORC2 signaling also results in increased lipolysis in vivo but the mechanism remains elusive. Overall, mTORC1 inhibition triggers a 20-30% decrease in lipid storage, while lipolysis is enhanced by 20%.

**mTOR inhibition in atherosclerosis**

Atherosclerosis is a chronic disease of the arterial wall associated with inflammation and an imbalance in lipid metabolism. Dysfunction of the endothelial layer results in the infiltration of LDL particles into the arterial wall, which in turn promotes infiltration of inflammatory cells and smooth muscle cell proliferation. Numerous reports have found that mTORC1 inhibition, either through genetic approaches or by administration of rapalogs, limits the progression of atherosclerosis in preclinical animal models despite dyslipidemia. Rapalog-mediated mTORC1 inhibition counters the disease by improving endothelial function, inhibiting smooth muscle cell proliferation, decreasing macrophage content in the plaque via autophagy and by minimalizing monocyte recruitment from the bloodstream. Importantly, mTORC1 inhibition also results in autophagy-mediated cholesterol efflux from plaque macrophages, thereby decreasing lipid accumulation in the plaque. These effects act together to inhibit the formation of foam cells, which play an important role in the development and progression of atherosclerosis.
In humans, most valuable data on mTOR inhibition and atherosclerosis come from transplantation recipients. These patients have a particularly high risk for cardiovascular disease (CVD), which could be attributed to the development of dyslipidemia following transplantation and immunosuppressive therapy.\(^7\) Administration of rapalogs significantly reduces cardiac allograft vasculopathy (CAV), a condition with some similarities to atherosclerosis seen in heart transplantation patient, compared to other immunosuppressive therapies.\(^8\) Furthermore, the risk of CVD is not higher in renal or liver transplantation patients receiving rapalogs despite significant dyslipidemia triggered by the treatment.\(^9,10\) Large studies focusing on atherosclerosis are, however, lacking.

It should be noted that most patients receiving rapalogs are also given statins in an attempt to manage dyslipidemia, drugs which are known to have pleiotropic anti-atherosclerotic effects well beyond their lipid-lowering activities and to reduce CVD as well as CAV in heart transplantation patients.\(^7,8,11\) Statins also possess immunosuppressive properties that could explain the lower rejection rates and improved survival.\(^12\) Moreover, some statins show inhibitory effects on the mTOR pathway making an additive, or even synergistic, action with rapalogs not entirely unthinkable.\(^13\) Consequently, combination of rapalogs with statins has become a standard practice in many cases and whether the above-mentioned positive effects can be attributed to rapalog treatment alone remains unclear for the moment.\(^7,8\) Furthermore, it is conceivable that also PCSK9 inhibitors can further circumvent the dyslipidemia associated with mTOR inhibition, as these drugs strongly lower plasma LDL cholesterol by increasing the life span of the LDL receptors in the liver.
Conclusion

A growing body of evidence shows a beneficial effect of rapalog-mediated mTOR inhibition on the progression of atherosclerosis despite induction of dyslipidemia. While this may seem paradoxical at first sight, it should be noted that mTOR inhibition has pleiotropic anti-atherosclerotic effects that could reverse dyslipidemia in the course of the disease. Moreover, activation of macrophage cholesterol efflux reduces lipid accumulation in the plaque, thereby impeding atherosclerosis regardless of plasma lipid levels. However, considering the role of dyslipidemia in CVD, a combination therapy of an mTOR inhibitor with a statin and/or a PCSK9 inhibitor seems to be a reasonable approach, although more research regarding this subject is still required.

References


Figure 1. mTOR-mediated effects on lipid metabolism. mTORC1 is a major regulator of lipid metabolism. When activated, mTORC1 inhibits lipolysis by impeding activity of lipases such as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL). Low density lipoprotein (LDL) clearance from the blood is also reduced by decreased expression of the LDL receptor (LDLR). Moreover, lipophagy as well as autophagy-mediated cholesterol efflux are inhibited. In addition, activated mTORC1 stimulates adipogenesis and lipogenesis. Much less control is asserted through mTORC2, which drives hepatic lipogenesis and inhibits lipolysis. Administration of rapamycin or its derivatives (known as rapalogs) inhibit mTORC1 and possibly, when given chronically, also mTORC2 with pronounced dyslipidemia as a result.