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AUTHOR'S VIEW

The mevalonate pathway as a metabolic requirement for autophagy–implications for growth control, proteostasis, and disease

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ABSTRACT
Autophagy is responsible for the degradation and recycling of cellular proteins and organelles. Our recent work shows that the mevalonate pathway influences cell size, growth, and proteostasis by regulating basal autophagic flux through geranylgeranylation of the small GTPase RAB11. The control of autophagy by the mevalonate/cholesterol pathway has potential implications for statin toxicity, inflammation, cancer, and neurodegenerative diseases.

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Regulation of basal autophagic flux by the mevalonate pathway

Autophagy is a conserved cellular pathway for the degradation and recycling of cellular organelles and proteins.[1] This process is initiated by the formation and elongation of a double membrane around the target destined for destruction (Fig. 1A). The resulting vesicle, the autophagosome, is then fused with lysosomes in a process called autophagosome maturation. Finally, the contents of the newly formed autolysosome are degraded by the acidic lysosomal hydrolases and reused.

Autophagy is mainly regulated through phosphorylation, but can also be influenced by metabolism. As we recently demonstrated,[2] one such example is the mevalonate pathway, which produces cholesterol, isoprenoids, and ubiquinone (Fig. 1A). Statins, inhibitors of 3-hydroxy-3-methyL-glutaryl-CoA reductase (HMGCR, the rate-limiting enzyme of the mevalonate/cholesterol pathway), have long been used as cholesterol lowering agents. However, as statins target an early step in the mevalonate pathway they also inhibit the biosynthesis of isoprenoids required for post-translational protein modification by prenylation. This inhibition of protein prenylation is a well-recognized effect of statins that is known to, for example, inhibit the mechanistic target of rapamycin (mTOR) pathway and thus stimulate the initiation of autophagy.[3]

Our recent data show that although inhibition of the mevalonate pathway promotes the initiation of autophagy, it simultaneously blocks the maturation of autophagosomes, leading to a reduced basal autophagic flux.[2] This block in the maturation of autophagosomes increases the levels of autophagic markers, which has often led to the incorrect conclusion in biomedical literature that statins increase autophagy. Our data further show that mevalonate pathway inhibition results in autophagosomal rather than lysosomal defects, as lysosomal activity increases in the presence of statins. Mechanistically, the blockade of autophagic flux was found to be caused by reduced prenylation, and more specifically geranylgeranylation, of RAB11 (Fig. 1A), a small GTPase required for normal recycling of endosomes and maturation of autophagosomes.[4] Importantly, the reduced autophagic flux was apparent with submicromolar statin concentrations in primary human cells,[2] suggesting that such effects could be physiologically relevant responses to statin therapy.

Growth and proteostasis effects of mevalonate pathway inhibition

The cell biological consequences of reduced mevalonate pathway activity and the consequent limited autophagy are widespread (Fig. 1B). While growth promoting processes such as protein synthesis are reduced, the breakdown of cellular components is also reduced. Furthermore, inhibiting the mevalonate pathway reduces, but does not completely stop, cell proliferation when using statin concentrations that strongly inhibit autophagy. As a consequence, while inhibition of an anabolic pathway, the mevalonate pathway, does reduce overall growth, it reduces catabolism even more, causing cells to accumulate protein. Thus, the unexpected net effect is that, despite the reduced growth rate, cell size and especially cellular protein density dramatically increase as proteins and organelles accumulate in the absence of normal autophagy.[2] Autophagy is also known to affect degradation of aggregation-prone proteins, and consistent with this we observed accumulation of protein aggregates in response to mevalonate pathway inhibition. Therefore, our data show that normal metabolic activity in one of the lipid biosynthetic pathways, the mevalonate pathway, is required for the maintenance of cell size homeostasis and proteostasis. These data corroborate our earlier work in which we

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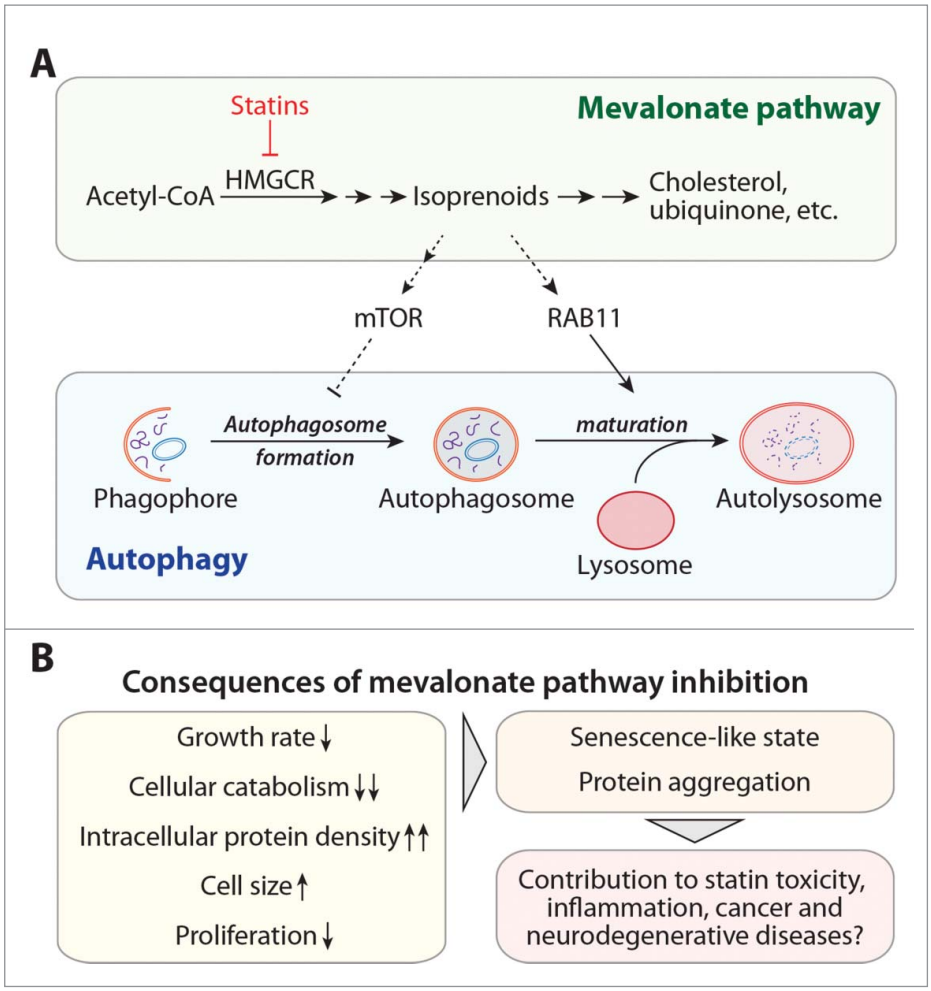

Figure 1. Mevalonate pathway regulates growth and proteostasis through autophagy. (A) The mevalonate pathway regulates autophagy at several steps, including autophagy initiation and autophagosome maturation. HMGCR is 3-hydroxy-3-methyl-glutaryl-CoA reductase, RAB11 is a small GTPase involved in vesicle transport, and the mTOR pathway is the mechanistic target of rapamycin pathway. (B) Genetic or pharmacological inhibition of the mevalonate pathway has various cellular consequences that are caused by reduced autophagy and have potential implications for human health.

identified an inverse correlation between cell size and mevalonate pathway gene expression *in vivo*,[5] indicating that mevalonate pathway is a physiologically important mediator of growth and cell size control.

Adverse effects of mevalonate pathway inhibition on human health

Could the mevalonate pathway have autophagy-mediated effects on human health? The cellular phenotype induced by mevalonate pathway-mediated reduction of autophagy resembles a senescence-like state, in which cell size is increased, proliferation decreased, and proteostasis is impaired. Consistent with this notion, autophagy has recently been shown to have a negative regulative role in cellular senescence as basal autophagy is required for maintaining the regenerative functions of muscle stem cells.[6] This, together with the observation that statin toxicity is intensified by blocking autophagy,[7] suggests that the reduced autophagic flux caused by inhibition of the mevalonate pathway may function as a mechanism for statin-induced myopathies, which are a relatively prevalent side-effect of statin use.[8] The reduced autophagy will also inhibit the clearance of damaged mitochondria, which may further exacerbate muscle toxicity and induce inflammation. Indeed, inhibition of autophagy has been suggested to induce inflammation in mevalonate kinase deficiency, a rare autoinflammatory disease caused by genetic blockage of mevalonate pathway activity.[9] In line with this, patients with this disease display myopathy as well as hepatosplenomegaly as common symptoms.

In recent years, statin use has been suggested to contribute to diseases such as cancer and neurodegeneration. The senescence-like state induced by statins might suggest a beneficial role for statin use in cancer, but the clinical evidence for cancer protective or suppressive effects remains controversial.[10] As defective autophagy can induce both tumor regression or progression depending on the context,[1] the role of autophagy should be further investigated when assessing the effects of statins on cancer.

Conclusions

Mevalonate pathway activity functions as a metabolic requirement for basal autophagic flux through geranylgeranylation of RAB11. This mechanism enables the mevalonate pathway to regulate cell size, growth, and cellular protein content through autophagy. Importantly, many of the symptoms caused by

genetic or pharmacological inhibition of the mevalonate pathway can be explained by reduced autophagy, suggesting clinical implications of these findings.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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