

# Therapeutic potential of statins in thyroid proliferative disease

Maurizio Bifulco

M Bifulco is Full Professor of General Pathology in the Department of Pharmaceutical Sciences, University of Salerno, Italy.

The thyroid gland is a frequent site of abnormal epithelial cell proliferation. Proliferative diseases of the thyroid follicular cells that arise as either sporadic or nontoxic multinodular goiter progress to neoplasia in ~5% of all cases. In addition, the incidence of thyroid cancer has risen rapidly over the past few years. In terms of histology, this endocrine malignancy predominantly comprises papillary thyroid cancer and follicular thyroid cancer, whereas medullary thyroid cancer and anaplastic thyroid cancer (ATC) occur less frequently. Nonetheless, ATC is considered one of the most aggressive forms of human neoplasia and is refractory to conventional therapeutic strategies. Innovative approaches are, therefore, currently underway to investigate novel treatments for thyroid proliferative disease. For example, statins have been reported to affect proliferation and survival of several tumor cell types (including thyroid) and display *in vivo* antitumor activity when used as single agents or in combination with other anticancer drugs.

Statins are cholesterol-lowering agents that are commonly prescribed to prevent cardiovascular and coronary heart disease. These drugs inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of isoprenoid and cholesterol biosynthesis. Inhibition of this enzyme prevents the reduction of HMG-CoA to mevalonate, the precursor of cholesterol. In addition to their lipid-lowering properties, statins are also thought to display immunomodulatory, anti-inflammatory, and antioxidant activity, and to reduce insulin resistance and progression of renal disease. These effects do not seem to be directly related to inhibition of cholesterol biosynthesis. Mevalonate is also the precursor of prenyl groups, which are transferred by farnesyl and geranylgeranyl transferases to small guanosine triphosphate-binding proteins of the Ras and Rho families. Protein prenylation is essential for anchoring these proteins to the plasma membrane and for subsequent activation of proteins involved in cellular proliferation, adhesion, and motility.

Expression and/or activity of HMG-CoA reductase, farnesyl transferase and geranylgeranyl transferase have been associated with cell proliferation, and aberrant expression of these enzymes seems to be a characteristic of tumor cells. Inappropriate activation of the Ras signaling pathway has a critical function in thyroid proliferative disease. In addition, it has been reported that geranylgeranylated Rho has important roles in cell proliferation and apoptosis beyond control of cell migration. As statins inhibit both farnesylation and geranylgeranylation (and hence Ras and/or Rho activation), it seems plausible that they might potentially inhibit expression of the malignant phenotype of tumor cells.

We have shown that lovastatin exerts antiproliferative activity in rat thyroid cells (without affecting cell differentiation) and induces apoptosis in proliferating human thyroid cells.<sup>1,2</sup> These activities occur by inhibition of protein prenylation. *In vivo* experiments have confirmed that administration of lovastatin to rats inhibits thyroid hypertrophy and hyperplasia induced by goitrogenic agents. This result suggests that lovastatin has antigoiner activity, and so provides a rationale for innovative therapeutic strategies that exploit statins in the treatment and/or prevention of human goiter.<sup>3</sup> In support of this hypothesis, a retrospective epidemiologic study in dyslipidemic patients showed that treatment with statins for at least 5 years was associated with a significantly lower prevalence, number, and volume of thyroid nodules, as well as a smaller thyroid size.<sup>4</sup>

Inhibition of Rho geranylgeranylation by lovastatin has been shown to exert growth-inhibitory and proapoptotic effects, and to induce differentiation of human ATC cells resistant to conventional therapies. Indeed, some studies have indicated that inhibition of geranylgeranylation (but not farnesylation) could be the main mechanism that regulates lovastatin-induced apoptosis.<sup>5,6</sup> By contrast, we found that the isoprenoid pathway was markedly altered in the FRTL-5 rat thyroid cell line upon transformation with *K-ras* (but not *H-ras*). This effect occurred *via* induction of

## Correspondence

Department of  
Pharmaceutical Sciences  
University of Salerno  
Via Ponte Don Melillo  
84084 Fisciano (Salerno)  
Italy  
maubiful@unisa.it

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farnesyl transferase activity, which resulted in the preferential farnesylation and functional activation of the oncogene product.<sup>7</sup> Treatment with lovastatin inhibited proliferation and induced apoptosis of the *K-ras*-transformed thyroid cells by modulation of the cellular redox state.<sup>8</sup> The preferential inhibition of a specific Ras isoform might, therefore, represent an alternative mechanism of lovastatin action and so provide a useful selective chemotherapeutic tool for tumors harboring *K-ras* mutations.

The findings discussed above should prompt further basic and clinical studies on the therapeutic potential of statins in thyroid cancer, particularly in order to clarify whether the antiangiogenic and anti-inflammatory effects are relevant to anticancer therapy. Additional studies are also needed to determine whether the antitumoral activities of statins are mediated solely by their effects on protein prenylation or if they also relate to the lipid-lowering activity. We are currently studying the molecular mechanism of lovastatin action in detail to determine whether the main cellular target is Ras, Rho or another prenylated protein, such as the novel membrane microtubule-associated protein 2',3'-cyclic nucleotide 3'-phosphodiesterase. We have previously shown in FRTL-5 cells that lovastatin induces cytoskeletal disorganization and disconnection of microtubules from the plasma membrane.<sup>8</sup> Evaluation of the cellular function of 2',3'-cyclic nucleotide 3'-phosphodiesterase might, therefore, provide additional insight as to how lovastatin could act as an anticancer agent *via* microtubule disassembly. Finally, gene therapy approaches for the treatment of ATC have also been investigated. In this regard, we have demonstrated that lovastatin increases adenoviral replication and enhances the *in vitro* and *in vivo* effects of the oncolytic adenovirus *dl1520* (Onyx-015, Onyx Pharmaceuticals, Emeryville, CA) in ATC cells. This observation suggests that lovastatin could be a useful combinatorial agent in gene therapy.<sup>9</sup>

Although usually well tolerated, statins have been associated with adverse effects such as myotoxicity and potential interactions with other drugs; however, lovastatin has been used extensively with negligible adverse effects and has a well-defined clinical pharmacokinetic profile. In a meta-analysis of randomized trials there was no evidence that statin therapy was associated with increased short-term cancer risk, and chemoprevention was supported by the

biological evidence, at least for colon cancer.<sup>10</sup> Nonetheless, the long-term latency effects of statin therapy remain to be evaluated as a small increased risk of thyroid cancer insurgence has been reported in men, but not women, who received lovastatin or simvastatin for 5 years.

In conclusion, both antiproliferative and proapoptotic effects of statins have been described in several experimental models. Statins show therapeutic potential in thyroid proliferative disease and might represent a novel approach to treat dedifferentiated thyroid cancer, although questions remain about the clinical significance of the antiproliferative activity of statins in the thyroid gland. Identification of the statin with maximal efficacy and specificity will directly influence the clinical application of statin therapy in the management of cancer. In addition, experimental and clinical trials must determine whether the promising protective effects of statins are applicable both to patients with and without hypercholesterolemia. Finally, inclusion of statins in combined therapies for the more aggressive thyroid cancers must also be evaluated.

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#### Competing interests

The author declared no competing interests.