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Tumour prevention and tumour progression: a dual role for statins?☆

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Simona Romano (master degree in Medical Biotechnology) has achieved a PhD in Molecular Oncology and Endocrinology and actually she is a research fellow at the Department of Biochemistry and Medical Biotechnology, Federico II University of Naples, Italy. Her research experience is especially valuable by a number of publications in the fields of apoptosis, cancer biology and vascular pathophysiology.

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Maria Fiammetta Romano, MD, specialized in Allergology and Clinical Immunology at the University of Florence, and in Oncology at the University of Naples, Federico II. Currently, she works as an aggregate professor, group leader at the Department of Biochemistry and Medical Biotechnology, Federico II University of Naples, Italy. Her research interest focuses on apoptosis regulation in human cell models and signalling transduction pathways that are deregulated in cancer and responsible for resistance to apoptosis. In particular, in the last decade her research group highlighted the relevant role of the immunophilin FKBP51 in melanoma progression and chemo-resistance and radio-resistance. Her research group is also involved in the study of the effects of FK506, rapamycin and statins, on proliferation and death of vascular cells. She has published over 50 manuscripts in these fields.

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The use of statins is essential for the treatment of hyperlipidemia as well as for the primary and secondary prevention of coronary artery disease and strokes. Statins decrease low-density lipoprotein (LDL) cholesterol levels by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA HMG-CoA reductase (HMGCR). HMGCR in turn catalyses the conversion of HMG-CoA into mevalonic acid, an important intermediate metabolite in hepatic cholesterol biosynthesis. Statins exert pleiotropic effects independent of their cholesterol-lowering activity, which are in part mediated by mevalonic acid, a precursor of the isoprenoid intermediates farnesyl and geranyl-geranyl pyrophosphate [1]. These compounds participate in the post-translational modification of intracellular G-proteins, such as Rho, Rac, and Ras. In turn, it is well-known that G-proteins drive signalling pathways that are widely involved in carcinogenesis [2], and their inhibition by statins has been proven to efficiently impair the growth of several tumours [3]. Furthermore, statins inhibit cellular matrix metalloproteinases and nuclear factor-κB (NF-κB) transcription factors that are, additionally, often deregulated in cancer. A large body of studies exists that support the efficacy of statins against several cancer types [3]. For this reason, these compounds has been proposed as adjuvant options in cancer therapies and in cancer prevention. Currently, recommendations and guidelines on statin use in malignancies do not exist; in addition, to date, results from randomised controlled trials are inconclusive regarding the question of whether cancer treatment may benefit from statins.

Very recently, a number of studies, have found that atorvastatin is a powerful stimulus for endoglin production [4–6]. For example, atorvastatin was shown to stimulate expression of endoglin in human umbilical vein endothelial cells (HUVEC), at both transcriptional and protein levels [4]. Endoglin mRNA levels meanwhile, were found to be increased in the endothelium of subjects that were statin recipients, in comparison with subjects that were not statin recipients [4]. In addition, high levels of endoglin were measured in the blood of subjects with familial hypercholesterolemia that were under chronic statin treatment [5]. Lastly, Nachtigal *et al.* also found that statin treatment significantly induced endoglin expression in the aortic endothelium in atherosclerosis models [6].

Endoglin, or CD105 as it was designated at the Fifth International Workshop on Human Leukocyte Differentiation Antigens, is an accessory receptor of the Transforming Growth Factor (TGF)-β family of proteins, which includes TGF-β, bone morphogenetic proteins (BMPs), and activins.

☆ Current Comments contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

Endoglin forms complexes with type I and type II TGF-β receptors (TβRI and TβRII), and modulates TGF-β signalling. Stimuli that increase endoglin expression promote the BMP signalling pathway, which is active during embryonic development and is reactivated during adult vasculogenesis. CD105 expression in vascular endothelial cells of de novo blood vessels is therefore considered to be potentially useful in the detection of cancer patients with high risks of disease recurrence and metastasis formation [7]. In addition, CD105 expression was found to be of particular significance in the evaluation of neoangiogenesis and prediction of prognosis in brain tumours [8]. Endoglin is predominantly expressed in proliferating endothelial cells that participate in tumour angiogenesis, with weak or no expression in the vascular endothelium of normal tissues; for this reason CD105 is considered as a suitable vascular target for antiangiogenetic cancer therapy.

Angiogenesis is a powerful element that drives tumour progression. Blockage of angiogenesis maintains tumours in a harmless state and constrains the outgrowth of metastases. Inability to initiate angiogenesis in disseminated tumour cells is considered as one of the main causes of tumour dormancy. Selective targeting of proliferating endothelial cells within tumour-associated blood vessels represents one of the most pursued approaches to limit tumour progression, with molecules that are overexpressed in actively proliferating endothelial cells being attractive targets for antiangiogenetic strategies. Among these targets, endoglin is considered to be of prime importance, due to the central role this molecule exerts in tumour angiogenesis.

Currently, there are no studies directly linking statins with endoglin production and tumour progression. In addition, an in-depth characterisation of the mechanism by which statins induce CD105 is still lacking. However, it is worth noting that several studies show conversely that statins can promote cancer [9], suggesting that pro-tumoural mechanisms might be, in addition, activated by these drugs.

The undoubtedly striking and specific inhibitory actions on tumourigenic pathways exerted by statins are consistent with a protective action for these agents in cancer prevention [10]. The efficient pro-apoptotic activities exerted by statins, at doses much higher than those used to lower cholesterol, suggest that these compounds could have an effective role, if used in concert with chemotherapy, in cancer treatment. However, the possibility cannot be excluded that statins may promote progression of pre-existing, asymptomatic and even dormant tumours because of their capacity to stimulate CD105. These observations are consistent with a dual role for statins in cancer prevention and progression. The role of statins in cancer represents an open question that requires urgent addressing and careful investigation, in both experimental and pre-clinical settings. Besides prospective studies, clinical trials may be required to define unambiguously the ultimate biological effects of statins in cancer intervention and thus the patient population that could benefit most from this treatment. Finally, it is worth emphasising that millions of healthy people, including both children and adults, are currently taking statin drugs.

References

1. Liao JK, Laufs U: **Pleiotropic effects of statins**. *Annu Rev Pharmacol Toxicol* 2005, **45**:89-118.
2. Dorsam RT, Gutkind JS: **G-protein-coupled receptors and cancer**. *Nat Rev Cancer* 2007, **7**:79-94.
3. Hindler K, Cleeland CS, Rivera E, Collard CD: **The role of statins in cancer therapy**. *Oncologist* 2006, **11**:306-315.
4. Giordano A, Romano S, Monaco M, Sorrentino A, Corcione N, Di Pace AL, Ferraro P, Nappo G, Polimeno M, Romano MF: **Differential effect of atorvastatin and tacrolimus on proliferation of vascular smooth muscle and endothelial cells**. *Am J Physiol Heart Circ Physiol* 2012, **302**:H135-H142.
5. Blaha M, Cermanova M, Blaha V, Jarolim P, Andrys C, Blazek M, Maly J, Smolej L, Zajic J, Masin V *et al.*: **Elevated serum soluble endoglin (sCD105) decreased during extracorporeal elimination therapy for familial hypercholesterolemia**. *Atherosclerosis* 2008, **197**:264-270.
6. Nachtigal P, Pospisilova N, Vecerova L, Micuda S, Brcakova E, Pospechova K, Semecky V: **Atorvastatin increases endoglin, SMAD2, phosphorylated SMAD2/3 and eNOS expression in ApoE/LDLR double knockout mice**. *J Atheroscler Thromb* 2009, **16**:265-274.
7. Marioni G, Marino F, Blandamura S, D'Alessandro E, Giacomelli L, Guzzardo V, Lionello M, De Filippis C, Staffieri A: **Neoangiogenesis in laryngeal carcinoma: angiogenin and CD105 expression is related to carcinoma recurrence rate and disease-free survival**. *Histopathology* 2010, **57**:535-543.
8. Yao Y, Kubota T, Takeuchi H, Sato K: **Prognostic significance of microvessel density determined by an anti-CD105/endoglin monoclonal antibody in astrocytic tumors: comparison with an anti-CD31 monoclonal antibody**. *Neuropathology* 2005, **25**:201-206.
9. Chang CC, Ho SC, Chiu HF, Yang CY: **Statins increase the risk of prostate cancer: a population-based case–control study**. *Prostate* 2011, **71**:1818-1824.
10. Pelton K, Freeman MR, Solomon KR: **Cholesterol and prostate cancer**. *Curr Opin Pharmacol* 2012. [Epub ahead of print].