Reviewer's report

Title: HMG-CoA reductase inhibition aborts functional differentiation and triggers apoptosis in cultured primary human monocytes: a potential mechanism of statin-mediated vasculoprotection

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Version: 1 Date: 4 May 2003

Reviewer: Carlos Guijarro

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

General comment.
The authors provide additional interesting evidence (although limited) suggesting complementary mechanisms of actions of statins potentially important in the pathophysiology of atherosclerosis. However, the interest of their data would have been greatly increased by expanding their results to different statins in real clinical use (almost all but mevastatin and cerivastatin). Additionally, several mevalonate derivatives such as farnesol and geranylgeraniol (+/-PP), easily available, could have been used to better define at least in a preliminary manner, the molecular mechanisms responsible for the proapoptotic effect statins (the direct evaluation of the role for prenylated proteins is clearly beyond the scope of the paper).

Compulsory revisions

Although the data presented in the paper is consistent with a modulation of monocyte differentiation (at least regarding a pattern of cytokine secretion) the conclusion that statins abort monocyte differentiation is perhaps an overstatement (unless a wider characterization of statin treated monocytes is presented). Perhaps: mevastatin interferes with / modulates / modifies /... monocyte differentiation would be more adequate.

For in vitro experimental work mevastatin must be converted to the active compound by treatment with alkali. Nothing is mentioned about this issue and must be clarified

It is unclear whether all 18 apoptosis experiments (3 per individual) were use for statistical calculations. The appropriate evaluation would be to average the three results corresponding to the same individual (essentially one datum, not three) and then to use the six available data for statistical calculations. Essentially the same comment is applicable to other experiments carried in dupli or triplicate

The second paragraph of page 9 might be interpreted as if gamma interferon also potentiate the LPS-induced IL-1B secretion by mevastatin treated monocytes. According to the graph, both LPS alone and LPS + interferon induced a similar IL1B secretion by mevastatin-treated monocytes. The fact that there is a delay in the detection of apoptosis (24-72h) has been already described in other cell types that do not undergo differentiation. It has been postulated that the action of statins may be mediated by the inhibition of the prenylation of proteins (particularly Rho) whose pool might need to be depleted for the effects of the statin. Therefore this delayed apoptotic action may be related to issues not necessarily related to macrophage differentiation, as assumed in the paper. This conclusion should be at least attenuated or at most offered as one possible alternative.
Discretionary revisions
It should be explained why mevastatin was chosen, since mevastatin is an old drug not in available for clinical use, whereas there is a variety of statins available both for clinical and laboratory use. The attempt of reversal of mevastatin effects by farnesol (or farnesyl-PP) and geranylgeraniol (or GGPP) would be of great interest. In this regard, a mention to the potential mevalonate derivatives involved in those phenomena (already proven in other cell lines), deserves some comment. Several authors have demonstrated that statins may inhibit not only MCP-1 secretion, but also other chemokines. This could be also mentioned in the discussion. Additionally, some early reports have suggested that statins may also inhibit M-CSF expression, thereby providing a potential mechanism whereby statins modulate monocyte proliferation and differentiation (Miner Electrolyte Metab 1996;22(1-3):147-52)
I concur with the authors that the nature of apoptosis in atherosclerosis must not be simplified as friend or foe. While promoting cell death in advanced plaques might contribute to instability and vascular events, it is likely that apoptosis plays a protective role in early stages (intimal thickening) and restenosis. Some authors have detected that some effects of statins may require a pre-incubation, perhaps to deplete some cellular mevalonate derivatives (or prenylated proteins). This possibility should be mentioned if the authors want to speculate beyond their own data regarding some time-dependent effects

Competing interests:
None declared.