The antitumour activities of statins

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Abnormally elevated levels of serum cholesterol have been demonstrated to contribute to atherosclerosis and coronary artery disease. Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are efficient and widely used drugs in the treatment of lipid disorders, especially hypercholesterolemia. In addition to their cholesterol-lowering effects, statins are reported to inhibit tumour cell growth [1,2]. Statins are also known to synergistically enhance the effects of chemotherapy [3,4] and to overcome chemoresistance [5]. Accordingly, statins prolong the survival of patients with hepatocellular carcinoma [4], and they reduce the risk of colorectal cancer [6] and breast cancer [7].

Statins induce apoptosis and reduce cell invasiveness in various cell lines, including malignant glioma [8], neuroblastoma [9], myeloid leukemia [10], and breast carcinoma [11]. Cancer cells overexpress HMG-CoA reductase [12]. The chemopreventive activity of statins against cancer is suggested to depend on inhibition of HMG-CoA reductase in cholesterol synthesis and, thereby, cell growth [13]. The Ras protein is important in the regulation of cell differentiation and proliferation. Statins are reported to inhibit the activation of *ras* [14]. The products of the mevalonate pathway are necessary for diverse cellular functions, including the G1–S phase transition of cell proliferation and the formation of cell membranes [15]. Statins may therefore inhibit cancer cell growth and lead to apoptotic cell death through their inhibition of the mevalonate pathway, although other mechanisms also have been suggested.

Interleukin-18 (IL-18), a monocyte-derived cytokine, is upstream of the production of interferon γ from T cells and natural killer cells [16,17]. Interleukin-18 is known to play an important role in regulating immune responses, exhibiting significant antitumour activity [18]. The antitumour effects of IL-18 are mediated by activation of natural killer cells and cytotoxic T lymphocytes [19]. In a previous study, we found that the statins pravastatin, fluvastatin, and simvastatin induced production of IL-18 by human monocytes [20,21]. The effects of pravastatin, fluvastatin, and simvastatin were abolished by the addition of mevalonate, indicating the involvement of HMG-CoA reductase in the action of the tested statins.

Angiogenesis is characterized by the formation of new capillaries from existing vessels. It is well known that tumour growth and metastasis both require growth of new blood vessels [22,23]. The statins lovastatin and cerivastatin are reported to inhibit tumour-induced angiogenesis by reducing metabolites of the mevalonate pathway that are pivotal in angiogenesis [24,25].

The foregoing observations suggest that the anticancer effect of statins depends on the apoptosis of cancer cells, the production of IL-18 by monocytes, and the inhibition of angiogenesis. However, the effects of statins on cancer are not completely understood. Further experimental research will be useful in clarifying this complex relationship.

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