Statins: novel weapons against granulomatous disorders and HIV infection?

The adhesion molecules LFA-1 and ICAM-1 are considered to be critically involved in cell fusion and multinucleated giant cell (MGC) formation (1).

Alveolar macrophages of patients with pulmonary sarcoidosis show increased expression of LFA-1 and ICAM-1 (2) and, importantly, it has been shown that MGC formation can be blocked by anti-LFA-1 and anti-ICAM-1 antibodies (1).

LFA-1/ICAM-1 interaction also plays an important role in the progression of HIV:
a) HIV stimulates LFA-1/ICAM-1 mediated aggregation of monocytes and MGC formation, which is supposed to facilitate intercellular transmission of the virus, and
b) HIV incorporates a vast array of host membrane molecules during its budding process, including ICAM-1. The engagement of ICAM-1 with LFA-1, on the cell surface, enhances virus infectivity by favoring cytosolic devlivery of viral material. In fact, the rolling of virus entity onto the cell surface due to the association between ICAM-1 and LFA-1 allows for the achievement of a sufficient number of interactions between gp120 and CD4 (3).

It has recently been shown that the HMG-CoA reductase inhibitors (statins) potently inhibit the expression of LFA-1 and ICAM-1 on leukocytes and also interfere with ICAM-1/LFA-1 interaction through binding to LFA-1 (4,5).

Therefore, given that LFA-1/ICAM-1 interaction is a key event in granuloma formation and also in HIV transmission, and given that statins inhibit the expression of LFA-1 and ICAM-1 and, more importantly, their interaction, these safe and inexpensive agents may prove valuable in the treatment of both granulomatous disorders and HIV infection.

As the routine anti-granuloma drugs such as allopurinol, tranilast and ACE inhibitors exert their therapeutic action through other mechanisms that inhibite the ICAM-1/LFA-1 interaction, i.e. through downregulation of P2X7 receptors and ICAM-1 (1), the addition of statins could provide a more potent inhibition of granuloma formation.

Also, the addition of statins to pyridoxal 5^{e}-phosphate, which is believed to hamper HIV entry to CD4^{+} cells via attachment to the CD4 molecule (6), may provide a more powerful inhibitor of progression of HIV.

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