Abstract:

It is widely assumed that glatiramer acetate (GA), an approved agent for the immunomodulatory treatment of multiple sclerosis, acts primarily as an antigen for T lymphocytes. Recent studies, however, indicated that in vitro, GA directly inhibits dendritic cells, a rare but potent type of professional antigen-presenting cell (APC). To investigate whether these in vitro observations are relevant to the actions of GA in vivo, we studied the effects of GA on monocytes, the major type of circulating APC. In a first series of experiments, we investigated the effects of GA on monocyte reactivity in vitro. Monocytes were stimulated with ligands for Toll-like receptor (TLR)-2 (peptidoglycan and lipoteichoic acid), TLR-4 [lipopolysaccharide (LPS)] and TLR-5 (flagellin), as well as two proinflammatory cytokines (interferon-gamma and granulocyte-monocyte colony-stimulating factor). Monocyte activation was measured by induction of the surface markers signalling lymphocytic activation molecule (SLAM), CD25 and CD69 (detected by cytofluorometry), and by production of monocyte-derived tumour necrosis factor (TNF)-alpha (detected by enzyme-linked immunospot assay). GA had a broad inhibitory effect on all measures of monocyte reactivity, regardless of which stimulator was used. It is unlikely that this reflects a simple toxic effect, because monocyte viability and CD14 expression were unaffected. In a second series of
experiments, we investigated the properties of monocytes cultured ex vivo from eight GA-treated multiple sclerosis patients, eight untreated multiple sclerosis patients and eight healthy subjects. We found that LPS-induced SLAM expression and TNF-alpha production were significantly reduced in monocytes from GA-treated patients compared with controls. These results demonstrate for the first time that GA inhibits monocyte reactivity in vitro and in vivo, significantly extending the current concept of the mechanism of action of GA.

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