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Immunosuppressant cytoprotection correlates with HMGB1 suppression in primary astrocyte cultures exposed to combined oxygen-glucose deprivation

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Abstract:
The protective potential of immunosuppressants has been reported in many experimental models of ischemia both *in vivo* and *in vitro*, suggesting a novel therapeutic application of these drugs. Because high-mobility group box 1 (HMGB1) protein has recently been reported to be involved in ischemic brain injury, the purpose of the present study was to determine whether treatment with immunosuppressants could decrease the expression and release of HMGB1 in astrocytes exposed to simulated ischemic conditions (combined oxygen-glucose deprivation, OGD). We also investigated whether immunosuppressive drugs could attenuate necrosis in astrocyte cultures exposed to OGD. Finally, we studied the influence of immunosuppressants on the expression of NFκB, inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2). Cells were treated with cyclosporine A, FK506 and rapamycin (all drugs at concentrations of 0.1, 1 and 10 μM). Our study provides evidence that immunosuppressants decrease the expression and release of HMGB1 in ischemic astrocytes. Our data suggest that HMGB1 release may be partly an active process triggered by oxidative stress because the antioxidant N-acetylcysteine (NAC) clearly attenuated HMGB1 expression and release. Furthermore, we show that the immunosuppressants, at the same concentrations that significantly suppressed HMGB1 expression and release, were also able to prevent the necrosis of ischemic astrocytes and inhibit the expression of inflammatory mediators (NFκB, iNOS and COX-2). These results provide further information about the cytoprotective mechanisms of immunosuppressants on ischemic astrocytes, especially in relation to the pathophysiology of ischemic brain injury. It appears that the protective effects of immunosuppressants can be mediated in part by the suppressing the expression and release of HMGB1 in astrocytes, which leads to the attenuation of ischemia-induced necrosis and neuroinflammation.

Key words:
HMGB1, cyclosporine A, FK506, rapamycin, astrocytes, ischemia, iNOS, COX-2