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S100B/RAGE-dependent chemoattraction of microglia

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The Ca^{2+}-binding protein of the EF-hand type, S100B, is abundantly expressed in and released by astrocytes, and leakage of S100B from damaged astrocytes occurs during the course of acute and chronic brain disorders [1]. Thus, the concept has emerged that S100B might act an unconventional cytokine or a damage-associated molecular pattern protein playing a role in the pathophysiology of neurodegenerative disorders and inflammatory brain diseases. S100B's pro-inflammatory effects require relatively high concentrations of the protein, while at physiological concentrations S100B exerts trophic effects on neurons. Most, if not all of the extracellular (trophic and toxic) effects of S100B in the brain are mediated by the engagement of RAGE (receptor for advanced glycation end products) [1-2]. For example, high S100B activates RAGE-dependently microglia, stimulating the release of IL-1β and TNF-α and upregulating the expression of the pro-inflammatory enzyme, COX-2 [3-4]. We show here that high S100B chemoattracts murine microglia via RAGE engagement and RAGE-dependent activation of Src kinase, Ras, PI3K, MEK/ERK1/2, RhoA/ROCK, Rac1/JNK/AP-1, Rac1/NF-κB and, to a lesser extent, p38 MAPK. Recruitment of the adaptor protein, diaphanous-1, a member of the formin protein family, is also required for S100B/RAGE-dependent chemoattraction of microglia. The S100B/RAGE-dependent activation of diaphanous-1/Rac1/JNK/AP-1, Ras/Rac1/NF-κB and, likely, Src/Ras/PI3K/RhoA/diaphanous-1 results in the upregulation of expression of the chemokines, CCL3, CCL5 and CCL12, the release and activity of which are required for S100B to chemoattract microglia. Lastly, RAGE engagement by S100B in microglia results in upregulation of the chemokine receptors, CCR1 and CCR5. These results suggests that S100B might participate in the pathophysiology of brain inflammatory disorders via RAGE-dependent regulation of several inflammation-related events including attraction and activation of microglia.

References

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