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Poster presentation

LPS-induced down-regulation of NO-sensitive guanylyl cyclase in astrocytes occurs by proteasomal degradation in nuclear bodies

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Background

We have previously shown that inflammatory agents (LPS, IL-1β, β-amyloid peptides) that induce reactivity and NOS-2 expression in glial cells down-regulate astroglial soluble guanylyl cyclase (sGC) *in vitro* and *in vivo* [1,2].

Results

Here we show that the decrease in sGC activity and β1 subunit protein induced by LPS (10 ng/ml, 24 h) in cultured rat cerebellar astrocytes is prevented by inhibitors of proteasome activity (MG132 5 μM; lactacystin 10 μM) whereas other protease inhibitors (calpain inhibitor 25 μM; ICE inhibitor II 100 μM and leupeptin 5 μM) were not effective. Furthermore, immunocytochemistry and confocal laser microscopy revealed that in LPS-treated cells a strong sGC β1 immunorreactivity is evident in aggregates in the cell nuclei where it co-localizes with 20S proteasomes and ubiquitin in clastosomes, nucleoplasmic substructures involved in ubiquitin-proteasome-dependent nuclear proteolysis, but do not colocalize with others proteasome-enriched structures include promyelocytic leukaemia bodies and splicing speckles. In contrast, in untreated astrocytes clastosomes are scarce and sGC β1 immunorectivity shows a diffuse cytoplasmic pattern, while in the nucleus it is very weak. A similar distribution is observed when cells are treated with LPS and the proteasome inhibitor MG132 or the protein synthesis inhibitor cycloheximide.

Conclusion

LPS orchestrates the recruitment of sGC-β1 protein and components of the ubiquitin-proteasome system to specialized nuclear bodies, clastosomes, suggesting a mechanism for inflammation-induced down-regulation of sGC in astrocytes.

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