

P028 Astrocyte–leucocyte interactions and the mechanisms regulating matrix degradation in CNS tuberculosis

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CNS tuberculosis results in extensive tissue damage leading to death if untreated. We hypothesized that astrocytes have a key role in regulation of MMPs which are involved in inflammatory cell influx and tissue destruction. Conditioned medium from *M. tuberculosis*-infected monocytes (CoMTB) stimulated MMP-1, -2, -3, -7 and -9 gene expression on real-time PCR but only MMP-9 secretion was detected both *in vitro* and in brain biopsies from patients. Conditioned medium from infected microglial cells or other astrocytes had no effect. MMP-9 activity was NF- κ B-dependent with nuclear translocation of the p65 component being 3-fold greater than that of p50. MMP-9 secretion was synergistically upregulated by IFN γ which interacts with IL-1 β and other mediators in CoMTB. CoMTB-induced MMP-9 secretion is jnk, erk and p38 mitogen activated protein kinase (MAPK) dependent and is regulated by AP-1 with c-jun, Fos-B and JunB subunits being activated. The synergistic interaction with IFN γ is regulated by p38 MAPK (which is phosphorylated in patients), jak-2, stat-1 and stat-3 dependent but only stat-3 is involved in driving synergy. Steroids, which are used in treatment of CNS tuberculosis, suppress CoMTB-induced MMP-9 secretion and abolish synergy with IFN γ . IFN γ suppresses CoMTB-induced TIMP-1/2 secretion and this effect is not steroid-sensitive. In summary, complex mechanisms regulate leucocyte-astrocyte networks driving MMP activity in tuberculosis which will result in a matrix degrading environment within the CNS; these may be potential therapeutic targets.