Objectives: Neutrophils are the major phagocytic cells in the lungs of patients with active pulmonary tuberculosis (TB). A matrix degrading phenotype in TB results in tissue damage, where the activity of matrix metalloproteinases (MMPs) is unopposed by their tissue inhibitors (TIMP). Factors regulating neutrophil MMP secretion in TB in vitro and in patients were investigated.

Methods: Human neutrophils were infected with *Mycobacterium tuberculosis* (Mtb) or stimulated with conditioned media from Mtb-infected monocytes (CoMTB). Analysis of MMP-8/-9 secretion and TIMP-1/-2 was by ELISA, Luminex array and zymography. Gene expression of MMP-8/9 was investigated using real-time PCR. Neutrophil granule formation was assessed by confocal microscopy. Induced sputum samples from 108 healthy controls and TB patients were analysed. Brain biopsies from patients with central nervous system-TB were studied by immunohistochemistry.

Results: Neutrophil MMP-8/-9 secretion is upregulated by Mtb over time and is dependent on TB multiplicity of infection. CoMTB stimulated neutrophils resulted in a 2 and 3 fold up-regulation of MMP-8/-9 secretion respectively (both p<0.001). TIMP-2 is increased 2-fold (p<0.001) but not TIMP-1. MMP-8 and -9 is increased 16 and 160 fold respectively compared to TIMP-2. MMP-8/-9 gene expression was increased 3.5 fold and 7 fold respectively by CoMTB stimulation at 24 hours (both p<0.001). Confocal microscopy demonstrated colocalisation of early endosome marker Rab-5 with MMP-8 and -9 indicating that MMP-8/-9 are newly synthesised. MMP-8/-9 is significantly elevated in induced sputum samples from TB patients compared to healthy controls and both correlate with the neutrophil markers neutrophil gelatinase associated lipocalin and myeloperoxidase. Brain biopsy specimens from patients with CNS-TB demonstrated neutrophils surrounding TB granulomas with MMP-8 and -9 present.

Conclusion: Neutrophil MMP-8/-9 gene expression and secretion is upregulated following direct infection with TB or stimulation by monocyte-dependent TB networks. The increase in MMP/TIMP ratio will result in a proteolytic environment...