[PS1.16]

Activation of MMP-9 by Human Lung Epithelial Cells in Response to *Burkholderia cenocepacia* Infection Reduced Wound Healing of Confluent Lung Epithelia

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Introduction: *Burkholderia cepacia* complex (Bcc) is a group of opportunistic pathogens that colonise patients with cystic fibrosis (CF). The two most clinically relevant species are *B. cenocepacia* (Bc) and *B. multivorans* (Bmv), of which Bc is most virulent. Bcc infection has been associated with chronic colonisation, a decline in lung function and, in a subgroup of CF patients, septicaemia and death. The aim of this work was to examine the role of MMPs in the pathogenesis of Bcc, which has not been explored to date.

Methods: Transcription of MMP genes in two lung epithelial cell lines in response to Bcc infection was determined by Rea-time PCR. Gelatinase zymography of conditioned cell media (CCM) was carried out to examine MMP activation. The effect of activated MMPs on confluent cell monolayers, wounded with a sterile pipette tip, was examined. *Pseudomonas aeruginosa* strain, PAO1, was used as a control.

Results: Bc infection resulted in up-regulation of MMP2 and MMP9 genes in CF lung cells, while MMP2, -7 and -9 were up-regulated in non-CF lung cells. CCM from both cell lines showed increased MMP9 activation following Bc infection relative to control (C), in contrast to Bmv (Fig 1). APMA activation of control CCM from both cell lines also resulted in clear activation of MMP9 and to a lesser extent MMP2. CCM from either Bc infected cells or following APMA activation significantly reduced the rate of wound healing in confluent lung epithelia ($p < 0.05$), in contrast to CCM from PAO1 infected cells, which showed predominant MMP-2 activation.

Discussion: APMA and Bc infection both result in activation of MMP-9. This suggests that MMP-9 is responsible for the reduced wound healing observed in response to Bc infection. This implies that MMP9 activation following Bc infection contributes to the virulence of, and lung damage associated with, Bc infection.

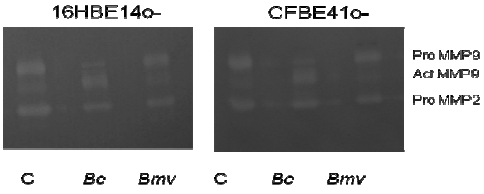

Fig 1: Gelatin zymography of CCM from Bcc infected cells relative to control (C).

Keywords: Metalloproteinases, Burkholderia cepacia complex, Lung epithelial cells, Cystic fibrosis