Cell Communication and Signaling BioMed Central

Meeting abstract

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The *Pasteurella multocida* toxin (PMT) induced differentiation of haematopoietic progenitor cells in macrophages and B cells

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from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A47 doi:10.1186/1478-811X-7-S1-A47

This abstract is available from: http://www.biosignaling.com/content/7/S1/A47

The *Pasteurella multocida* toxin (PMT) is a highly mitogenic toxin that mainly affects domestic and wild animals, but can also affect humans through animal bites. PMT induces porcine atrophic rhinitis that is characterised by bone resorption and loss of nasal turbinate bones. PMT acts intracellularly and activates heterotrimeric G proteins by an unknown mechanism. The N-terminus of PMT includes the receptor-binding and translocation domain that supposedly binds to ganglioside type receptors, whereas the C-terminus contains the biologically active domain.

Our data show that PMT induces proliferation and differentiation of haematopoietic progenitor cells into macrophages and B-cells. To investigate the influence of PMT on proliferation of haematopoietic progenitor cells we performed cell proliferation ELISAs that showed a significant increase of growth in PMT-treated cells compared to the unstimulated control. To identify the cell types that differentiated from the isolated bone marrow cells (BMC) we stimulated BMCs for 7 days with PMT. To exclude the possibility that LPS contaminations triggered the observed cell growth, an N-terminal PMT fragment containing only the translocation domain, or a PMT fragment lacking the complete catalytic domain were used and found to be inactive. BMCs were then analyzed by FACS analysis, which revealed differentiation of the PMT-stimulated cells in populations that were missing in the unstimulated cells. We identified the generated populations using fluorescently labelled surface marker-specific antibodies and found CD45R (B-cells) and CD11b (macrophages) expression significantly increased in stimulated cells. The macrophage population was further characterised in a phagocytosis assay using fluorescent latex beads and found to be as effective as control macrophages generated with L-cell-conditioned media. To investigate whether PMT directly stimulates cell differentiation or induces the secretion of other soluble factors, we assayed the IL6 production that stimulates the differentiation of B-cells and macrophages, in PMT-treated BMCs compared to unstimulated cells. The data show a significant increase of IL6 secretion of PMT-stimulated cells supporting the idea that PMT induces cytokine production in BMCs. Using BMCs from toll like receptor (TLR) -2 deficient mice that are unresponsive to LPS we investigated whether PMT would still be able to cause cell differentiation. However, this was not the case. While LPS stimulates osteoclast activity, it does not allow osteoclast differentiation from progenitor cells. Also PMT mutants without biological activity were unable to stimulate cell differentiation. We therefore propose an LPS-independent mechanism where PMT activity needs TLR2 as an essential cofactor.