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SOCS-1 potentiates *Pasteurella multocida* toxin induced cell transformation

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Pasteurella multocida toxin (PMT) is a mitogenic protein toxin that modulates mammalian signalling cascades. In pigs, PMT causes atrophic rhinitis characterized by loss of nasal turbinates. Experimental nasal infection leads to excess proliferation of bladder epithelial cells suggesting it has carcinogenic properties. Recently we showed that PMT induces signal transducers and activators of transcription (STAT) activity through Gαq mediated activation of JAK kinases. Activation of the JAK-STAT pathway is persistent, as PMT does not induce expression of suppressor of cytokine signalling (SOCS) proteins.

We overexpressed SOCS-1 in HEK293 cells to investigate if this would downregulate PMT-induced STAT activation. However, STAT activity was not abrogated; instead, SOCS-1 enhanced STAT3 activity significantly. To test if this effect was specific for SOCS-1, we expressed SOCS-1, -3 or CIS and monitored STAT3 transcriptional activity. Hyperactivation of STAT3 correlated with the nuclear localization of the SOCS protein and SOCS-1 was a much stronger activator than SOCS-3, while CIS did not enhance STAT activity. However, a CIS mutant containing the SOCS-1 nuclear localisation sequence (NLS) acted as potently as SOCS-1. We next determined the phosphorylation status and expression of the STAT3 activating tyrosine kinase JAK2. Interestingly, JAK2 expression levels were increased in the presence of SOCS-1 eventually leading to hyperphosphorylation of JAK2. It is known that SOCS proteins act as E3 ubiquitin ligases that target proteins, for example JAK kinases, to proteasomal degradation. Oncogenic kinases such as Bcr-Abl can overcome this process through activation of pathways that lead to serine phosphorylation of SOCS-1. It is believed that Pim serine/threonine kinases are crucial for this. Pim kinases are STAT dependent genes and the protein was shown to interact with SOCS-1 directly. Cells stimulated with PMT showed high Pim-1 expression that increased with time and were strongest after over-night stimulation, while IL6-stimulated cells downregulated Pim-1 expression within 3 hours. Incubation with a Pim-1 specific inhibitor reversed the SOCS-1-dependent transcriptional hyperactivity of STAT3 to a great extent. In addition, we found that SOCS-1 is heavily threonine phosphorylated after PMT-stimulation but not after stimulation with IL-6. We hypothesise that persistent expression of Pim-1 leads to phosphorylation of SOCS-1, which protects JAK2 from proteasomal degradation. JAK2 accumulates, leading to hyperactivation of STAT3 and probably enhanced transforming potential. In a colony formation assay using HEK293 cells PMT was able to induce anchorage independent cell growth. This effect was even more pronounced in the presence of SOCS-1. In summary, we show that PMT is able to hijack signalling cascades much in the same way than oncogenic tyrosine kinases and that its capacity to transform cells is enhanced by SOCS-1.