

P017 The role of SIRT1 on IL-8 production through deacetylation of NF- κ B

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Sirtuins are nicotine adenine dinucleotide (NAD⁺) dependent protein deacetylases. Sirtuin type 1 (SIRT1) is one of seven human sirtuins and is localised to the nucleus as well as cytoplasm. SIRT1 has been implicated in prolonging cell longevity and increasing resistance to oxidative stress. This might be particularly relevant in diseases like severe asthma and chronic obstructive pulmonary disease (COPD), where higher level of oxidative stress is seen. Few studies have focused on the effect of SIRT1 on inflammatory cytokine production. Thus, the aim of this study was to explore, in A549 cells, the impact of SIRT1 on production of IL-8, which is a neutrophil chemotactic factor and abundant in COPD. Nicotinamide, a sirtuin inhibitor, concentration-dependently (10-1000 μ M) and selectively enhanced IL-1 β -induced IL-8 production, but not GM-CSF. This was also confirmed in SIRT1 knockdown cells by RNA interference. We also showed that H₂O₂-mediated oxidative stress decreases SIRT1 activity without changing levels of protein expression and H₂O₂ treatment enhanced IL-1 β -induced IL-8 production. As for the molecular mechanism, we demonstrated that SIRT1 inhibition induced hyperacetylation of NF- κ B p65 and this acetylated p65 was able to bind IL-8 promoter region preferentially over GM-CSF promoter. Furthermore, sirtuin activator (resveratrol) and SIRT1 overexpression inhibited IL-8 production. This finding might give new insight on understanding how IL-8 is selectively increased in COPD or under oxidative stress, and aid development of new therapies for COPD.