

P033 Toll-like receptor 2 is essential for the sensing of oxidants during inflammation

Mark J. Paul-Clark, Shaun K. McMaster, Rosalinda Sorrentino and Jane A. Mitchell

Cardiothoracic Pharmacology, Unit of Critical Care Medicine, Imperial College London, Royal Brompton Hospital, Dovehouse Street, London SW3 6LY.

Oxidant signalling is an integral part of inflammation. The mechanisms by which oxidants are sensed, initiate inflammation and influence pathology are not well understood. Interestingly, inflammation provoked by oxidants is similar to that produced by pathogens which are sensed by pattern recognition receptors which including Toll like-receptors (TLR). It is now increasingly recognised that TLRs may mediate inflammation in more general terms, by recognizing host-derived factors such as fibrinogen and heat shock proteins (60 and 70). In the current study we have investigated the potential that TLR2 may be a surrogate receptor for oxidants. The oxidants H₂O₂ and cigarette smoke extract (CSE) induced inflammation in C57BL6 mice. In contrast, TLR2^{-/-} mice were resistant to these inflammogens, implicating this TLR2 in the sensing of oxidants. Furthermore we found that these oxidant stimuli activated macrophages *in vitro* to release CXCL8 which was inhibited by an anti-TLR2 antibody and associated with rapid phosphorylation of IRAK1, the primary phosphorylation step in TLR2 activation. Further evidence that TLR2 is a sensor of oxidants was provided by HEK293 cells stably transfected with TLR2, TLR1/2 or TLR2/6. These cells released CXCL8 (CXCL8; IL-8) when stimulated with a range of oxidants, which was in contrast to null transfected cells that were insensitive to oxidant stimulation. These observations indicate that TLR2 is essential for the sensing of oxidants and may have implications for lung and cardiovascular disease.