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HYDROGEN PEROXIDE TRIGGERS A DUAL SIGNALING AXIS TO SELECTIVELY SUPPRESS CXCL11/CXCR3 –ACTIVATED HUMAN T LYMPHOCYTE MIGRATION

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Reactive oxygen species (ROS) are known to influence the outcome of T cell responses. Depending on concentration, exposure time, and microenvironment, the effects of ROS on T cells can be very distinct and affect a variety of physiological events, including cell proliferation, host defense, differentiation, apoptosis, senescence, and activation of growth-related signaling pathways. T cells can produce low levels of H_2O_2 upon TCR and chemokine stimulation, which have been shown to facilitate T cell activation. Additionally, T lymphocytes also express NADPH oxidase enzymes NOX_2 and DUOX1 that catalyze the reduction of molecular oxygen to generate superoxide O_2, which can dismute to generate ROS species. These ROS participate in host defense by killing or damaging invading microbes. Additionally, in several human pathologies, including cancer and a variety of auto- immune disorders, high levels of pro-oxidants are known to induce T lymphocyte hypo responsiveness. H_2O_2 is an early danger cue required for innate immune cell recruitment to wounds, but little is known about the effect of H_2O_2 on migration of human adaptive immune cells to sites of inflammation. However, oxidative stress is known to impair T cell activity, induce actin stiffness, and inhibit cell polarization. In this study, we show that H_2O_2 selectively impedes chemokinesis and chemotaxis of previously activated human T cells to CXCL11, but not other chemokines. This deficiency in migration is due to a reduction in inflammatory chemokine receptor CXCR3 surface expression and cellular activation of lipid phosphatase SHIP-1. Moreover, pharmacological evidence indicates that H_2O_2 acts via a Src kinase to activate the lipid phosphatase SHIP-1, a negative regulator of PI3K signaling. Thus, while H_2O_2 can function as an early recruitment trigger for innate immune cells, it appears to operate as an inhibitor of T lymphocyte immune adaptive responses that are not required until later in the repair process.

Biography

Stephen Ward is Head of Pharmacy and Pharmacology at the University of Bath and has held several personal fellowships and received funding from the Wellcome Trust, MRC, BBSRC and Royal Society. He has published over 110 primary research articles and reviews in the field of Inflammatory Cell Biology and has supervised over 35 PhD students. This research has often involved close collaboration with industry that has enhanced student training by allowing them to spend time in industrial laboratories.

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