New insights into the molecular processes of immune regulation

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Researchers from the Department of Pharmacy & Pharmacology have made an important discovery that might lead to novel therapies to combat chronic inflammation.

The work, jointly funded by the Biotechnology and Biological Sciences Research Council (BBSRC) and Wellcome Trust, is published in the *Journal of Immunology* and focuses on so-called danger signals such as reactive oxygen species that are released by damaged or dying cells during wounding or infection, and their impact on the subsequent immune response.

The research team led by Professors Steve Ward from the Department of Pharmacy and Pharmacology and Will Wood (University of Bristol) studied the effect of hydrogen peroxide, one such danger signal, on the movement of T lymphocytes which orchestrate the immune response to infection and wound healing.

Hydrogen peroxide is an early danger cue that is already known to be required for other immune cells to migrate to wounds, where these cells provide the first-line of defence to damage or infection

By taking T lymphocytes from healthy human volunteers, the team were explored the ability of the T lymphocytes to migrate and respond to inflammatory stimuli in the presence of hydrogen peroxide and other reactive oxygen species.

Curiously, their work revealed that in contrast to the effects on other immune cells, reactive oxygen species actually suppress the movement of T lymphocytes toward pro-inflammatory stimuli.

Lead author Dr Jennifer Ball in the Department of Pharmacy and Pharmacology, said: "Biologically, T cells are required later in the immune response process as they provide a specific and long-lasting protection. Our research indicates that hydrogen peroxide could be a key regulator in co-ordinating the recruitment of immune cells in the order of their biological importance. We propose that once recruited by other inflammatory signals, the T cells are then immobilized by hydrogen peroxide and therefore restricted to the inflamed sites, this facilitating the resolution of inflammation. In a pathological setting however, high levels of reactive oxygen species could cause widespread suppression of T lymphocyte migration and prolong chronic infection or delay resolution of inflammation or wound healing".

The team also provided some insight into the molecular processes by which hydrogen peroxide might impair the the movement of T lymphocytes. Remarkably, hydrogen peroxide was able to activate a molecule called SHIP-1, a key negative regulatory protein which suppresses a major activating signaling pathway linked to facilitating cell movement.

This effect on SHIP-1 could also be mimicked by novel pharmacological tools that activate SHIP-1, underlining the potential therapeutic opportunities of targeting SHIP-1 in T cell driven pathologies including cancer, autoimmune disease and allergies.

More information: Jennifer A. Ball et al. Hydrogen Peroxide Triggers a Dual Signaling Axis To Selectively Suppress Activated Human T Lymphocyte Migration, *The Journal of Immunology* (2017). DOI: 10.4049/jimmunol.1600868

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