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LPS-induced tolerance to TNF-α in human pro-monocytic THP-1 cells

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Following an initial pro-inflammatory cytokine response to lipopolysaccharide (LPS), macrophages show a much-diminished response to a subsequent stimulatory dose of LPS. This phenomenon, called LPS or endotoxin tolerance, probably evolved as a mechanism to prevent serious complications of an over exuberant inflammatory response to gram-negative bacterial infections (e.g., septic shock). It has been demonstrated that the inflammatory cytokine TNF-α can induce macrophages to produce large amounts of TNF-α. Presumably, this serves as an amplification loop for the inflammatory response. However, it has been demonstrated that TNF-α pretreatment of macrophages induces a tolerant state in which the subsequent response of these cells to LPS is greatly diminished. Though it is not known whether macrophages made tolerant to LPS are refractory to subsequent stimulation with TNF-α. In other words, can the TNF-α produced by macrophages in response to a gram-negative bacterial infection overcome the LPS-induced tolerant state?

To investigate this question, human pro-monocytic THP-1 cells were stimulated with LPS for 2 hr and allowed to 'recover' for 14 hr in fresh media before being challenged with stimulatory doses of either LPS or TNF-α. The initial LPS stimulation generated a dose-dependent primary TNF-α protein response within 4 hours, with very little to no TNF-α protein secreted after this time point. As expected, LPS-stimulated cells were non-responsive to subsequent LPS challenges. When the LPS-stimulated cells were challenged with TNF-α, the cells remained in a tolerant state. These data suggest that high levels of TNF-α produced by macrophages in response to endotoxin during a gram-negative bacterial infection cannot overcome tolerance.

Biography

Christopher Loosbroock is currently a third year graduate student at the University of Nevada, Reno in the Cellular and Molecular Biology PhD program. His anticipated graduation is May 2014. Prior to returning to graduate school, Christopher worked at Charles River Laboratories, Preclinical Services as a Project Scientist in the GLP-compliant Lab Sciences department developing and validating immunoassays for toxicokinetic and immunotoxicity assessments.

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