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The pivotal role of proteasome subunits in lipopolysaccharide mediated immune response

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Statement of the Problem: During pathogen-mediated inflammation, host peripheral blood mononuclear cells/monocytes/macrophages (PBMC/MO/M ϕ) play a critical role in exacerbating or resolving disease by (a) priming of naïve and resident cells for selective host responsiveness; (b) extensive release of cytokines, reactive oxygen species, and nitric oxide; and, (c) development of hyporesponsiveness (tolerance/refractoriness) where selective host responses are repressed. Mechanisms of bacteria-triggered development of diseases in patients provide a prototype example of each of the responses elicited to various extents during disease progression/resolution. It is well-established that the human host innate immune system has developed the capacity to recognize and respond immunologically to multiple bacterial structures, such as lipopolysaccharides (LPS), peptidoglycan, and CpG DNA. However, all cells behave differentially with respect to agonists. The mechanisms underlying the modulation of these immune cells with respect to LPS are not well defined and conflicting results are reported. The purpose of this study is to understand the role of LPS in innate immune responses, such as induction of growth factors, priming, proliferation, differentiation, cytokines, nitric oxide, autophagy and death in PBMC/MO/M ϕ based on the proteasome's proteases (a complex that degrades key regulatory proteins). A novel model based on the function of subunits of the proteasome was developed in both human and murine cells, based on genomics, proteomics, and signaling pathways. Several hormones, dietary nutrients, and vitamins were also tested in PBMC/MO/M ϕ from normal and diseased subjects with surprising results.

Conclusion & Significance: The innate immune response induced by LPS in human monocytes (huMO) and mouse M ϕ , as described above is largely dependent on the change in composition/function of cellular proteasomes in cells. This novel information will lead to the development of drugs for sepsis, diabetes, asthma, cancer, AIDS, and neurological diseases, based on solid findings on the modulation of proteasomes in immune cells.

Biography

Dr Nilofer Qureshi has more than 40-years' experience in LPS related research (> 150 publications), and has played a pioneering role in studies related to cholesterol biosynthesis, structure and biosynthesis of mycolic acids in *Mycobacterium tuberculosis*; purification, structure and biology of several LPS/lipid A; and the mechanisms by which LPS alters innate immunity via proteasomes and causes disease. She has expertise in designing lipid A molecules for use as adjuvants such as MPLA and RsdPLA, which is a powerful LPS antagonist in both *in vitro* and *in vivo* systems. She has recently developed a new cell model that explains how LPS or other agonists activate inflammatory processes in various cell types, based on proteasomes. Proteasomes are present in all cells and play an integral role on the activity of the immune system. The proteasome is a central regulator of macrophage function and inflammation involved in several diseases. This model will be useful for designing novel drugs for sepsis, diabetes, asthma, cancer, AIDS, and neurological disease based on modulating the activity of proteasomes. This research was supported by NIH grants.

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