Summary

Cadmium and its compounds are most common environmental toxicants with potential for bioaccumulation and persistence in the body that produce versatile biotic changes in all ecosystems. The heavy metal cadmium is an environmental toxicant that induces pathophysiological changes in many organ systems. Response to cadmium induced cellular stress involves marked immunological changes. Macrophages play a critical role in the body’s defense system by eliminating microorganisms from infected tissue as a part of the body’s non-specific defense mechanism. Functions of splenic and peritoneal macrophages from cadmium exposed mice have been examined (both in vivo and in vitro) and any alteration in the functional activities of these cell types, particularly morphological alteration, chemotactic migration, phagocytosis, intracellular killing, enzyme release, DNA fragmentation of the cells and other primary immune responses (humoral and cell mediated) have been determined and reported. Our results demonstrate that cadmium chloride, an inorganic divalent form, markedly impairs differentiated features of murine blood monocyte-derived macrophages residing in spleen. Inhibition of macrophagic differentiation by a clinically relevant concentration of CdCl₂ may therefore lead to deleterious adverse effects in cadmium exposed patients. Relevance of these mechanisms is strengthened by in vivo studies which showed a decrease of chemotaxis, phagocytic activity and antibacterial response in mice treated with cadmium as compared to control. Again, decreased enzyme release also contributed towards the impairment of macrophage function. Taken together, our results demonstrated that murine macrophages constitute sensitive targets for inorganic cadmium, the latter contributing to immunotoxicity. Indeed, our data likely indicate that cadmium can reduce the pool of
functional macrophages by 1) inhibiting macrophagic differentiation of blood monocytes and 2) impairing features of differentiated monocyte-derived macrophages, notably phagocytosis. Relevance of these mechanisms is strengthened by *in vivo* studies reporting a decrease of phagocytic activity and antibacterial response in mice treated with cadmium. Thus immunosuppressive properties of this environmental contaminant include affecting of both enzyme catalysed reactions and cellular activations. Inhibition of these functions in response to antigenic challenge to immune cells which are rapidly proliferating and differentiating becomes critically important. All these highlight an immunocompromised state following cadmium exposure in the mice.

The result in this study also provides a baseline for subsequent studies on the role of inflammatory cells in the pathogenesis of *S. aureus* including sepsis during cadmium intoxication. The studies reported herein indicate that many important issues await examination, including intracellular trafficking and constitution of *S. aureus* as well as role of macrophage in the development of sepsis. The activation of any immune response is dependent upon the production and release of cytokines. Cytokines are released as one of the first steps of immune responses and quantitative alterations has been used as a measure of immunomodulation meditated by cadmium which establishes its role as an anti-inflammatory agent. The present study also reports *in vitro* treatment with cadmium enhances the malfunctioning of macrophages due to cadmium exposure that reduces the duration and amplitude of cellular activity on target cells.
Correlations between \textit{in vitro} and \textit{in vivo} data (IVVC) are often used during pharmaceutical development in order to reduce development time and optimize the formulation. A good correlation is a tool for predicting \textit{in vivo} results based on \textit{in vitro} data. Our study has proven to be a good correlate between \textit{in vivo} and \textit{in vitro} studies.