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Exploring the boundaries of systemic inflammation

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Understanding the mechanisms that limit or propagate tissue injury during systemic inflammation may provide the basis for preventing secondary organ dysfunction during serious infections. Endotoxin, an outer membrane component of gram-negative bacteria, is the archetypal microbial factor that mediates inflammation associated with these infections. Since the turn of the 20th century, the administration of endotoxin to humans has been used both as a therapy and as a tool to understand human inflammatory responses (1-4). Endotoxin has been administered to humans as a challenge agent by many different routes: intravenous infusions, lung exposure by inhalation or direct instillation, intradermal injection, application to the nasal mucosa and oral ingestion. The resultant inflammatory responses depend on several factors including dose and route of administration as well as host factors including gender, age and diet. The availability of a reproducible model of human inflammation has afforded investigators the opportunity to study different components of the response using both pathway specific and non-specific therapies to alter these responses (i.e., cyclooxygenase inhibitors, corticosteroids, cytokine inhibitors, anticoagulants) (1).

When given intravenously, a series of dose-related phenomena occur. Very low doses (< 1ng/kg body weight) result in minimal changes in vital signs, low levels of cytokines and a short periods of depressed mood, reduced appetite, fatigue and cognitive impairment (5). Larger doses (2- 4 ng/kg), endotoxin elicits a series of symptoms and signs that are qualitatively similar to the earliest phases of a true gram-negative infection including malaise, myalgias, headache, fever, increased heart and respiratory rates, a leukocytosis, a decrease in blood pressure and the induction of a wide variety of inflammatory mediators in the blood. In contrast, when the lung is exposed by direct instillation of endotoxin into a segmental bronchus, a brisk local pulmonary inflammatory response ensues with minimal systemic effects including low level increases in blood IL-6, IL-1ra, G-CSF, C-reactive protein and a mild leukocytosis (6, 7). These models of inflammation are convenient but have several limitations. Endotoxin is only one of many microbial factors that are capable alone or with others to activate innate immune responses. Unlike bacteria, endotoxin is non-

replicating and a single low dose exposure leads to a relatively short acute inflammatory response. It is within this narrow window of early inflammatory events that investigators attempt to define mechanisms associated with normal host immunity.

How do local or systemic inflammatory responses communicate with other tissue compartments (i.e., blood, lung, liver, brain) to alter vital signs, produce acute phase proteins, activate cells and lead to symptoms of illness? Conveying these responses across different tissue boundaries is presumed to occur in part through the integrated effects of transmigrating activated myeloid cells, circulating mediators and neurohumoral factors. Previous studies in humans have shown that some communication exists between endotoxin-induced systemic inflammation and the lung compartment. Within the first 6 hours after intravenous endotoxin exposure, alveolar macrophages are primed to produce greater amounts of inflammatory mediators upon secondary stimulation (8). Further, the lung exhibits increased clearance of small radiolabelled molecules suggesting an increase in lung permeability (9). Low levels of IL-8, IL-6, and G-CSF are present in bronchoalveolar lavage (BAL) at baseline and these levels in the lung do not increase after intravenous endotoxin challenges (10) despite 10 – 100 fold peak increases in the blood.

In this volume, Plovsing et al (11) used both intravenous and lung endotoxin challenges to understand the interactions of systemic and local inflammatory responses. Healthy male subjects were randomized to undergo either an endotoxin challenge in the lung (by direct bronchial instillation) or a systemic challenge (iv administration). All the subjects underwent bronchoscopy with bronchoalveolar lavage at baseline and then at one of five time points (2, 4, 6, 8, and 24h) after either their respective lung or intravenous endotoxin challenge. This approach allowed the authors to describe a time course of inflammatory events in each compartment (blood and lung) following either the intravenous or lung exposure. As noted by other investigators, intravenous endotoxin compared to lung challenge resulted in more intense signs and symptoms, elevated plasma levels of TNF, IL-6 and C-reactive protein and higher levels of circulating total leukocytes and neutrophils (1, 4). Lung challenge with endotoxin led to mild elevations of blood leukocytes, plasma IL-6 and CRP. The consequences of systemic inflammation on the lung were much less intense compared to the inflammatory response associated with direct lung challenge. At 8 or 24 hours after the intravenous challenge, BAL levels of total leukocytes and IL-6 were increased modestly without a concomitant increase in BAL total protein or albumin.

Was the secondary inflammatory response in the lung after intravenous endotoxin limited by the administered dose (4 ng per kg body weight)? A case report of the self-administration of an intravenous dose 3,750 times the dose given in the current study provides some insight into this question. The large dose of endotoxin resulted in vasopressor-dependent shock, acute kidney injury but only mild non-cardiogenic pulmonary edema requiring 4 liters of supplemental oxygen without the progression to severe acute lung injury (12). These data suggest that other factors (i.e., sustained inflammatory responses, other pathogen associated mediators, host genetic background) are required to cause disruption of lung alveolar – capillary integrity and lead to significant lung injury.

The authors of the current study conclude that a single dose of endotoxin elicited both primary and secondary inflammatory responses depending on the site of the initiating inflammatory stimulus. The novelty of their study was the simultaneous interrogation of both the lung and systemic compartments after either was exposed to endotoxin. However, the study was limited by its small size (i.e., each time point for BAL was performed on three subjects) and disproportionate changes in some of the measurements of left and right lung BAL biomarkers after intravenous endotoxin (i.e., one would expect comparable changes in biomarkers from different lung segments). This study demonstrates a temporal sequence of inflammatory events in the lung and may provide opportunities to use this approach to understand the signals and mechanisms that originate during systemic inflammation to affect lung function.

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