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Role of metabolic derangements in disease development of Sepsis and Burn Injury

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Metabolic derangements, including insulin resistance, muscle wasting hyperlactatemia and mitochondrial dysfunction, are a major complication of critical illness (e.g., sepsis, burn injury) and negatively affect clinical outcomes of critically ill patients. However, the underlying mechanisms of critical illness-induced metabolic disturbances remain to be clarified. In addition, whether metabolic derangements have a pathogenic role in critical illness is not clear. We have shown that burn injury induces: (1) insulin resistance, as indicated by suppressed IRS-1 expression and impaired insulin-stimulated phosphorylation of the IRS1-Akt pathway along with basal hyperactivation of mTORC1; (2) the Warburg effect, as indicated by induction of HIF-1α and its downstream glycolytic genes, and increased lactate secretion; and (3) mitochondrial dysfunction/disintegrity in mouse muscle. Moreover, our recent data show that deficiency of myostatin (a myokine and a potent inducer of muscle atrophy) improves survival and bacterial clearance and mitigates organ damage and inflammation in septic mice (Fig. 1). These results suggest that muscle cachexic changes (e.g., alterations in myokines and metabolites secreted by skeletal muscle) may drive disease development in septic mice. Hyperlactatemia is a predictor of mortality of critically ill patients. Lactic acid can induce immunosuppressive phenotypes in macrophages and T-cells, while it can also prolong inflammatory response in immune cells. It is suggested that hyperlactatemia may contribute to the concomitant presence of immune suppression and persistent inflammation, a feature of sepsis and burn injury. Our data show that myostatin deficiency as well as HIF-1α knockout in skeletal muscle blocks sepsis-induced hyperlactatemia in mice. Together, these findings suggest that prevention of hyperlactatemia may be a contributor to the protective effects of myostatin deficiency in septic mice. Overall, these studies indicate that the myostatin pathway and the HIF-1α pathway in skeletal muscle are novel, potential molecular targets to improve clinical outcomes of septic patients and burn patients.

Biography

Masao Kaneki's laboratory has been the front-runner in research on metabolic derangements (e.g., insulin resistance, muscle wasting, the Warburg effect, hyperlactatemia) in burn injury and sepsis. Masao Kaneki's expertise includes Endocrinology and Metabolism, intracellular signal transduction and development of new biochemical assays. He has employed an integrated translational and reverse translational approach, consisting of mechanistic studies in mice and observational and intervention studies in patients with sepsis and severe burn injury. Based on previous studies by his laboratory and others, he proposes that "metabolic inflammatory complex", in which metabolic aberrations and inflammatory response enhance each other by the positive feed-forward mechanisms, plays a major pathogenic role in critical illness (e.g., sepsis, burn injury). His research team has identified nitic oxide (produced by iNOS) and protein S-nitrosylation, protein farnesylation, and lactic acid secreted by skeletal muscle as mediators of "metabolic inflammatory complex".

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