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Title

Mechanisms underlying vulnerability to inflammatory stress in old age

Abstract

Aging is associated with reduced stress tolerance. Elderly people are far more vulnerable to mild injury or infection, becoming very sick and even dying due to insults that are not at all serious for younger people. Our laboratory has been studying vulnerability to inflammatory stress in old age using mouse models of acute critical diseases including sepsis and acute pancreatitis. These studies are highly relevant to clinical conditions in which elderly patients exhibit significantly elevated mortality rates compared to younger patients (*Aging and Disease* (2014) 4:126; *Aging Cell* (2012) 11:760). When mice at various ages are subjected to inflammatory insults, such as injection with bacterial endotoxin or induction of abdominal sepsis, we clearly observe an age-dependent increase in mortality accompanied with augmented systemic inflammation, coagulation, and multiple organ injury. Age-dependent suppression of an anti-coagulant mechanism appears to be a contributing factor for vulnerability in old age (*Blood* (2010) 115:4886; *Am J Physiol* (2015) 308:H83). Visceral white adipose tissues are a major source of inflammatory cytokines and pro-coagulant mediators under acute stress. Age-associated changes in the inflammatory nature of visceral adipose tissues contribute to increased inflammation and thrombosis in old animals (*Aging Cell* (2013) 12:194). Fat loss, mediated by dietary manipulation appears to effectively improving tolerance to inflammatory stress in old animals (*Critical Care Med* 2016 *in press*). In summary, the mechanisms by which the elderly are more susceptible to various acute inflammatory conditions can be investigated using animal models with aged rodents.