

論文の内容の要旨

Macrophages maintain insulin sensitivity and body weight by interacting with the intestinal microflora through an Akt-dependent pathway

(マクロファージにおける Akt を介した代謝恒常性維持機構の検討)

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Immunological responses have been implied to be important in the pathogenesis of diet induced obesity and type 2 diabetes. Akt is a serine threonine protein kinase which relays signals in multiple signaling pathways. Such signaling in macrophages, a key player in the innate response, has been reported to be important in the maintenance of homeostasis though the functional role of Akt has been elusive. We therefore attempted to elucidate the regulation of homeostasis through Akt in macrophages. We utilized myeloid specific conditional knockout mice (LysM Cre Akt1f/f Akt2f/f mice, LysMDKO mice), lacking Akt in macrophages, and assessed macrophage function and metabolism *in vivo*. When obesity was induced by a high fat diet, Akt in macrophages was insensitive to lipopolysaccharide (LPS), as in Akt deficient macrophages. When fed a normal chow diet, LysM DKO mice weighed more, and were insulin resistant. Transcriptome analyses

revealed that Akt deficient macrophages expressed less IL-10, possibly involving PI3K, mTOR, and the IL-13 signal. Liver steatosis and insulin resistance were evident in obese LysMDKO mice orally treated with vancomycin, leading to a state in which LPS producing gram negative bacteria are increased in the intestinal flora. Upon adenoviral gene transfer of IL-10, genes associated with liver steatosis and gluconeogenesis were suppressed to levels similar to control mice. Our results imply that macrophages produce IL-10 through an Akt dependent pathway in response to the gram negative intestinal flora, and perhaps extracellular signals associated with processes such as feeding, and maintain homeostasis by alleviating liver steatosis and insulin resistance.