スポーツ科学研究, 11, 35-68, 2014 年

Lipopolysaccharide-stimulated inflammatory responses by macrophages are suppressed at the post-transcriptional level in middle-aged mice.

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The intensities of macrophage inflammatory responses to bacterial components gradually decrease with age. Given that a reduced rate of protein synthesis is a common age-related biochemical change, which is partially mediated by increased phosphorylation of eukaryotic initiation factor-2α (eIF-2α), we investigated the mechanism responsible for the deterioration of macrophage inflammato- ry responses, focusing specifically on the age-related biochemical changes in middle- aged mice. Peritoneal macrophages isolated from 2-month-old (young) and 12-month- old (middle-aged) male BALB/c mice were stimulated with lipopolysaccharide (LPS). Although LPS-stimulated secretion of tumor necrosis factor-α (TNF-α) by the macrophages from middle-aged mice was ignificantly lower than that from young mice, LPS caused marked increases in levels of TNF-α mRNA in macrophages from middle- aged as well as young mice. Moreover, LPS evoked similar levels of phosphorylation of c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) in young and middle- aged mice. In contrast, the basal level of phosphorylated eIF-2α in macrophages from middle-aged mice was higher than that in macrophages from young mice. Salubrinal, an inhibitor of the phosphatase activity that dephosphorylates eIF-2α, suppressed the LPS-stimulated inflammatory responses in a murine macrophage cell line RAW264.7. These results suggest that post-transcriptional suppression of macrophage inflammatory responses during middle age requires phosphorylation of eIF-2α.