Modulation of Expression of the Geriatric Cytokine, Interleukin-6

Geriatrik Sitokin Interlökin-6 Ekspresyonunun Modülasyonu

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ABSTRACT Age-related diseases are mainly the result of chronic inflammation Although these various affections appear different according to the tissue affected, they have some general aspects in common, such as the production of inflammatory cytokines, among which the geriatric cytokine Interleukin-6 (IL6). Actually, IL6 is a pluri-potent cytokine, of which the expression needs to be tightly regulated in order to keep the organism in a balanced and homeostatic condition.

The IL6 gene is induced by a dual activation scheme: i.e. 1) the cytoplasmic activation of the general stress factor NF-kB, which after stimulation migrates to the nucleus and occupies its position on various gene promoters, and 2) the activation of the nuclear kinase MSK1, that phosphorylates the NF-kB p65 subunit at Ser 276 (to generate a fully transcription-competent enhanceosome), as well as the Histon-3 tails at Ser 10 (that is the onset of chromatin relaxation).

Glucocorticoid hormones (GCs) remain the mainstay for the treatment of various inflammatory disorders, because of their great efficacy. The long-term usage of GCs is, however, overshadowed by the occurrence of debilitating side-effects, like osteoporosis, skin and muscle atrophy, diabetes and neurological disorders.

GCs exert their functions through binding to the glucocorticoid receptor (GR), a transcription factor that regulates genes in a positive or negative way. Direct binding of activated GR in the promoter of target genes is believed to be the main pathway leading to metabolic gene expression (causing side-effects), whereas the interference of GR with the activity of other transcription factors, such as NF-kB or AP-1, greatly contributes to its desired anti-inflammatory capacities. Dissociated ligands aim to separate GR-mediated transcriptional activation from transcriptional repression in order to achieve better side-effect profiles.

Plant extracts have been used for many centuries as a popular remedy against several health disorders. In recent years, however, a renewed interest in folk medicine and herbal treatments is seen, and at present, the healing capacities of plant-derived compounds are being analysed at the cellular and molecular level. We have studied the molecular properties of a compound derived from the Withania species, growing in Palestine and used by the migrating shepherds in the desert. The major compound of the extract (Withaferin A) is a particular inhibitor of the activation pathway of NFkB, i.e. the main transcription factor for inflammatory gene expression and cell survival. This compound was shown to strongly exhibit anti-inflammatory capacities, both in vitro (cell cultures) and in vivo (mouse). Current efforts for its usage include the specific killing of malignant cells, which may be superior than chemotherapy or radiation therapy.

Soy isoflavones (very popular in Asia) do not block NF-kB activation, but in contrast inhibit the necessary MAP kinase pathway (and thus MSK1 activity), thus decreasing inflammatory gene transcription.

A stabilized compound (CpdA), originally derived from a shrub (salt bush) in the Kalahari deserts of South-Africa and Namibia, has anti-inflammatory properties in vitro (i.e. in cell culture) as well as in vivo (mouse and rat). Furthermore, CpdA displays 'dissociated' activities, thus repressing inflammatory gene transcription but not stimulating steroid-driven gene expression. Compared to treatment with classical glucocorticoids, CpdA may avoid the harmful side effects of cortisone and thus give a better 'benefit-to-side effect' ratio than the presently used steroidal drugs. Moreover, CpdA does not lead to GC resistance, after prolonged treatment, like GCs do.

Key Words: Cytokine, Geriatry, Interleukin-6, Inflammation

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