Interleukin-6

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Interleukin-6 (IL-6) is a cytokine of a pro-inflammatory nature, and it can be produced by various cell types of the immune system as well as by some nonimmune cells, including fibroblasts. IL-6 is cytokine important for the initial phase of immune response that is recognized by 2 types of receptor. Overproduction of IL-6 is associated with aging, chronic inflammation, cancer and severe viral infections such is COVID-19. This molecule is not produced by immune cells but also by cancer-associated fibroblasts and cancer cells. Control of its production or inhibition of IL-6 receptors could have the therapeutic consequences.

Keywords: IL-6 ; IL-6 receptor ; Cancer ; Aging ; COVID-19 ; Cancer-associated fibroblast

1. Introduction

Interleukin-6 (IL-6) is a bioactive protein known under numerous synonyms (Table 1). Regarding the anatomical distribution of Il-6, it was identified in the lungs, urinary bladder, adipose tissue, muscles, vermiform appendix, etc. (The Human Protein Atlas, [1]).

Table 1. Synonyms for interleukin-6 (IL-6).

Name	Author
Interferon β-2	Zilberstein et al., 1986[2]
26K factor	Haegeman et al., 1986[3]
B-cell stimulatory factor	Hirano et al., 1985[4]
Hybridoma growth factor	Brakenhoff et al., 1987[5]
Plasmacytoma growth factor	Nordan et al., 1987[6]
Hepatocyte stimulatory factor	Gauldie et al., 1987[7]
Haematopoietic factor	Ikebuchi et al., 1987[8]
Cytotoxic T-cell differentiation factor	Takai et al., 1988[9]

The main cell types acting as producers of IL-6 are shortlisted in Table 2.

Table 2. Examples of cells producing IL-6.

Type of cell	Author
Keratinocyte	Groeger and Meyle, 2019[10]

Enterocyte	Pritts et al., 2002[11]
Urothelium	Uehling et al., 1999[12]
Hepatocyte	Schmidt-Arras and Rose-John, 2016[13]
Pneumocyte and bronchial epithelial cell	Cheung, 2005[14]
Smooth muscle	Kyotani et al., 2019[15]
Skeletal muscle	Barbalho et al., 2020[16]
Osteoblast	Kovács et al., 2019[17]
Adipocyte	Xie et al., 2019[18]
Macrophage	Shapouri-Moghaddam et al., 2018[19]
Neuron	Shapouri-Moghaddam et al., 2018[19]

IL-6 is recognised by its transmembrane receptor (IL-6R), which forms a complex with glycoprotein 130 (gp130). This receptor has tyrosine kinase activity and activates signal transducer and activator of transcription 3 (STAT3) via phosphorylation. On the other hand, the extracellular portion of IL-6R can be cleaved from the intramembranous domain of the receptor by membrane protease ADAM-17. Soluble IL-6R without tyrosine kinase activity interacts with gp130 outside the cell and forms a complex of IL-6, soluble IL-6R and gp130, which is docked back to the cell membrane[20]. This arrangement of the IL-6–IL-6R axis can be functionally variable when the actual function of IL-6 signalling is dependent on the type of cell and the type of interacting receptor. While the interaction of IL-6 with transmembrane IL-6R and gp130 participates in anti-inflammatory pro-cancerogenic signalling, the interaction of IL-6 with soluble IL-6R and gp130 stimulates inflammation[20].

2. Physiological Functions of IL-6

The family of IL-6-related proteins consists of members with remarkable and distinct biological activities that are structurally similar to IL-6, such as IL-11, IL-31, cardiotrophin-1, ciliary neurotrophic factor (CNTF), cardiotrophin-like cytokine (CLC), granulocyte colony-stimulating factor (G-CSF), leptin, leukaemia inhibitory factor (LIF), neuropoietin, and oncostatin[21]. This cytokine family is defined by sharing common IL-6 family signalling receptor gp130 more than by any structural homology of its members. It is therefore not surprising that the IL-6 family cytokines not only display partially overlapping, but also, more significantly, very different biological activities[22].

IL-6 knockout mice are available for research purposes[23]. Interestingly, their embryonic and foetal development is not hampered, and knockout animals do not have any apparent developmental abnormalities. On the other hand, these mouse strains were highly susceptible to several pathogens, and they failed to generate acute-phase responses[24].

IL-6 contributes to the host defence by stimulation of the acute phase immune response, including elevation of body temperature[25]. In this context, IL-6 positively influences the maturation of B lymphocytes and cytotoxic T lymphocytes[26][27]. In the same motion, IL-6 deficiency in an experimental model leads to protection against triggering autoimmune encephalomyelitis[28].

IL-6 also belongs to the family of myokines such as IL-8, IL-15, irisin, myostatin, fibroblast growth factor (FGF)21, leukemia inhibitory factor (LIF), brain-derived neurotrophic factor (BDNF), and insulin like growth factor-1 (IGF-1) that influence the function of skeletal muscle with metabolic impacts on the whole organism[16], namely by interaction with adipocytes and factors produced by these cells[29]. In knockout mice, surviving animals had reduced age-related obesity development[30].

The role of IL-6 in the bone metabolism was also confirmed by the stimulation of osteoclast activity[31]. This is in good agreement with the observed protection against the bone loss after ovariectomy in a mouse knockout model[32].

The function of IL-6 in the aging, cancer and viral infection is discussed.

These few examples demonstrate the complex and multifaceted role of IL-6 both in physiological and pathological conditions in the human body.

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