Myokines

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Myokines are small proteins (5–20 kDa) and proteoglycan peptides that are produced and secreted by skeletal muscle cells in response to muscle contractions.

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1. Introduction

With aging, the secretion of apelin, BAIBA, BMP-7, decorin, IGF-1, IL-15, irisin, SDF-1, sestrin, SPARC, and VEGF-A decreased, while that of IL-6 and myostatin increased. Aerobic exercise upregulates apelin, BAIBA, IL-15, IL-6, irisin, SDF-1, sestrin, SPARC, and VEGF-A expression, while anaerobic exercise upregulates BMP-7, decorin, IGF-1, IL-15, IL-6, irisin, and VEGF-A expression. Myostatin is downregulated by both aerobic and anaerobic exercise.

2. Apelin

Human apelin was identified and isolated in 1998 as an endogenous ligand of the G-protein-coupled receptor APJ and was named the APJ endogenous ligand. The apelin gene located at chromosome Xq25–26.1, encodes a 77 amino acid preproprotein[1][2]. After the cleavage of the signal peptide, the protein is processed into various bioactive endogenous peptides, such as apelin-13, -16, -17, and -36[3], which are widely expressed in various organs. Apelin regulates a wide range of physiological processes, including blood pressure[4], cardiac contractility[5], and angiogenesis[6], and is involved in pathophysiological processes underlying hypoxia[7], obesity[8], diabetes[9], and various cancers[10].

3. β-aminoisobutyric Acid (BAIBA)

BAIBA ($C_4H_9NO_2$) is a small, non-protein myokine with a molecular weight of 103.6 Da that was first discovered in human urine in 1951[11]. It is secreted by contracting muscles via the action of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and acts in a myokine-specific manner[12][13]. It is involved in various metabolic processes, such as acting on white adipose tissue to upregulate brown adipose tissue-specific genes, enhancing PGC-1α expression to increase lipid oxidation, suppressing inflammation in skeletal muscles, inhibiting cardiometabolic risk factors, and suppressing endoplasmic reticulum stress in hepatoblastoma cells. Blood BAIBA levels increase in response to continuous exercise[12][14][15][16]. The myokine properties of BAIBA suggest that many small molecule metabolites may have myokine functions.

4. Bone Morphogenetic Protein 7 (BMP-7)

In 1965, Urist recognized BMP as an important factor in osteogenesis and bone formation[17]. BMP-7, also called osteogenic protein-1, is a member of the TGF-β superfamily of cysteine-knot fold cytokine-growth factors[18]. Human *BMP-7* has been isolated and mapped to chromosome 20q13.31. This has been proposed as a possible locus for the Holt-Oram syndrome, which manifests as skeletal abnormalities of the upper limbs and hands[19][20][21]. BMP-7 is a multifunctional growth factor involved in cell proliferation, apoptosis, organ repair, and differentiation of brown adipose tissue, but its most important function is inducing cartilage and bone formation[22][23][24][25].

5. Decorin

Human decorin is a small leucine-rich proteoglycan of 90–140 kDa that is associated with collagen fibrils in all connective tissue. The gene is located on chromosome 12q23[26] and regulates transforming growth factor (TGF)-beta 1 activity as well as the cell cycle[27]. Decorin suppresses myostatin activity, which is associated with obesity and diabetes[13]. In 2014,

decorin was first recognized as a myokine, and its levels in both plasma and skeletal muscle increase in response to physical activity[28].

6. Insulin-Like Growth Factor 1 (IGF-1)

In 1957, IGF-1 was first recognized by Salmon and Daughaday as a “sulfation factor” that stimulates sulfate incorporation in rat cartilage[29]. In 1978, Rinderknecht and Humbel purified a human IGF-1, a protein of 70 amino acids with structural resemblance to proinsulin[30]. In 1983, the human IGF-1 cDNA was cloned, and in 1984, IGF-1 was found to be located on chromosome 12q23.2[31][32]. Although IGF-1 is a multifunctional peptide, its main physiological function is as a growth hormone (GH) essential for normal bone and tissue growth and development[33]. In 2012, IGF-1 was recognized as a myokine produced and secreted by the muscle fibers[34].

7. Interleukin-15 (IL-15)

Human IL-15 was reported simultaneously by two groups in 1994 as a T-cell growth factor. *IL-15*, located on chromosome 4q31, encodes a 14–15 kDa glycoprotein incorporating a four α-helix bundle[35][36][37]. In humans, *IL-15* expression is detected in various cells and tissues, including skeletal muscle, epithelial cells, monocytes, and dendritic cells[38]. The primary biological functions of IL-15 are to activate and proliferate T-cells and NK cells, inhibit apoptosis, and accelerate CD8(+) antitumor immunity[39][40][41]. Brandt and Pedersen suggested in 2010 that muscle-derived IL-15 is a myokine constitutively expressed by skeletal muscles and is regulated in response to strength training[42].

8. Interleukin-6 (IL-6)

IL-6 is a cytokine that plays multifunctional roles in the regulation of the immune system, nervous system, and glucose homeostasis[43][44]. IL-6 has several names, including interferon beta-2 (IFNB2), B-cell stimulatory factor 2 (BSF2), hepatocyte stimulatory factor, and hybridoma growth factor. Zilberstein et al. and Hirano et al. cloned full-length cDNAs encoding human IFNB2—a 23.7 kDa protein comprising 212 amino acids—and human BSF2—a novel interleukin comprising 184 amino acids—respectively[45][46]. Using in situ hybridization, Sutherland et al. identified that *IFNB2* is located on chromosome 7p15.3[47]. The extramembrane (IL-6r) and intramembrane (gp130) domains of the IL-6 receptor were cloned in 1988 and 1990, respectively[48][49]. IL-6 is the first myokine produced and released into the supernatant when C2C12 myotubes and skeletal muscle fibers are induced to contract by electrical pulse stimulation[50][51].

9. Irisin (Fibronectin Type III Domain Containing 5 [FNDC5])

Irisin, which is a novel myokine discovered in 2012, is expressed in a PGC-1α-dependent manner to produce FNDC5. This is followed by cleavage of the N-terminal signal peptide and C-terminal hydrophobic domain, resulting in the production of a 12 kDa glycoprotein that is secreted into the bloodstream and is involved in fat metabolism. FNDC5 is predominantly localized in the endoplasmic reticulum[52]. Genomic sequencing analyses indicate that *FNDC5* contains six exons and this gene has been mapped to chromosome 1p35.1[53]. Although the irisin receptor is unknown, irisin is highly conserved in all mammalian species, which suggests highly conserved biological functions[54]. Recently, irisin has been hypothesized to be involved in the downregulation of insulin resistance pathway (ROS → p38 MAPK → PGC-1α → irisin → insulin resistance pathway), which is positively controlled by exercise and negatively controlled by aging[55].

10. Myostatin (Growth/Differentiation Factor-8 [GDF-8])

Myostatin (GDF-8), a member of the TGF-β superfamily, plays an important role in the negative regulation of skeletal muscle growth and is specifically expressed in developmental and adult skeletal muscle[56][57]. Myostatin, inhibited by follistatin, has recently attracted attention as a useful pharmacological target for preserving muscle mass and preventing atrophy[58]. McPherron et al. and Gonzalez-Cadavid et al. isolated and characterized the mouse myostatin and human myostatin genes, respectively[56][59]. In one study, plasma myostatin concentration in three groups of subjects (19–35, 60–75, and 76–92 years) were highest in the 76–92-year-old group, which suggests that plasma myostatin could be used as a biomarker for diagnosing age-associated sarcopenia[60].

11. Stromal Cell-Derived Factor 1 (SDF-1)

The expression of SDF-1—also called CXC motif chemokine ligand 12 (CXCL12), intercrine reduced in hepatomas (IRH), and pre-B cell growth-stimulating factor—is expressed in many cell types (i.e., fibroblasts, myoblasts, muscle fibers)[61]. This chemokine was originally described as a B-cell precursor stimulating growth factor secreted by a bone marrow

stromal cell line[62]. CXCR4 and CXCR7 are the primary physiological receptors of SDF-1[63][64], and the gene coding for this protein is located on chromosome 10q11.1[65][66]. SDF-1-CXCR4 signaling occurs in the mesenchyme of limbs during early development and is directly responsible for the development of appropriately sized muscles[67], which indicates its important role in skeletal muscle regeneration[68][69].

12. Sestrin

Sestrin was first discovered in 1994 as a target of the tumor suppressor *p53* and was referred to as p53-activated gene 26 (PA26). The gene coding for sestrin is located on chromosome 6q21[70][71]. In mammalian cells, three different sestrin isoforms, which share high sequence homology, are encoded by genes located on different chromosomes, Sestrin1 on chromosome 6, Sestrin2 on chromosome 1, and Sestrin3 on chromosome 11[72]. Sestrin acts as an intracellular leucine sensor to negatively regulate the target of rapamycin complex 1 (TORC-1) signaling by activating AMP-dependent protein kinase (AMPK), which prevents the development of sarcopenia and extends the life span[73]. Pathophysiological stressors, such as DNA damage and oxidative stress, upregulate sestrin expression, which negatively regulates aging by activating the AMPK/autophagy pathway and inhibiting the TORC1 signaling[74].

13. Secreted Protein, Acidic, Rich in Cysteine (SPARC; Osteonectin/Basement-Membrane Protein 40)

In 1989, the human *SPARC* was first demonstrated to be located on chromosome 5q33.1[75], and since then, it has been confirmed that the SPARC protein functions in a Ca^{2+}-ion-dependent manner[76]. SPARC is a 43 kDa secretory matricellular glycoprotein that has multiple biological functions, including tumor-suppressing activity, cell differentiation, and cell adhesion in several organs and cell types[77][78][79]. SPARC was first recognized as a myokine in 2013 as a result of cell-stretching stimulation experiments on C2C12 myocytes[80].

14. Vascular Endothelial Growth Factor A (VEGF-A)

VEGF-A, first discovered in 1983[81], is encoded by a gene located on chromosome 6p21.1; the cDNA encoding VEGF-A was isolated in 1989[82]. VEGF-A is a secreted, 46 kDa homodimer glycoprotein containing a highly conserved receptor-binding cysteine-knot structure. VEGF-A is one of the most important factors in the growth and survival of skeletal muscle in humans and animals[83].

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