

The Effect of IL-6 Enhancement Due to Oral Cavity Infection on Skeletal Muscle

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ABSTRACT

One of the cytokines that often play a role in the body's response mechanism to infections, inflammation, and various other diseases is *Interleukin-6* (IL-6). The role of IL-6 is determined by the signaling mechanism involving various intracellular molecules. Oral infection that can cause an increase in IL-6 level mainly is periodontitis. In periodontitis, the increased level of IL-6 do not only occur locally, but also systemically, in which it affects several tissues, one of which is skeletal muscle. Several studies have proven that the enhancement of IL-6 levels which are caused by oral cavity infections influences the skeletal muscle tissue in both humans and experimental animals. The results of the IL-6 signaling can result in the reduction of muscle mass. The mechanism of IL-6 level enhancement, which results from the host response to oral cavity infections affecting skeletal muscle, is still being discussed and investigated further.

Keywords: IL-6 periodontitis, skeletal muscle.

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INTRODUCTION

Periodontal disease is a disease that attacks the periodontal tissue, which can be either gingivitis or periodontitis. According to data from the Global Burden of Disease in 1990-2010 showed that severe periodontitis is the sixth highest prevalence of disease (11.2%) and suffered by around 743 million people in the world and increased in prevalence of 57.3% in the 10 years (1,2). One of periodontal disease is periodontal abscess in the periodontal tissue (3,4), if not properly treated it can cause the spread of infection to other parts of the body organ (5-7).

In 1900, William Hunter stated that oral microorganisms were responsible for systemic conditions, which is also known as the focal concept of infection. Focal infection can affect systemic conditions through inflammatory reactions to other body organs (8,9). In periodontitis, the activation of inflammatory mediators apparently influences the systemic host response (10-12). It was found an increase in IL-6 cytokine levels on plasma patients with periodontitis in addition to increased levels of IL-6 saliva in patients with periodontitis compared with non-periodontitis patients (13,14).

Increased inflammatory mediators including cytokines can result in a reduction in muscle mass. Cytokines can affect muscle cell metabolism by causing an increase in muscle fiber lysis and influencing the differentiation of muscle cells (15,16). Interleukin-6, as one of the cytokines, is known to trigger the breakdown of muscle proteins (17). In the process of protein breakdown, the mechanism of IL-6 signaling produce a reduction of *Insulin Growth Factor-1* (IGF-1) concentration, where IGF-1 has a function in the growth and adaptation of muscles (18).

Interleukin-6 signaling process can be taken through two mechanisms, the classical and trans-signaling. In classic, IL-6 binds to IL-6R where IL-6R can only be expressed by certain cell types so that the effect is limited to certain tissues.

While in the trans-signaling process, there is sIL-6 which can bind to IL-6 for later activate gp130 in cells that do not express IL-6 receptors so that can expand the target tissue of IL-6 including skeletal muscle tissue (19,20).

The aim of this study is to review the effect of IL-6 enhancement due to oral infections, mainly periodontitis on skeletal muscle metabolism seen from the point of signaling pathways [1].

IL-6

Interleukin-6 is a cytokine that is involved in the process of inflammation and infection, moreover the regeneration processes, regulation of metabolism, and neural processes also controlled by IL-6 (19). There are 10 kinds of cytokines that are classified into IL-6, the cytokines are distinguished by glycoprotein 130 (gp130) chain. Interleukin-6 is secreted by macrophages, macrophages, B cells, T cells, dendritic cells and many more cells that are included in activated immune cells. Non-immune cells such as endothelial cells, keratinocytes, and fibroblasts also secrete IL-6. The IL-6 transcription mechanism is induced by Nuclear Factor Kappa B (NK- κ B) after activated by Lipopolysaccharide (LPS), Tumor Necrosis Factor α (TNF- α), IL-1, and IL-17 (21).

In chronic inflammation, IL-6 has functions in various cells. Furthermore, IL-6 also works for plasma cell development and triggers the production of immunoglobulins (22,23). There are several infections that can cause a rise in systemic IL-6 levels, including oral infections.

IL-6 signaling mechanism

There are two types of receptors for IL-6, the membrane IL-6 receptor (mIL-6R) which attaches to the cell membrane and Soluble IL-6 (sIL-6R). Soluble IL-6R are generated from the mIL-6R proteolysis process through ADAM 10 and ADAM 17 as well as the results of alternative splicing mRNA (24). Besides IL-6R, there is also gp130 in the membrane which is

a type 1 cytokine receptor complex, it can activate intracellular signals for later produce a process of proliferation and apoptosis (25).

The coupling process and the limited proteolytic process of IL-6 receptor produce a form of soluble and secreted receptors known as sIL-6R, which can be found in body fluids. Soluble Interleukin-6 Receptor has the ability to bind with IL-6, furthermore the IL-6 - sIL-6R complex can also bind the gp130 homodimer and activate it in cells that do not secrete mIL-6R [2]. This will cause the process to trigger trans signaling and elevate potential of the IL-6 target network, as well as increasing its activities (19). IL-6/mIL-6R is known as the classic pathway that mediates anti-inflammatory reactions, while trans-signal pathway through IL-6/sIL-6R mediates proinflammatory reactions (26,27).

The bonding complex between IL-6 and its receptor will bind to gp130 and produce signal transduction that involves the activation of Janus kinase (JAK) through the process of transphosphorylation, Janus kinase is a family of tyrosine kinase [3]. Activation of JAK will cause the transcription factors activation of Signal Transducers and Activators of Transcription (STAT), which then changes into a dimer and move to the nucleus for later trigger gene transcription, which in turn can produce inflammatory processes, angiogenesis, cell defenses, and cell proliferation. Another signaling pathway from IL6 is through mitogen-activated protein kinase (MAPK) (28).

Under physiological conditions, there is a protein inhibitor Suppressor of Cytokine Signaling (SOCS) which is able to inhibit the signaling pathway of IL-6/JAK/STAT (29). Suppressor of Cytokine Signaling acts as a feedback inhibitor, an increase in the formation of SOCS is triggered through the JAK/STAT pathway, but the formation of SOCS will inhibit the function of STAT as a signal transduction mediator (28). Suppressor of Cytokine Signaling 1 and SOCS3 potentially inhibit IL-6 signaling through their effect on JAK and inhibit gp130, STAT, and JAK phosphorylation (30,31). Because of the effects on JAK, SOCS1 and SOCS3 can influence the activation of different types of STAT (28).

Oral cavity infections and increased levels of IL-6

Infection in the oral cavity can produce improvement of cytokines IL-6 systemically, mainly periodontitis. Periodontitis is characterized by periodontal soft tissue inflammation, damage to periodontal ligaments and alveolar bone, this disease includes an inflammatory disease (32). The growing development of research in the field of immunology has also led to the unfolding of the involvement of the host immune response in periodontitis (33). During the process of periodontitis, cytokines have a very important role. Cytokines are modulators that bridge the state of homeostasis and inflammatory processes by acting as the first response against pathogens (34). Activation of inflammatory mediators in periodontitis significantly influences the host's response to inflammation systemically (10).

There is an enhancement of the levels of IL-6 and TNF- α in periodontitis. Interleukin-6 and TNF- α plasma levels are higher in people with periodontitis compared to people who do not have periodontitis (13,35). Besides there is an increasing concentration of IL-6 plasma people suffering periodontitis, there is also an improvement in concentration of IL-6 saliva (14,36). Many studies describe the role of IL-6 in periodontitis. A total of 21 studies reviewed by meta-analysis show that IL-6 174G/C polymorphisms are associated with susceptibility of a person experiencing chronic periodontitis (37).

In the early stages of periodontitis, the local tissue damage caused by microbes generate secretion of immune cells including specific T cell subsets (Th17), antigen presenting cells (APCs), and mononuclear phagocytes (MNP).

Interaction between microbes and all host cells will cause cytokine secretion, such as IL-1, IL6, and TNF, known as proinflammatory cytokines (38).

Effect of increased IL-6 on skeletal muscles

One of the systemic effects that can be caused by inflammatory mediators is a reduction in muscle mass due to cytokine activation (15). Immunological factors such as cytokines and myeloid cells can affect muscle cell metabolism. Cytokines can affect muscle cell metabolism since it can cause an improvement of lysis muscle fibers, and affect the muscle cells differentiation (16). Visser's research (39) proved a reduction in muscle mass and strength in elderly humans with increasing concentration of IL-6 and TNF- α . Regarding oral infections, Tidball and Villalta's research (16) shows that changes in the systemic inflammatory profile caused by odontogenic infections can affect the process of muscle catabolism during exercise procedures [4].

Interleukin-6 can trigger muscle protein breakdown, in transgenic experimental animals with higher IL-6 production, there is an atrophy in gastrocnemius muscles compared to normal experimental animals. Further studies have shown that improvement concentration of IL-6 result in increased activation of lysosomal cathepsin B and L enzymes which involved in the process of muscle catabolism (17,40). Another pathway from the effect IL-6 level increase on muscle degradation can be seen from how it inhibits the anabolic effect of IGF-1, in which it triggers sarcopenia (41). Mice with higher levels of IL-6 within their body circulation in the early stages of life had normal levels of growth hormone, yet a subsequent decrease in concentration of IGF-1 and improvement of muscle SOCS3 mRNA. Provision of IL-6 in a short time in normal mice and humans also reduce IGF-1 levels in circulation (42,43).

The Liver produces IGF-1 for later bound to IGF-binding protein-3 (IGFBP-3), the highest amount of IGFBP in circulation is in the form of heterotrimeric complexes, which also contain acid-labile subunit. Acid-labile subunit is a form of glycoprotein (44). In transgenic animals that are overexpressed with IL-6 experience a decrease in IGF-1 in their circulation, whereas IGF-1 production in the liver and the number of acid-labile subunit in the serum does not change, but IGFBP-3 levels in the circulation decrease along with the increase in proteolysis (42). A reduction in IGFBP-3 levels was also found in IL-6-induced mice. Hence, it can be concluded that decreased IGF-1/IGFBP3/acid-labile subunit complex formation will reduce the half-life of IGF-1 in the blood and increase its cleansing from the circulation (41). The research of De Benedetti *et al.* in 1997 and 2001 showed that decreased concentration of IGF-1 and IGFBP-3 in the circulation occurs when a person experiences a chronic increase in IL-6 levels.

The activation of STAT3 and SOCS3 transcription can be induced by administration of IL-6 in muscle for 2 weeks triggers, which is in line with the decrease in myofibrillar protein. This indicates the involvement of SOCS in decreasing muscle mass (18). As a negative feedback mechanism, the formation of SOCS3 can reduce IL-6 signaling in this mechanism. SOCS3 is proven to trigger muscle loss in the arm until there is a 25% reduction in body weight in cancer-induced mice (45).

However, other studies have shown no changes in SOCS3 expression in cachectic muscle model mice despite an increase in SOCS3 mRNA. In experimental animals modeled with high levels of IL-6, induction by transfection of plasmids that express active STAT3 caused a significant decrease in muscle fiber compared to experimental animals without STAT3 expression. This shows the role of JAK/STAT in triggering an increase in SOCS3 proteolytic

degradation to maintain the STAT3 signaling process, which can be inhibited by SOCS3. The results of this study show that STAT3 is the main mediator in the process of muscle loss (46-51).

CONCLUSION

The increased concentration of IL-6 due to oral infection mainly periodontitis can systematically cause an improvement in IL-6 level. The elevated level of IL-6 in circulation can reduce IGF-1 level which work in the process of muscle growth and adaptation. Thus, the decrease of IGF-1 level can cause reduction in muscle mass. In addition, the enhancement of IL-6 plasma causes an increase in the activation of cathepsin B and L which play a role in the process of muscle protein breakdown. Decreased muscle mass which is caused by enhancement of IL-6 can be seen from the role of STAT as one of the mediators in the IL-6 signaling process.

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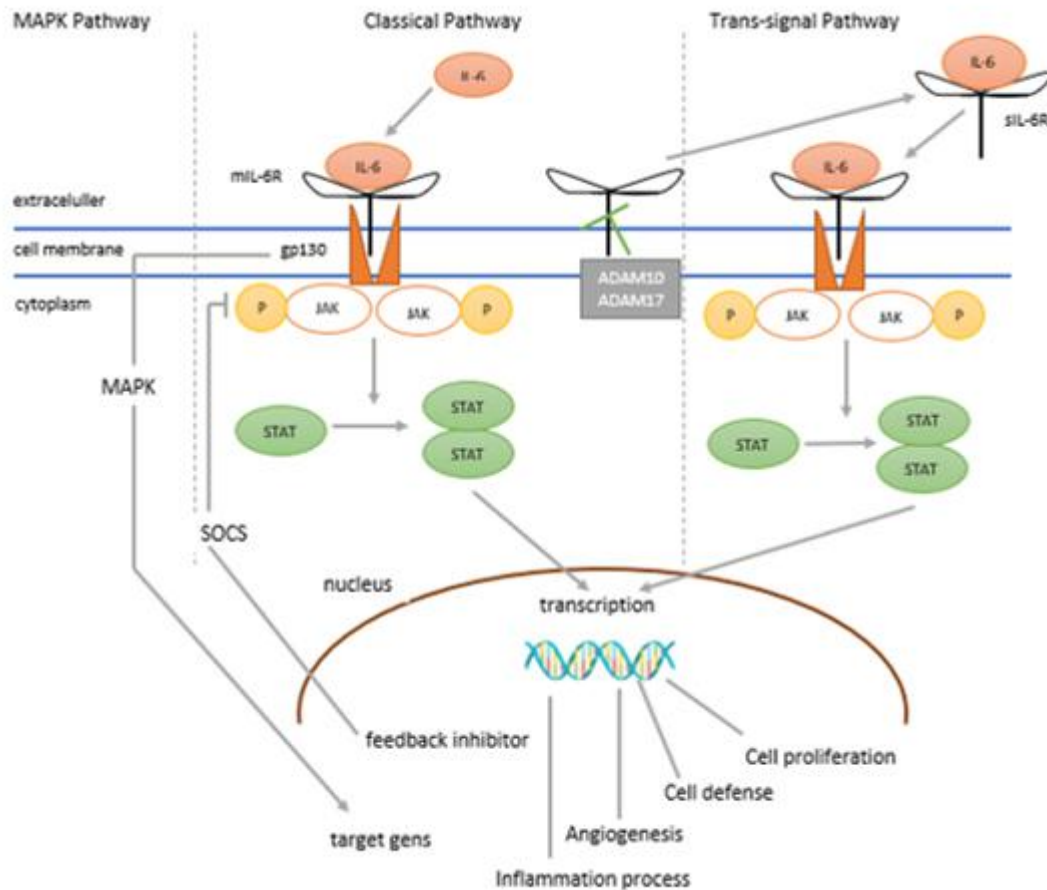


Figure 1: IL-6 signaling pathway. There are three signaling mechanisms of IL-6 : (1) classical pathway, where IL-6 binds to IL-6 receptors in the cell membrane (mIL-6R) for later activates gp130 to then occur JAK phosphorylation that activates STAT; (2) trans-signal pathway where IL-6 binds to sIL-6 then activates gp130 resulting in phosphorylation of JAK and activated STAT; (3) MAPK pathway where activated gp130 can trigger the work of MAPK to activate the target gen ini nucleus. In classical and trans-signal pathway, activated STAT will translocate to the nucleus for later regulate transcription and formation of SOCS as feedback inhibitor that can inhibit JAK.

The Effect of IL-6 Enhancement Due to Oral Cavity Infection on Skeletal Muscle

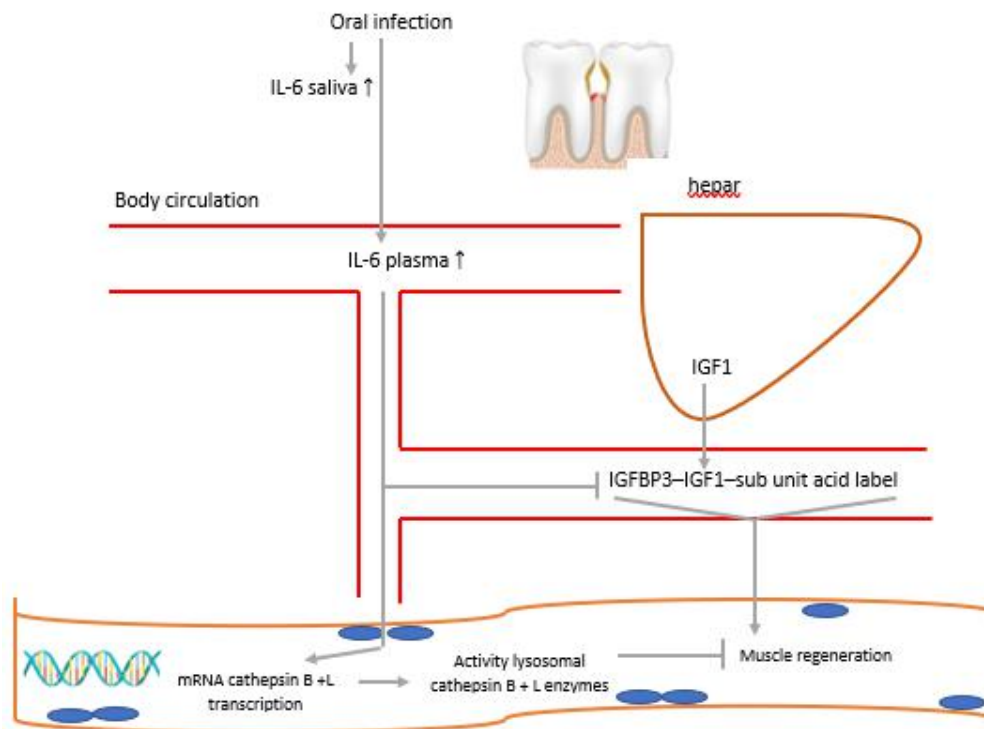


Figure 2: Effect of IL-6 enhancement due to oral cavity infection on skeletal muscle. Oral infection will cause an increase of IL-6 saliva and IL-6 plasma. Increased plasma IL-6 will cause a decrease in IGF1 where IGF1 will bind to sub-unit acid label and IGF1 produced by the liver to help the process of muscle regeneration. In addition, elevated IL-6 plasma will trigger mRNA cathepsin B and L transcription and activation of lysosomal cathepsin B and L enzymes which can cause an increase in muscle protein breakdown⁴⁷.