

Association of Neopterin and Wound Healing Process

Neopterin ve Yara İyileşme Süreci İlişkisi

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ABSTRACT

Human monocytes/macrophages produce neopterin when stimulated by the cytokine interferon- γ . The concentration of neopterin in body fluids such as serum, cerebrospinal fluid and urine can be measured and increased concentrations of neopterin provides information about infections states. Nowadays, neopterin is as a marker in neurological and cardiovascular diseases during cellular immune activation.

Keywords: Antioxidant, immune system activation, neopterin, wound healing

INTRODUCTION

Neopterin is a derivative of pyrazine-pyrimidine, 2-amino-4-hydroxy-6-(D-erythro-1',2',3'-trihydroxypropyl)-pteridine, and is synthesized from guanosine triphosphate (GTP) through the reaction catalyzed by GTP cyclohydrolase I (GTPCH, EC.3.5.4.16) enzyme (1-8). The biosynthesis of neopterin is shown in Figure 1. Monocyte-derived macrophages and dendritic cells produce neopterin, which is known as an indicator of immune activation (9-18).

Neopterin is also produced in cell types such as human endothelial cells and B-lymphocytes (19). Neopterin is a stable molecule, relatively polar, *molecular sizes* 253 Da, which is inert in human body and its half-life ($t_{1/2}$) is only affected by renal elimination (20).

Neopterin was first isolated in 1967 from human urine. In 1979, Wachter et al. have shown that neopterin found in the urine of cancer patients is one of the molecules responsible for fluorescence (19). Thus, it is possible to easily determine the concentration of neopterin at certain wavelengths. Neopterin can be detected in the majority of body fluids such as blood, urine, and cerebrospinal fluid (1). Increased neop-

ÖZ

İnsan monositleri/makrofajları, sitokin interferon- γ tarafından uyarıldığında neopterin üretir. Serum, beyin omurilik sıvısı ve idrar gibi vücut sıvılarında neopterin konsantrasyonu ölçülebilir ve artan neopterin konsantrasyonları enfeksiyon durumları hakkında bilgi sağlar. Günümüzde neopterin, hücrel immün aktivasyonu sırasındaki nörolojik ve kardiyovasküler hastalıklarda bir belirteç olarak kullanılır.

Anahtar Kelimeler: Neopterin, yara iyileşmesi, antioksidan, immün sistem aktivasyonu

terin concentration is related to different diseases including immune disorders, inflammation, and coronary artery diseases, and associated with strong monocyte macrophage activity (21). In different studies it has been observed that the neopterin level of were increased (22-26). Moreover, it was reported that the increase of neopterin level are related to endothelial damage, organ dysfunction, rheumatoid arthritis, and coronary artery disease (27-29).

It is suggested that using neopterin as the diagnostic and prognostic criteria for macrophage and immune activation because of neopterin is detected in blood, cerebrospinal fluid, and urine (30-33). Moreover, it was reported that increased level of neopterin serum was used as a biomarker in the diagnosis of acute atherothrombotic plaque inflammation and coronary artery disease (34). Neopterin excretion begins before the onset of clinical symptoms and the level is used as an indicator of the clinical severity of the disease (31). It was reported that neopterin levels may be useful in determining the grade of the disease, and in assessing therapeutic response (35).

It is thought that there is a relationship between the wound healing process and neopterin, because the high neopterin

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level indicates the presence of inflammation. Wound healing is the repair process occurring after a trauma or surgical procedure. Wound healing consists of inflammation, proliferation, matrix deposition, and remodeling phases. Wound healing is the repair process occurring after a trauma or surgical procedure. Wound healing includes coagulation, inflammation, granulation tissue formation, epithelization, neovascularization collagen synthesis and remodeling phases. Vasoconstriction occurs in the early stages of injury, in the first twenty minutes, followed by the development of vasodilation via serotonin, histamine, and prostaglandins. The factors released from platelets, the products formed in the coagulation chain, and the factors inflicted as a result of necrosis resulting from tissue damage change the endothelial permeability in the vicinity of the wound. Alteration of endothelial permeability casuses the passage of plasma into the extravascular space, which is manifested by generalized edema. Primary suture applied surgical incisions also fills the wound with the clot and creates endurance in the wound. When the clot is dehydrat-

ed, the wound turns into a scab, which protect the wound from infection and prevent secondary bleeding. The first cell of inflammation is neutrophils which come from leukocytes through blood circulation first in clotting (35-37). Neutrophils reach its peak intensity at 24 and 48 h (27,30), and work in the defense system to remove cell destruction products, bacteria and other foreign bodies entering the body (38). In addition, reactive oxygen species are released from neutrophils granules with proteases such as gelatinase, elastase, collagenase. If there is no infection in the wound, neutrophils decrease rapidly after the 3rd day of the wound. Neutrophils complete their tasks leave that area with macrophages (39). Macrophages that come to the wound area are involved in wound healing by proinflammatory peptides such as interleukin-1 (IL-1) and interleukin-8 (IL-8) and release of tumor necrosis factor (TNF). The major cytokines released by macrophages are TNF- α , PDGF, IGF-1, TGF- β and IL-1. These cytokines rapid the wound healing process. Wound repair is initiated by clotting and neutrophils and continued by macrophages (4).

Maximal stimulation of macrophages in infected wounds can cause scar tissue formation. Macrophages involved in wound healing cause an increase in neopterin level. Neopterin is important in immune dysfunction as well as oxidative stress. Oxidative stress is known to act an important role in the pathogenesis of autoimmune, chronic diseases and cancer (9). Neopterin oxidation shows accelerator (pro-oxidant) property and leads to an increase in reactive oxygen species (40). It was also found that neopterin inhibited the activity of xanthine oxidase and NADPH-oxidase. Therefore, neopterin is directly associated with oxidative stress (26). The biochemical effects of neopterin and their derivatives are shown in Figure 2

In order to prevent the formation of reactive oxygen species and their damage, many defense mechanisms, which is called antioxidant defense systems have been developed in the body.

Antioxidants protect cells against the unwanted effects of free radical reactions, both directly and indirectly. Increased oxidative stress caused by disruption of antioxidant and oxidant balance causes cell damage and this damage affects the healing process. As a result of inflammation that occurs in the wound area, endothelial cells create superoxide radical (O⁻) and H₂O₂. Free radicals and oxidants delay the wound healing process. The presence of high level of ROS indicates that there is a strong inflammation in the wound and the presence of oxidative stress. The maximum amount of ROS in wound healing is in the inflammatory phase. Therefore, ROS should be prevented in the wound area (41).

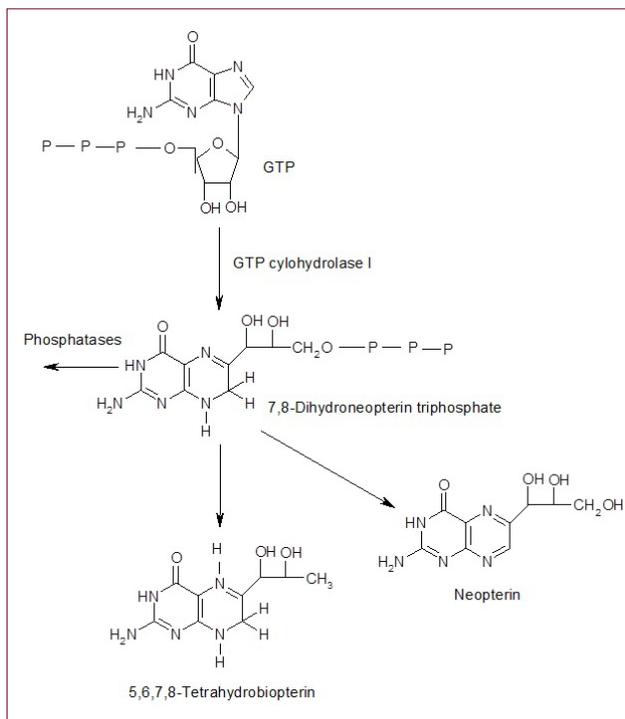


Figure 1. The biosynthesis of neopterin

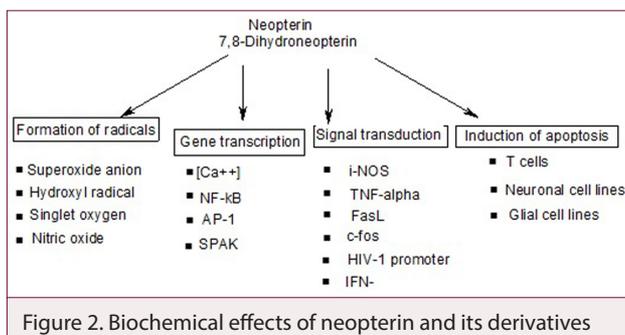


Figure 2. Biochemical effects of neopterin and its derivatives

CONCLUSION

As a result, neopterin increases in viral and bacterial infections, transplantation complications, some malignant diseases, burns, wound sites and autoimmune diseases related to immune activation. Neopterin may be useful in determining the degree of these diseases. Although it is clear that neopterin is of interest to researchers in recent years, further studies are needed on neopterin and wound healing.

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