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Cell Growth Factors

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Abstract
My study's importance is evaluate the structural properties of cell growth factors (GFs) their functions in interactions among cells based on these properties. Glycoproteins synthesized by the effect of genes bound to receptors on the cell surface and stored in the extracellular matrix are called as growth factors. Growth factors, unlike hormones, can be excreted by many cells. These factors can stimulate or suppress cell division, differentiation, migration, or genetic activities by affecting cellular activity. They also help hematopoietic stem cells to transform into blood cells. These growth factors can work in the cell by binding only to an appropriate receptor. According to the structural characteristics, they are divided into eight categories: vascular endothelial growth factor, epidermal growth factor, fibroblast growth factors, platelet - derived growth factor, transforming growth factor, insulin - like growth factor, hematopoietic growth factor, and nerve growth factor. Today these growth factors have been used for preparing wound - burn cover materials, removing skin wrinkles, controlling cholesterol levels, strengthening immune system, and developing healthier hair and nails. These factors can be used in treating many diseases, particularly cancer, repair of damages on nerve tissues, dwarfism therapy, and deceleration or interception of cell aging. In addition, attempts are being made to develop new systems for the most effective and efficient use of these growth factors.
Keywords: Biotechnology, Anti - aging of cells, Treatment of neuron damage, Treatment of wound burn, Apoptosis.

1. Introduction

Growth factors (GFs) comprise an important class of proteins that are produced by the effect of genes in deoxyribonucleic acid (DNA). They have receptors on the surface of cells. Most of them are stored in the extracellular matrix, and their molecule weights range between 4000 and 80000 Da (Carpenter and Cohen 1990). Although the function and mechanism of action of hormones are similar to those of GFs, they are evaluated as a different group. The most obvious difference between hormones and GFs is that GFs can be excreted by many cells while hormones are synthesized and excreted by certain endocrine glands. GFs can be isolated from organs, tissues or cell cultures (Carpenter and Cohen 1990). They affect cellular activities and can stimulate or suppress cell division, cell differentiation, cell migration or genetic efficiencies (Berberoğlu 2007; Masi et al. 2016). They stimulate chondrocyte metabolism and chondrogenesis and help in the transformation of hematopoietic stem cells in to blood cells (Kansu 2006). During the wound healing process, the expression of GFs on the wound area increases, thus accelerating angiogenesis and healing process by increasing oxygenation in the environment (Ural and Alptekin 2015; Başbuğ et al. 2016).

Breast milk contains many GFs including particularly epidermal growth factor (EGF), "transforming growth factor (TGF - α and TGF - β), "nerve growth factor (NGF) and insulin - like growth factor - I (IGF - I). These factors influence many systems including primarily gastrointestinal system, central nervous system and respiratory system (Giray 2004; Didişen and Gerçek 2015). The placenta is also very rich in hormones and GFs (Hasegawa et al. 2004; Samandari et al. 2004; Tosi et al. 2005; Özçelik and Yavuz 2006). GFs can affect any cell and exert their effects by binding to an appropriate receptor on the cells (Jerome et al. 2003; Keleş and Türkeli 2005). Every cell has a different number of receptors for different GFs (Scholz et al. 2001; Deveci 2003). This review study aimed to evaluate the structural properties of GFs and their functions in interactions among cells based on these properties.

2. Classification of GFs

GFs are classified as follows:

2.1. Based on the area where they are synthesized and the area in which they operate

According to this classification, GFs are categorized into five groups:
2.1.1. GFs demonstrating an autocrine effect: They affect the cells that produce them.
2.1.2. GFs demonstrating a paracrine effect: They affect the neighboring cells and not the cells that produce .them because the latter lack appropriate receptors
2.1.3. GFs demonstrating an endocrine effect: They are synthesized in any part of the body and transported through blood circulation to the target cells.
2.1.4. GFs demonstrating juxtacrine effect: They establish a connection between two neighboring cells.
2.1.5. GFs demonstrating intrakrin effect: In this case, a receptor - GF complex is created within the cell.

2.2. Based on the structural features

According to this classification, GFs are categorized into the following eight groups.

2.2.1. Vascular endothelial growth factor

The molecular weight of vascular endothelial growth factor (VEGF) is 45000 Da. It is found in lung alveolar cells, kidney glomeruli, proximal tubules, liver hepatocytes and brain (Ferrara 2000; Kleespies et al. 2004; Erol 2007; Yazır 2007). It binds to VEGF receptors (VEGFRs). It is activated by binding to VEGFR - I and VEGFR - II tyrosine kinase receptors (Achen and Stacker 1998; Ortega et al. 1998; Reinmuth et al. 2003; Sridhar and Shepherd 2003; Erdoğan et al. 2005; Yücel and Kurnaz 2005). It stimulates the proliferation, migration and differentation of endothelial cells (Yazır 2007). It regulates vasculogenesis and angiogenesis, increases vascular permeability and has a protective effect on neurons (Yazır 2007). It is the only factor that has an angiogenic effect and increases vascular permeability within the factors stimulating angiogenesis (Yazır 2007).

2.2.2. Epidermal growth factor

The molecular weight of epidermal growth factor (EGF) is 6040 Da. It is found in in liver, placental cells and platelets (Carpenter 1981; Harris et al. 2003). It binds to EGF receptors (EGFRs). EGFRs are found in urine, saliva, milk, blood, stomach, pancreatic fluid, cerebrospinal fluid, seminal fluid and prostatic fluid (Abban et al. 2007). The number of EGFRs is directly proportional to the developmental stage of living beings (Singh and Haris 2005).

The biological activities of EGF are as follows: (1) normal growth effect; (2) role in the neoplastic growth; and (3) effect on wound healing. It plays an important role in cell growth, proliferation and differentiation by stimulating DNA synthesis (Harris et al. 2003). It is involved in embryogenesis, angiogenesis and regeneration of tissues and vascular system (Tonini et al. 2003; Konukoğlu and Turhan 2005). The number of EGFRs on the cell surface of cancer cells has been shown to increase abnormally, leading to uncontrolled cell growth (Güllü 2004; Erarslan and Türkay 2007). EGF also accelerates the healing of burns and corneal injuries (Longaker and Adzick 1991; Özgenel 2004). It stimulates epithelialization and formation of granulation tissue and new blood vessels, resulting in wound healing (Bhora et al. 1995).

2.2.3. Fibroblast growth factors

The molecular weights of fibroblast growth factors (FGFs) range from 17000 to 34000 Da, and their biological half - lives are very short (< 2 - 3 min) (Tabata et al. 1999; Çetin and Çapan 2004). FGFs are of two types: acidic (FGF - I) and basic (FGF - II). They bind to four basic receptors including FGFR - I, FGFR - II, FGFR - III, and FGFR - IV (Ornitz and Itoh 2001; Çetin and Çapan 2004). They are found in fibroblasts, osteoblasts, smooth muscle cells, endothelial cells and chondrocytes, with powerful mitogenic activities for melanocytes, neurotrophic properties and heparin binding properties (Borland et al. 2001; Ornitz and Itoh 2001; Böttcher and Niehrs 2005). They contribute to organogenesis (Nunes et al. 2016). They participate in endothelial cell proliferation, migration and stimulation of angiogenesis (Rosen 2002; Güran et al. 2004). They protect neurons against free radicals, nitric oxide, hypoglycemia and asphyxiation (Çetin and Çapan 2004). They play an important role in treating central nervous system diseases (Çetin and Çapan 2004). They control the differentiation of hematopoietic stem cells (Ateş 2016).

2.2.4. Platelet - derived growth factor

The molecular weight of platelet - derived growth factor (PDGF) is 32000 Da. It is released from α granules in the platelets, monocytes, activated macrophages, fibroblasts, endothelial cells and bone matrix (Ross 1986; Cirri et al. 2005). It binds to PDGF receptors. It stimulates mitosis in connective tissue including bones (Schmitz and Hollinger 2001; Sanchez et al. 2003; Nisbet 2007). It stimulates the differentiation of osteoprogenitor cells and collagen synthesis (Nisbet 2007). At the same time, it stimulates bone resorption by increasing the number of osteoclasts (Liao and Liu 2014) and accelerates the re - formation of bones (Sanchez et al. 2003; Nisbet 2007). It is involved in embryonic development, cell proliferation, cell migration, angiogenesis (Sanchez et al. 2003; Nisbet 2007) and proliferation of periodontal ligament cells and osteoblasts (Berberoğlu 2007).

2.2.5. Transforming growth factor

Transforming growth factor (TGF) is a polypeptide just like EGF. It has two forms: TGF - α and TGF - β (Ozkan et al. 2007). It causes the release of FGF and PDGF by stimulating monocytes (Soyöz and Özçelik 2007). It binds to EGFRs. It regulates cellular processes such as proliferation, differentiation, motility, adhesion and cell death (Parkar et al. 2001; Momose et al. 2002; Berberoğlu 2007) by stimulating DNA synthesis (Fausto 2000; Akça and Dinçer 2004). It contributes to angiogenesis, wound healing, regulation of immune response and embryogenesis (Sporn et al. 1986; Court et al. 2002).

2.2.6. Insulin - like growth factor

Because of insulin - like effects and structural properties, it is called insulin - like growth factor (IGF). The IGF system comprises IGF (IGF - I and IGF - II), "IGF connective proteins (IGFBP - I to IGFBP - VI), "and IGF receptors (type - I and type - II) (Jones and Clemmons 1995; Darcan and Mir 1998; Schlessinger 2000; Topgül et al. 2004; Küçükkaya and Kan 2007; Biggs et al. 2016). IGF exerts its effect between G1 and S phases of the

cell cycle (Giovannucci 1999). It stimulates immune system and helps in cell and organ regeneration and regulates blood sugar and cholesterol levels (Keleş and Türkeli 2005). It also regulates bone formation and differentiation and maturation of osteoblasts (LeRoith et al. 1995; Whitley et al. 1996). IGF plays a key role in normal development during fetal and childhood stages (Toparslan et al. 2015). It reduces the signs of aging by reducing wrinkles and making the skin appear younger (Jones and Clemmons 1995). It has a positive effect on Ca^{+2}, Mg^{+2}, and K^{+} hemostasis (Durmuş and Topal 2005; Keleş et al. 2006). It increases body resistance through maturation of mastocytes (Scheiwiller et al. 1986; Johnzon et al. 2016). IGFs are important regulatory peptides in lung cancer (Gederet et al. 2004; Abban et al. 2007).

2.2.7. Colony - stimulating factor

Three most well - known colony - stimulating factors are erythropoietin, granulocyte colony - stimulating factor and granulocyte - macrophage colony - stimulating factor. They are responsible for the regulation of hematopoiesis (Jaques et al. 1998) and facilitate monocyte cytotoxicity (Deveci 2003). Hematopoietic stem cells proliferating in the bone marrow of individuals and stimulated with these factors move into the blood circulation, leading to hematopoiesis (Barnes 2000; Yıldırım 2004; Beksaç 2006).

2.2.8. Nerve growth factor

The molecular weight of nerve growth factor (NGF) is 26000 Da. It is released from the prostate gland, brain, kidney and placental cells (Darling and Shooter 1984; Sporn and Roberts 1991; Ural 2006). NGF binds to two receptors called Track - A and low - affinity NGF receptor. It is involved in the development of nervous system during the embryonic stage. In adults, it ensures the continuity of nerve cells and neural transmission (He and Garcia 2004). It participates in the regeneration of axons and dendrites and provides the continuity of sympathetic nerves and motor neurons (Özgenel et al. 2001). NGF is the first and the most important of all known GFs (Reid et al. 2002; Ayan et al. 2007). NGF and hepatocyte growth factor are involved in the formation of relevant tissues, organs and systems by the differentiation of embryonic germ layers (Schuldiner et al. 2002). NGF plays an important role in the development of immune system (Schuldiner et al. 2002; Özgenel and Filiz 2003; Ayan et al. 2007).

3. Discussion

GFs play a key role in the cell cycle (Öztürk and Denkbaş 2003). It has been observed that when these factors are removed from the body environment, a pause occurs in the cell cycle leading to cell deterioration and ultimately apoptosis (Dinçel and Kul 2016). GFs have a wide range of applications in biotechnology (Mitchell et al. 2015; Gomez et al. 2016). The first is the preparation of wound - burn cover materials. It has been found that wound healing on applying GFs in rats was more rapid (83.24 % on the 15th day of application compared with the control group) (Masi et al. 2016). Modern biotechnological and medical advancements have helped in developing natural medicines containing GFs. These products have been shown to have many beneficial effects such as removing skin wrinkles, losing weight, regulating sleep, developing healthy hair and nails, bodybuilding, controlling cholesterol levels, strengthening immune system and so forth. (Öztürk and Denkbaş 2003; Özçelik and Yavuz 2006). Functions of growth factors on different organs systems are shown in Table 1. Cartilage and soft tissue damages, tendon injuries and muscle pain have been treated successfully using GFs (Akgün 2016). Hematopoetic stem cells are transplanted in 55 - 60 thousand patients per year successfully using GFscompared with peripheral blood stem cells and finally cord blood stem cells (Arat 2016). Another area in which GFs are commonly used is the treatment of degenerated tissues. Anti - VEGF agents are increasingly used for treating neovascular age - related macular degeneration (Erol 2007). GFs are natural materials used in treating lumbar disk degeneration (Nakagami et al. 2002). They have also shown positive results in the treatment of cancer. Angiogenesis is the most important event in the development of a tumor. The inhibition of GFs or the existence of GF inhibitors has been shown to decrease angiogenesis (Nakagami et al. 2002; Deveci 2003). Also, a reduction in VEGF and FGF may inhibit tumor development (Karakuş et al. 2016).

Table 1: Functions of growth factors on different organs systems

Organs	Functions
Brain	Nerve cell differentiation
Blood vessel	Vascular development, smooth muscle cell proliferation, blood pressure control
Lungs	Morphogenesis of bronchi and bronchioles
Skeletal system	Arm and leg development
Muscle	Myogenesis
Bone	Bone healing, cartilage tissue formation
Hematopoiesis	Formation and development of granulocytes, formation of megakaryocytes and induction of stem cells
Reproductive system	Spermatogenesis
Skin	Melanogenesis, wound healing

4. Conclusion

The present study showed that GFs are promising candidates for treating many diseases in the future. Particularly nerve tissue damages, injuries and dwarfism (Masi et al. 2016). It is well known that nerve cells cannot multiply and repair themselves. However, GFs can promote the multiplication of nerve cells. Large - scale studies on GFs in the future may assist in developing interventions to slow or stop cell aging and effective therapies for cancer patients. Also, attempts are being made to develop new systems for the most effective and efficient use of GFs (Öztürk and Denkbaş 2003).

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