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Physiology, Growth Factor

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Introduction

A growth factor, as initially defined, is a secreted biologically active molecule that can affect the growth of cells. This definition has been expanded to include secreted molecules that promote or inhibit mitosis or affect cellular differentiation. Growth factors can act on specific cell surface receptors that subsequently transmit their growth signals to other intracellular components and eventually result in altered gene expression. The general process of transmitting an external molecular signal to a cell to evoke a cellular response is called signal transduction.[1][2][3]

Protein phosphorylation cascades play a key role in transmitting growth signals. Enzymes with kinase activity or phosphatase activity are important in this signaling process. Kinases put a phosphate group on a protein, and phosphatases take off a phosphate group. Many growth factors are peptides/proteins, and this type of growth factor typically binds with high affinity to a specific surface receptor which is a plasma membrane-bound protein. A peptide is defined as having between two and 50 amino acid residues, whereas a protein has more than 50 amino acid residues. The receptor binding site for peptide/protein growth factors is on the outer cell membrane surface, in other words, the extracellular domain. Most cell surface receptors for growth factors show tyrosine kinase activity, meaning they put a phosphate group on a downstream protein tyrosine residue. An exception is the surface receptors for the transforming growth factor-beta (TGF-beta) family of cytokines. When activated by the binding of TGF-beta cytokines, this receptor can phosphorylate downstream proteins on serine and threonine residues. “Downstream” here means an event triggered after TGF-beta binding to its receptor.[4]

Some growth factors are small peptides called cytokines. While all cytokines affect signal transduction pathways, only those cytokines affecting cell growth/differentiation signaling pathways are considered growth factors. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an example of a cytokine growth factor since it promotes the production of white blood cells by stem cells. Examples of protein growth factors are vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). Growth factor specificity to particular cells types can be achieved by the expression of highly specific cell surface receptors. For example, some growth factors act only hematopoietic cells which are cells derived from bone marrow.

Some growth factors like lipid-soluble steroid hormones, do not have a surface receptor and can directly pass through the cell's plasma membrane, bind to an intracellular protein receptor, or nuclear receptors, and then transmit a growth signal. All hormones are produced by glands and are secreted into the circulatory system. Estrogens, androgens, and progestogens are examples of steroid hormones that are growth factors. Not all hormones are growth factors, only those affecting cell growth/differentiation. Even simple small molecules such as nitric oxide or reactive oxygen species (ROS) can act as growth factors.[5]

Cellular

Wound Healing and Growth Factors

Wound healing is a normal, multiphase, physiological process and is of obvious importance after surgery. Growth factors play key roles in all 3 phases of wound healing: (1) the inflammatory phase, (2) the proliferative phase, and (3) the remodeling phase. Platelets are the key cell type for the inflammatory phase because they release platelet-derived growth factor (PDGF) and TGF-beta, both of which are growth factors that attract macrophages and neutrophils. Neutrophils are white blood cells that can kill bacteria and thereby prevent sepsis at the wound site. Macrophages secrete growth factors that both attract fibroblasts and also play a key role in the second phase of wound healing, the proliferative phase. TGF-beta is also secreted by macrophages and plays a role in wound fibrosis. VEGA can be secreted by both macrophages and endothelial cells, and this growth factor promotes angiogenesis (growth of new blood vessels). Macrophages also secrete epidermal growth factor (EGF), and it stimulates fibroblasts to secrete collagenase which is important during the remodeling phase. There is evidence suggesting that the complex and changing mixture of growth factors occurring during wound healing modulates macrophage functions.[6][7]

Development

Growth Factors and Cancer

Genetic alterations in signal transduction pathways contribute to many cancers phenotypes such as increased cellular growth, cellular motility, and angiogenesis. One of the key pathways activated by growth factor binding (for example, EGF or insulin-like growth factor 1 [IGF-1]) to a surface receptor is the PI3K/AKT pathway. When activated by a surface receptor, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) can phosphorylate and activate AKT which is serine/threonine-specific protein kinase. When AKT has activated it, in turn, promotes cell survival, cell motility, angiogenesis and also inhibits apoptosis. Apoptosis is programmed cell death. Many cancer cells show resistance to apoptosis giving these cells a survival advantage. Many of the processes activated by AKT are known to contribute to cancer. There has, therefore, been considerable effort to develop chemotherapeutic agents that block the activation of the AKT pathway.

Angiogenic growth factors important in cancer include vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) which are both proteins. Tumor growth is very dependent upon the growth of new blood vessels and blocking this process can kill tumor cells.[8][9][10]

Organ Systems Involved

VEGF, Angiogenesis, and Eye Diseases

VEGF is a key factor for initiating and promoting the abnormal growth of new retinal blood vessels (neovascularization) as occurs in diabetic retinopathy and age-related macular degeneration. Age-related macular degeneration is the most common cause of vision loss in people 65 and older. The macula is small region near the center of the retina and is responsible for detailed vision. A lack of oxygen supply to the retina can cause the secretion of VEGF, which then promotes the growth of new retinal blood capillaries (angiogenesis). Drugs that block VEGF can be effective at stopping some forms of macular degeneration and diabetic retinopathy. Once such drug, ranibizumab, can be injected directly into the retina. The “mab” in “ranibizumab” means the drug is from a monoclonal antibody.[11][7]

Clinical Significance

Growth factors are important in both normal physiological processes such as wound healing and abnormal processes such as cancer and diabetic retinopathy. Diabetic retinopathy can be caused by the abnormal growth of retinal blood vessels and is a major cause of blindness. Mutations in kinases and phosphatases are common in cancer cells. Some cancer drugs block the action of growth factors.

Questions

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