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OVERVIEW OF CELL SIGNALING AND CELL COMMUNICATION

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ABSTRACT

Cell Signaling is an important facet of biological life. It allows cells to perceive and respond to the extracellular environment allowing development, growth, immunity, etc. Additionally, errors in cell signaling may result in cancer growth, diabetes. By understanding the processes that govern these pathways, scientists may understand the flow of information and transmission thereby allowing humans to treat diseases and grow tissues. There are many different ways for cells to communicate with each other and the outside environment. They may communicate directly through juxtacrine signaling, over short distances through paracrine signaling and over large distances through endocrine signaling.

Keywords: Signals, Receptors, G Couple Protein Receptors, Integrins.

INTRODUCTION

Cell-to-cell communication, or signaling, is an important part of understanding cell functions as well as system functions. There are several types of signaling, such as neurotransmitters that are recognized in the synapse, antigens triggering antibody responses, and target cells responding to specific hormones. Cells are in constant communication within the immune system - this ensures that there is a coordinated and well-regulated response [1]. Often, dysfunction within the immune system (as well as malignancies of cells involved in the immune system) is related to abnormal cellular signaling. Some cells require cell-to-cell contact in order for communication to occur. For this there are gap junctions which connect the cytoplasms of two cells together. In most cases, a molecule carries the signal from one cell and receptors on the other cell bind to the signal molecule thereby allowing communication. Afterwards, many pathways occur which ultimately trigger a cellular response. Juxtacrine signaling are reactions when proteins from the inducing cell interact with receptor proteins of adjacent responding cells. The inducer does not diffuse from the cell producing it. There are three types of juxtacrine interactions. In the first type, a protein on one cell binds to its receptor on the adjacent cell [2]. In the second type, a receptor on one cell binds to its ligand on the extracellular matrix secreted by another cell. In the third type, the signal is transmitted directly from the cytoplasm of one cell through small conduits into the cytoplasm of an adjacent cell.

Paracrine signaling is a form of cell signaling in which the target cell is near the signal-releasing cell. Some signaling molecules degrade very quickly, limiting the scope of their effectiveness to the immediate surroundings. Others affect only nearby cells because they are taken up quickly, leaving few to travel further, or because their movement is hindered by the extracellular matrix. Growth factors and clotting factors are paracrine signaling agents. The local action of growth factor signaling plays an especially important role in the development of tissues. Endocrine signaling can be contrasted with two other modes of signaling: neural signaling and paracrine signaling. A key difference is the distance that the regulatory molecule travels to reach its target. Neurons are connected to their target cells via synapses. A neurotransmitter crossing a synaptic cleft will travel between 10 and 20 nanometers. A paracrine will travel only a few millimeters before it is broken down, so it can only act on nearby cells. By contrast, hormones travel via the circulation to reach their targets, which may be multiple tissues that are far apart and distant from the

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endocrine cells. Thus, hormones could be said to have systemic effects. Note that the timing involved in endocrine signaling also differs markedly from neural signaling. Neural signaling is brief and discrete, generally beginning and ending in less than a second. The timing of endocrine signaling is longer: the hormone takes more time to reach its target, the response of target cells takes longer, and hormones are more stable and capable of signaling over longer times [3,4].

Cell Communication in humans

Communication within the body can take one of three different forms.

Autocrine signaling - a form of signaling where cells can communicate with themselves. In this pathway, the cell directly affects its own function by secreting substances which can act on the cellular receptors.

Paracrine signaling - cells can also communicate with cells in the immediate environment. Paracrine signaling is especially important in the local immune response.

Endocrine signaling - signaling at a distance. Occurs through the presence of hormones. Hormones are biologically active substances which are secreted into the bloodstream. Many of the regulators of white cell growth and development, for example, are hormones [5,6].

Effects of signaling molecules

Signaling molecules usually have an effect within the cell by affecting gene transcription. This in turn alters the proteins which are made by that cell which can have a structural or a functional effect. Interleukin 2, for example, is a cell signal which is secreted by activated T lymphocytes and results in increased transcription of genes coding for the HLA molecules in macrophages - macrophages then become more adept at presenting antigen to the T cells resulting in an enhanced immune response.

Nuclear receptors

Small nuclear receptors are often lipid molecules. For this reason, they can diffuse directly across the lipid bilayer of the cell membrane and the nuclear membrane. In the nucleus, they can bind directly to the DNA material and enhance expression. In the immune response, two important molecules are corticosteroid agents and vitamin D, both results in an immunosuppressive response.

Cell signaling Receptors

Most cell signaling molecules are proteins which must bind to specialized receptors on the surface of cell membranes. These receptors take many forms, often relying on downstream signaling molecules which can either act as second messengers to transmit the message or modify the signal by amplifying it, changing it to another form, splitting it or combining it with other signals. The involvement of these downstream signaling molecules results in a cascade. Two important molecules involved in downstream signaling are intracellular calcium and the small protein molecule, rat associated sarcoma was first discovered as an important molecule in rat malignancy. It binds to the internal surface of plasma membrane. It is activated by binding the high energy compound guanidine triphosphate (GTP) and is inactive if guanidine diphosphate is bound. It is known as a small G protein because it is activated by this mechanism. The enzymes responsible for catalysing the conversion of GDP to GTP are known as guanine-nucleotide exchange factors (GEFs). Calcium is a divalent cation which, in resting cells, is stored within membranous organelles (especially the mitochondrion). If the cell is activated, calcium is released resulting in downstream signaling. It is important that the calcium influx is regulated and terminated. Calcium is bound to calmodulin in the cell and pumps act quickly when calcium is released to return it to the organelles [7-9].

G protein associated receptors

G protein-associated receptors are also called serpentine receptors because they consist of a protein molecule which passes through the cell membrane seven times. G protein receptors are ubiquitous in the human body. Some important examples include the olfactory receptors and the rods and cones which are responsible for vision. In the immune system, G protein receptors are important as chemokine receptors. G protein receptors are linked to a molecule which is bound on the internal surface of the cell membrane. This molecule consists of three parts – α, β, and γ subunits and is inactive when bound to GDP. On activation of the G protein-linked receptor, GDP is phosphorylated to GTP which enables the α subunit to dissociate from the βγ subunit. The α subunit has an intrinsic GTPase activity and rapidly terminates the activation of the receptor. This has downstream effects including [10,11].

Cell Linkages- integrins

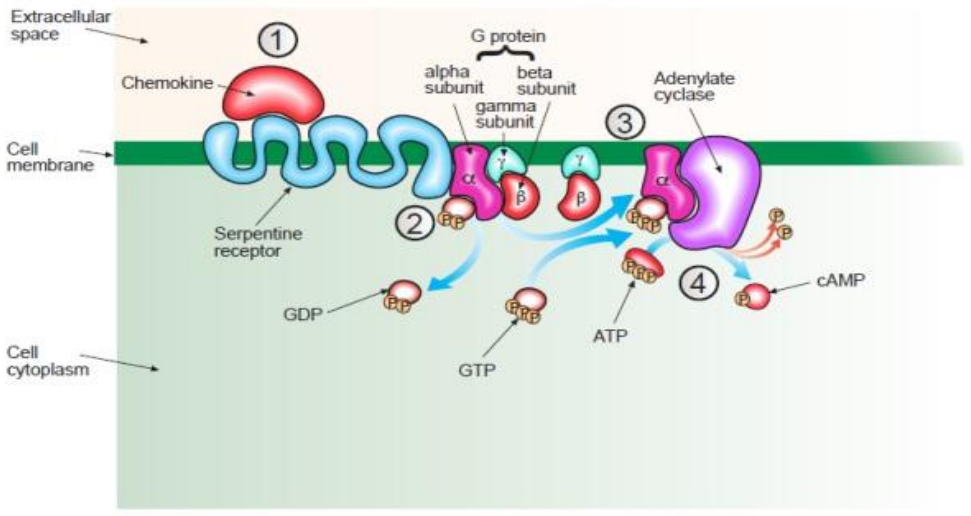
Communication is the name of the game, especially in cells; specialized receptors called integrins provide vital communication links between the interior and exterior of the cell. integrins are trans membrane proteins that act as mechanotransducers and signal conductors, providing a physical link between the extracellular matrix (ECM) and the cell's cytoskeleton. Although integrins do not have intrinsic enzymatic activity, they can interact with enzymes such as kinases that have specific signaling functions. integrins are involved in many cellular processes, such as differentiation, migration, proliferation, and ECM protein

expression, activation of growth factors, apoptosis, and cell survival. Interestingly, integrins work from either direction: They can bind to extracellular ligands, thus triggering intracellular signal cascades, or they can be activated by factors from within the cell to influence the relationship of the cell with its environment. integrins are heterodimers, meaning that they are composed of two distinct subunits termed α and β. Humans produce 18 different alpha chains (the larger subunit weighing 120–180 kDa) and 8 different betas (smaller subunits weighing 90–110 kDa), which combine to form different integrins. So far, 24 human integrins have been identified, each named for their two-component subunits (α2β1, for example) [12]. Studies of invertebrate species such as *Drosophila melanogaster* and *Caenorhabditis elegans* have revealed the presence of integrins (though there are fewer varieties), and the basic heterodimer structure is highly conserved among all animals. Proteins very similar to integrins are found in plants, fungi, or prokaryotes; these proteins may be important in touch (thigmo) responses in these organisms, in gravity perception in plants, and in the binding of a pathogenic fungus to fibronectin. Integrins typically span the cell's plasma membrane with the N- or aminoterminus of both subunits extending into the extracellular matrix, providing potential ligand binding sites. The subunits interact with each other and exist in either a low-affinity or a high-affinity conformation depending on external and internal signals. The integrins are normally bent in the low-affinity state, but "open like a switchblade" upon activation via phosphorylation of the β subunit's cytoplasmic end [13-15].

Integrins and Cellular Signaling

Inactive integrins are dispersed over the cell surface. Upon binding to ECM proteins, integrins migrate within the cell membrane to cluster and form focal adhesion sites in a process called activation. These sites may then include interactions with several additional proteins such as focal adhesion kinase (FAK), paxillin, talin, and tensin. Integrin interactions between talin, vinculin, α-actinin, and paxillin provide a physical linkage between the ECM and the actin cytoskeleton; these links are critical for cell anchorage and migration. Phosphorylation of the β tail, in the cytoplasm, disrupts the talin–integrin interaction, thus permitting cell movement. Integrin activation via external factors can set off a cascade of events; this is called outside-in signaling. These interactions can involve several proteins, in which the integrin has a critical mediating role. Outside-in signaling can result in modification of the cytoskeleton, cause cellular proliferation or migration, and determine cell survival or apoptosis. One example is the MAPK/ERK (mitogen activated protein kinase or extracellular signal-related kinase) signal pathway, which is turned on by integrin-extracellular ligand interactions [16,17].

Figure 1. G-protein linked - chemokines - adenylate cyclase



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