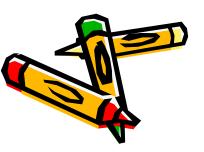
Histochemistry (304 C)

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Extra Cellular Matrix (ECM) Fibronctin, Iaminins, vitronectin and proteoglycans

(Structure, Synthesis, Function, Disease)

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Fibronectins

- Is a high-molecular weight (~440kDa) glycoprotein of the extracellular matrix. Two types of fibronectin are present in vertebrates:
- soluble plasma fibronectin is a major protein component of blood plasma (300 µg/ml) and is produced in the liver by hepatocytes.
- insoluble cellular fibronectin is a major component of the extracellular matrix. It is secreted by various cells, primarily fibroblasts, as a soluble protein dimer and is then assembled into an insoluble matrix in a complex cell-mediated process.

- The principal function of the extracellular matrix protein fibronectin is to connect cells to matrices that contain fibrillar collagen.
- At least 20 different forms of fibronectin have been identified.
 - All of them arise from alternative splicing of a single fibronectin gene.

• The soluble forms of fibronectin are found in tissue fluids.

• The insoluble forms are organized into fibers in the extracellular matrix.

• Fibronectin fibers consist of crosslinked polymers of fibronectin homodimers.

- Fibronectin proteins contain six structural regions.
 - Each has a series of repeating units.

- Fibrin, heparan sulfate proteoglycan, and collagen:
 - bind to distinct regions in fibronectin
 - integrate fibronectin fibers into the extracellular matrix network
- Some cells express integrin receptors that bind to the Arg-Gly-Asp (RGD) sequence of fibronectin.

Laminins

Laminins provide an adhesive substrate for cells

- Laminins are a family of extracellular matrix proteins.
 - They are found in virtually all tissues of vertebrate and invertebrate animals.
- The principal functions of laminins are:
 to provide an adhesive substrate for cells
 - to resist tensile forces in tissues

Laminins provide an adhesive substrate for cells

 Laminins are heterotrimers comprising three different subunits wrapped together in a coiled-coil configuration.

- Laminin heterotrimers do not form fibers.
 - They bind to linker proteins that enable them to form complex webs in the extracellular matrix.

Laminins provide an adhesive substrate for cells

• A large number of proteins bind to laminins, including more than 20 different cell surface receptors.

Vitronectin

Vitronectin facilitates targeted cell adhesion during blood clotting

- Vitronectin is an extracellular matrix protein.
 It circulates in blood plasma in its soluble form.
- Vitronectin can bind to many different types of proteins, such as:
 - collagens
 - integrins
 - clotting factors
 - cell lysis factors
 - extracellular proteases

Vitronectin facilitates targeted cell adhesion during blood clotting

• Vitronectin facilitates blood clot formation in damaged tissues.

 In order to target deposition of clotting factors in tissues, vitronectin must convert from the soluble form to the insoluble form, which binds clotting factors.

Proteoglycans provide hydration to tissues

- Proteoglycans consist of a central protein "core" to which long, linear chains of disaccharides, called glycosaminoglycans (GAGs), are attached.
- GAG chains on proteoglycans are negatively charged.
 - This gives the proteoglycans a rodlike, bristly shape due to charge repulsion.

 The GAG bristles act as filters to limit the diffusion of viruses and bacteria in tissues.

- Proteoglycans attract water to form gels that:
 - keep cells hydrated
 - cushion tissues against hydrostatic pressure

 Proteoglycans can bind to a variety of extracellular matrix components, including:

- growth factors
- structural proteins
- cell surface receptors

Hyaluronan is a glycosaminoglycan enriched in connective tissues

 Hyaluronan is a glycosaminoglycan.
 It forms enormous complexes with proteoglycans in the extracellular matrix.

- These complexes are especially abundant in cartilage.
 - There, hyaluronan is associated with the proteoglycan aggrecan, via a linker protein.

Hyaluronan is a glycosaminoglycan enriched in connective tissues

- Hyaluronan is highly negatively charged.
 - It binds to cations and water in the extracellular space.
 - This increases the stiffness of the extracellular matrix .
 - This provides a water cushion between cells that absorbs compressive forces.
- Hyaluronan consists of repeating disaccharides linked into long chains.

Hyaluronan is a glycosaminoglycan enriched in connective tissues

- Unlike other glycosaminoglycans, hyaluronans chains are:
 - synthesized on the cytosolic surface of the plasma membrane
 - translocated out of the cell
- Cells bind to hyaluronan via a family of receptors known as hyladherins.
 - Hyladherins initiate signaling pathways that control:
 - cell migration
 - assembly of the cytoskeleton

Heparan sulfate proteoglycans are cell surface coreceptors

- Heparan sulfate proteoglycans are a subset of proteoglycans.
 - They contain chains of the glycosaminoglycan heparan sulfate.
- Most heparan sulfate is found on two families of membrane-bound proteoglycans:
 - the syndecans
 - the glypicans

Heparan sulfate proteoglycans are cell surface coreceptors

- Heparan sulfates are composed of distinct combinations of more than 30 different sugar subunits.
 - This allows for great variety in heparan sulfate proteoglycan structure and function.
- Cell surface heparan sulfate proteoglycans:
 - are expressed on many types of cells
 - bind to over 70 different proteins

Heparan sulfate proteoglycans are cell surface coreceptors

- Cell surface heparan sulfate proteoglycans
 - assist in the internalization of some proteins
 - act as coreceptors for:
 - soluble proteins such as growth factors
 - insoluble proteins such as extracellular matrix proteins
- Genetic studies show that heparan sulfate proteoglycans function in:
 - growth factor signaling
 - development

Glycoproteins and Proteoglycans

Glycoproteins

Proteins conjugated to saccharides lacking a serial repeat unit

Protein >> carbohydrate

Proteoglycans

Proteins conjugated to polysaccharides with serial repeat units

Glycosaminoglycans Mucopolysaccharides Carbohydrate >> protein

Glycoproteins

- Proteins that contain oligosaccharide chains (glycans) covalently attached to polypeptide side-chains, in a co-translational or posttranslational modification.
- (N- Glycosylation), the addition of sugar chains can happen at the amide nitrogen on the side chain of the asparagine.
- (O- Glycosylation), the addition of sugar chains can happen on the hydroxyl oxygen on the side chain of hydroxy-lysine, hydroxy-proline, serine, or threonine.

Functions of Glycoproteins

- Structural
- Reproduction
- Hormones
- Enzymes
- Carriers
- Inhibitors
- Immunological

THANK YOU Dr. Rasha Zahran

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