CELL AND MOLECULAR BIOLOGY

I M.Sc ZOOLOGY

BY
Dr.S.J.SREEJA

CELL ADHESION

Cell Adhesion

- Cell adhesion is the process by which cells interact and attach to a surface, substrate or another cell, mediated by interactions between molecules of the cell surface
- Cell adhesion occurs from the action of transmembrane glycoproteins called cell adhesion molecules (CAMs)
- Examples of these proteins include selectins, integrins, syndecans and cadherins
- Cellular adhesion is essential in maintaining multicellular structure
- Cellular adhesion can link cells in different ways and can be involved in signal transduction
- Cell adhesion is also essential for the pathogenesis of infectious organisms

Cell Adhesion Molecules (CAMs)

- CAMs proteins are typically transmembrane receptors and are composed of three domains: an **intracellular domain** that interacts with the cytoskeleton, **transmembrane domain**, and an extracellular domain that interacts either with other CAMs of the same kind or with other CAMs or the extra cellular matrix (heterophilic binding)
- One classification system involves the distinction between calcium-independent CAMs and calcium- dependent CAMs
- There are five principle classes of CAMs : **cadherins, the immunoglobulins (Ig), selectins, mucins and integrins**
- Cell- cell adhesion involving cadherins and selectins depends on Ca^{2+} ions, where as interactions involving integrins and Ig super family CAMs do not

- Many cells use several different CAMs to mediate cell-cell adhesion
- The integrins mediate cell matrix interactions where as the other types of CAMs participate in cell-cell adhesion
- There are four major classes of functions: **the tight junction, gap junction, cell-cell and cell-matrix junctions**

Ca^{2+} Dependent Homophilic Cell-cell Adhesions

- Cadherins, a family of Ca^{2+} dependent CAMs are the major molecules of cell-cell adhesion and play a critical role during tissue differentiation
- The most widely expressed, particularly during early differentiation, are the E-, P- and N- cadherins
- Each cadherin is a type I integral membrane glycoprotein of 700-750 amino acids
- The cadherin molecule consists of an N-terminal extracellular region, a single transmembrane spanning segment, and a c-terminal cytoplasmic tail
- The extracellular domain contains repeated sequences that are sites necessary for Ca^{2+} binding and cell-cell adhesion

- The cytoplasmic domain associates with the cytoskeleton
- on average 50-60 percent of the sequence is identical among different cadherins
- Importantly, each cadherins has a characteristic tissue distribution
- During differentiation and in some disease, the amount or nature of the cell-surface cadherins changes, affecting many aspects of cell-cell adhesion and cell migration
- For example, the metastasis of tumour cells is correlated with the loss of cadherins on their cell surface
- In adult vertebrates, E-cadherin holds most epithelial sheets together
- Sheets of polarized epithelial cells

- Such as those that line the small intestine or kidney tubules, contain abundant E-cadherin at the sites of cell-cell contact along their lateral surfaces
- When a monoclonal antibodies, to E-cadherins is added to a monolayer of cultured epithelial cells, the cells detach from one another, directly demonstrating the requirement for E-cadherin in cell-cell adhesion
- The removal of Ca^{2+} from the medium also disrupt cell-cell adhesion, showing that E-cadherin-mediated interactions require Ca^{2+}
- If E-cadherins-mediated adhesion is blocked during cell aggregation, none of the specialized cell junctions between epithelial cells are generated

- E-cadherin, like the other cadherins, preferentially mediates homophilic interactions
- This phenomenon was demonstrated in experiments with L cells, a line of cultured transformed mouse fibroblasts that express no cadherins and adhere poorly to themselves or to other cultured cells, lines of transfected
- L cells that expressed either E-cadherin or P-cadherin were generated, such cells were found to adhere preferentially to cells expressing the same class of cadherin molecules
- For instance, E-cadherin expressing L cells adhere tightly to one another and to epithelial cells from embryonic long that express E-cadherin; they do not attach to untransfected L cells or to L cells expressing P-cadherin

- L cells expressing P-cadherin adhere to one another, and to other types of cells that express this cadherin
- Thus, cadherins directly cause homotypic interactions among cells

N-CAMs mediate Ca^{2+} Independent Homophilic Cell-cell Adhesion

- N-CAMs, a group of Ca^{2+}-independent cell-cell adhesion proteins in vertebrates, belong to the Ig superfamily of CAMs
- Their full name-Nerve Cell Adhesion Molecules- reflects their particular importance in nervous tissue like cadherins, N-CAMs primarily mediate homophilic interactions, binding together cells that express similar N-CAM molecules
- Unlike cadherins, N-CAMs are encoded by a single gene; their diversity is generated by alternative mRNA splicing and by diffrences in glycosylation

- Like N-cadherin, N-CAMs appear during morphogenesis, playing an important role in differentiation of muscle and nerve cells
- Their role in cell adhesion has been directly demonstrated by use of specific antibodies
- For instance, adhesion of cultured retinal neurons is inhibited by addition of antibodies to N-CAMs
- The adhesive properties of N-CAMs are modulated by long chains of sialic acid, a negatively charge sugar
- N-CAMs that are heavily sialylated form weaker homophilic interactions than do less sialylated forms, possibly because of repulsion between the negatively charged sialic acid residues
- In embryonic tissues such as brain, poly sialic acid constitutes as much as 25 percent o the mass of N-CAMs, in contrast, N-CAMs from adult tissues contain only one third as much sialic acid

- The lower adhesion properties of embryonic N-CAMs enable cell-cell contracts to be made and then broken, a property necessary for specific cell contracts to form in the developing nervous system
- The higher adhesive properties of the adult forms of N-CAM stabilize these contacts
- Thus, the strength of cell-cell adhesions is modified during differentiation by differential glycosylation of the N-CAMs