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INTEGRATING CELLS INTO TISSUES

REVIEW THE CONCEPTS

1. The diversity of adhesive molecules has arisen from 1) duplication of a common ancestor gene followed by divergent evolution producing multiple genes encoding related isoforms; and 2) alternative splicing of a single gene to yield many mRNAs, each encoding a distinct isoform. Integrins are heterodimers of α and β subunits. Combinatorial diversity of 18 α and 8 β subunits yields at least 24 functional integrin heterodimers.

2. Homophilic interactions are those between like cell types (e.g., epithelial cells with epithelial cells). One approach to demonstrating homophilic cell interactions experimentally is to use L cell lines transfected with E-cadherin. L cells adhere poorly to each other and express no cadherins. When transfected with E-cadherin, L cells adhere tightly through homotypic E-cadherin interactions among cells. Ca^{2+} is required for cadherin interaction. Removing extracellular Ca^{2+} disrupts interaction between the E-cadherin expressing cells.

3. Actin and myosin filaments form a circumferential belt in a complex with adherens junctions. This belt functions as a tension cable that can internally brace the cell and control its shape.

4. Tight junctions define apical and basolateral plasma membrane domains in polarized epithelial cells and control the flow of solutes between cells in an epithelial sheet. Several things can happen to cells when tight junctions do not function. In hereditary hypomagnesemia, defects in tight junctions prevent the normal flow of magnesium

through tight junctions in the kidney. Low blood-magnesium levels result, which can lead to convulsions. Altering tight junctions in hair cells of the cochlea of the inner ear can result in deafness.

5. This phenomenon is called electrical coupling. Although gap junction communication can be regulated by pH, Ca^{2+} concentration, phosphorylation, and voltage-gating, myometrial connexin Cx43 expression is upregulated to increase the number and size of gap junctions for parturition and decreases rapidly postpartum.

6. Collagen is a major component of the extracellular matrix in animal cells. It is a protein that has a trimeric structure with rodlike and globular domains that form a two-dimensional network. Collagen is synthesized in its precursor form by ribosomes attached to the endoplasmic reticulum. These pro-α chains undergo a series of covalent modificationsandarefoldedintoatriple-helicalprocollagen molecule. The folded procollagen is transported through the Golgi and the chains are secreted to the outside of the cell. Once outside the cell, peptidases cleave the N- and C-terminal propeptides. The triple helices are then able to form larger structures called collagen fibrils.MutationsincollagenIVorautoimmuneantibodies that disrupt collagen IV are associated with progressive renal failure, hearing loss, lung hemorrhage, and sight abnormalities.

7. Structural studies have shown that integrin exists in both a non-active, low-affinity , or "bent," form and an active, high-affinity , or "straight," form. In outside-in signaling, molecules of the ECM can bind to the extracellular portion of inactive integrin and induce conformational changes that lead to the straightening of the intracellular, cytoplasmic tails of integrin. The straightening of the cytoplasmic tails can stimulate intracellular components such as the cytoskeleton and parts of signaling pathways. This structure also facilitates inside-out signaling. For example, when the metabolic state of the cell is altered, adapter proteins inside the cell can interact with the cytoplasmic tails of integrin and cause either straightening or association. This would result in straightening or bending of the integrin extracellular domains and either promote or inhibit interaction of the integrin with the ECM.

8. Proteoglycans are highly viscous glycoproteins that cushion cells and bind to a wide variety of extracellular molecules. Collagen is fibrousandprovidesstructural integrity, mechanical strength, and resilience. Soluble extracellular matrix proteins such as laminin and fibronectinbindandcross-linkcell-surfacereceptors and other ECM components.

9. Syndecans in the hypothalmic region of the brain participate in the binding of antisatiety peptides to cell-surface receptors. In the "fed" state, the extracellular domain of syndecans is released from the surface by proteolysis. When this happens, the activity of antisatiety peptides is suppressed along with feeding behavior.

10. The RGD sequence on fibronectinmediatesbindingtointegrinproteins.IfRGD-containing peptides were added to a layer of fibroblastsgrownonafibronectin substrate in tissue culture, the RGD peptides would compete with fi bronectin for binding to the integrins present in the fibroblastextracellularmatrix.Asaresult, the fibroblastswouldlikelyloseadherencetothefibronectinsubstrate.

11. Three types of proteases can degrade ECM components as well as non-ECM components such as surface adhesion receptors: MMPs (matrix metalloproteases), ADAMs (a disintegrin and metalloproteinases), and ADAMTS (ADAM with thrombospondin motifs). These proteases can be integral membrane proteins or secreted proteins, some of which bind tightly to membrane receptors. ECM degrading proteases are associated with a variety of diseases, including metastatic cancer.

12. Fibronectin contains RGD- and fibrin-bindingdomains.Bindingoffibronectinto a fibrinclotrecruitsplateletsthroughinteractionofthefi bronectinRGDdomain with a platelet integrin.

13. The dystrophin gene, which is defective in Duchenne muscular dystrophy, is an adapter protein that binds to cytoskeletal components such as actin as well as to the cell-adhesion molecule dystroglycan. Normally, dystrophin and dystroglycan function in an important part of the signaling relay linking the extracellular matrix on the outside of the muscle cell to the cytoskeleton and signaling components inside the muscle cell. When any of these components is defective, the muscle cells do not develop or function properly and muscular dystrophy results.

14. The process is called extravasation. Infl ammatory signals including chemokines are released in the area of infection. These signals activate the endothelial cells lining blood vessels in the area. P-selectin exposed on the surface of activated endothelial cells mediates weak adhesion of passing leukocytes. Weakly bound leukocytes roll along the surface of the endothelium. At the same time, chemokines and other signaling molecules including the platelet-activating factor (PAF) also activate β2-containing integrins on the cell surface of the leukocytes. Upon activation, the integrins change conformation in to their high-affi nity form. Activated integrins bind to IgCAMs on the surface of endothelial cells. Tightly bound leukocytes stop rolling, spread out on the surface of the endothelium, and eventually crawl between adjacent endothelial cells into the underlying tissue.

15. Small molecule hormones, called auxins, induce the weakening of the cell wall. This permits expansion of the intracellular vacuole by uptake of water, leading to cell elongation.

16. Plasmodesmata, gap junctions, and tunneling nanotubes are channels that directly connect the cytosol of one cell to that of an adjacent cell. However, in plasmodesmata and tunneling nanotubes, the plasma membranes of the adjacent cells are merged to form a continuous channel. Membranes of the cells at a gap junction are not continuous. Plasmodesmata may also contain an extension of the endoplasmic reticulum, the desmotube, that passes through this continuous channel (the annulus). Animal cells do not contain desmotubes.