
CHAPTER 2

Tissue Structure/Unit Cell Processes

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2.1 WORKING/OPERATIONAL DEFINITIONS

Tissue

An aggregation of similarly specialized cells united in the performance of a particular function. Cells serving the same general function and having the same extracellular matrix.

Connective Tissue

The matrix-continuous tissue which binds together and is the support of the all of the structures of the body. The predominant structural protein comprising the extracellular matrix of connective tissue is collagen.

Organ

Two or more tissues combined to form a larger functional unit.

Unit Tissue Structure

The smallest repeating unit of a tissue or organ comprising a cell and its surrounding matrix (synthesized by the cell).

Development

The process of growth and differentiation of tissues and organs.

Embryology

The science of the development of the individual during the embryonic stage (2 weeks after fertilization of the ovium to the end of the eighth week) and, by extension, in several or even all preceding and subsequent stages of the life cycle.

Regeneration

The renewal of a tissue or organ at the completion of healing.

Repair

The formation of scar at a site of injury at the completion of healing.

Remodeling/ Maintenance/ Turnover

The process by which extracellular matrix is replaced in a process of degradation followed by synthesis.

Endogenous Mechanical Force

Force generated within a control volume of the unit cell process (e.g., by cell contraction).

Exogenous Mechanical Force

Force applied to a control volume of the unit cell process.

Autocrine

Denoting the influence of chemical factors secreted by a cell on itself.

Paracrine

Denoting influence of one cell on other cells in the vicinity.

Endocrine

Refers to tissues and organs whose function is to secrete into the blood or lymph a substance (e.g., hormone) that has a specific effect on another organ or tissue.

Hyperplasia

The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue.

Hypertrophy

The enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.

Atrophy

A diminution in the size of a cell, tissue, organ, or part.

2.2 Tissue Composition/Structure

Content not available.

2.3 Types/Classification of Tissue

Content not available.

2.4 UNIT CELL PROCESSES

2.4.1 Cell Activities

"Packaged" sequences (cascades) of cell activities/functions with an identifiable beginning and an end.

2.4.1.1 Mitosis (Proliferation)

Mitosis is a complex of processes leading to the division of a cell such that the two daughter nuclei receive identical complements of the number of chromosomes characteristic of the cells of the species. All cells arise from the division of pre-existing cells. The process of mitosis is divided into four phases: a) prophase-formation of paired chromosomes; disappearance of nuclear membrane, b) metaphase-chromosomes separate into exactly similar halves, c) anaphase-the two groups of daughter chromosomes separate and move along the fibers of a central "spindle", and d) telophase-the daughter chromosomes resolve themselves into a "reticulum" and the daughter nuclei are formed; the cytoplasm divides, forming two complete daughter cells.

The term mitosis is used interchangeably with cell division, but strictly speaking it refers to nuclear division whereas cytokinesis refers to division of the cytoplasm.

2.4.1.2 Synthesis (e.g., ECM structural proteins, enzymes)

Synthesis refers to the putting together of a chemical compound by the cell through the union of the elements comprising the compound or from other suitable starting materials. The chemical compounds can be proteins that serve as structural elements (e.g., collagen), enzymes (e.g., collagenase), regulators of other cells (e.g., hormones), immunoglobulins, etc. The compounds can be carbohydrates, lipids, or other macromolecules required in cell, tissue, or organ function. The products of cell synthesis can be stored in the cytoplasm or excreted by the cell.

2.4.1.3 Exocytosis (including degranulation)

Exocytosis refers to the process by which a cell excretes particles that are too large to diffuse through the cell membrane. It is considered to be the opposite of endocytosis.

2.4.1.4 Endocytosis

Endocytosis refers to the uptake by a cell of material too large to diffuse through its membrane. In the process of ingesting the material the cell invaginates its membrane, collecting the material in the fold produced by the invagination. Particles of the material larger than approximately one micrometer are "phagocytosed." In this process the cell membrane binds to the particle through a membrane receptor. Particles less than one micrometer are collected in the folds of the invaginated membrane with or without receptor binding, referred to as receptor-mediated endocytosis and pinocytosis, respectively. Fluid is taken up by the cell through the process of pinocytosis.

2.4.1.5 Migration

Migration refers to the movement of cells as a result of the action of intracellular cytoskeletal and contractile proteins and the receptor-mediated adhesion of the cell to extracellular matrix components (by integrins).

2.4.1.6 Contraction

At the cell level, contraction refers to the shortening of a cell and the concomitant development of tension in the matrix, as a result of the action of intracellular contractile proteins. The contractile proteins facilitating cell contraction are of the same family as facilitate cell migration.

2.4.2 Cell Protagonists

Requires a specific differentiated cell protagonist (Table 2.1). The process begins when the cell becomes the protagonist when expresses a specific phenotype or engages in a specific activity.

2.4.3 Chronology

Can appear at different sites at different times in different physiological and pathological sequences (i.e., modular; Table 2.2).

2.4.4 Matrix

Requires an insoluble matrix component/substrate (Table 2.3) for the cell activity. Cell acts on a substrate (e.g., extracellular matrix) through a membrane receptor (e.g., integrin) and a series of stereospecific biochemical reactions initiated by a signal (i.e., soluble regulator; see sec. 2.4.8). The matrix can serve as an insoluble regulator of cell function/activity.

2.4.5 Products

Results in a product that is a stable insoluble structure, soluble fragment, and/or mechanical force (Table 2.4). The quality of the product is invariant but the quantity is not; the product is quantifiable with respect to amount and direction/orientation, thus making the product a vector quantity.

2.4.5.1 Macromolecular Aggregates (Macromolecule) or Soluble Fragments

An example is collagen. The structure of a macromolecule is its conformation. In this case only one cell type is required (e.g., fibroblast) in the unit cell processes of synthesis and degradation.

2.4.5.2 Acellular Multicomponent Structure (Matrix)

Examples are basement membrane and clot. The structure comprises two or more types of macromolecules and may include nonviable cells. The structure of a matrix is its architecture.

2.4.5.3 Tissue (Cell + Matrix)

A system of multicomponent structures with viable cells. The structure of a tissue is its morphology.

2.4.6 Examples

Examples of unit cell processes are given in Tables 2.5 and 2.6.

2.4.7 Composite Processes

Two or more unit processes can combine to form a composite process (Table 2.7).

2.4.8 Regulators

Unit cell processes are regulated by diffusible soluble substances (Tables 2.8 - 2.11) acting on the cell protagonist directly or by mechanical forces acting on the cell indirectly through the matrix (e.g., by deforming the matrix). The regulators signal the start and the termination of the process. They also serve as connecting links between processes that comprise a composite process (e.g., the "coupling factor" between bone resorption and bone formation). In addition, regulators can control the rate of the process by acting on the cell and the substrate.

2.4.8 Rates of Processes

If the time period over which the unit cell process acts is t , then the rate of the process could be considered to be the quantity of product divided by t .

2.4 UNIT CELL PROCESSES

TABLE 2.1

Cell Protagonists

Cells of the same kind associate to form tissues. Tissues are divided into four types: connective tissue, epithelia, muscle, and nerve. Organs are formed by the combination of two or more tissues.

A. Connective Tissue (Matrix-Continuous)

1. Blood (Cells floating freely in a fluid matrix until clotting; then a fibrillar matrix)
 - a. Neutrophil
 - b. Eosinophil
 - c. Basophil
 - d. Monocyte
 - e. Lymphocyte
 - f. Plasma cell
 - g. Platelet
 - h. Red blood cell

2. Reticular Tissue (Cells in semi-solid matrix comprising reticular fibers, i.e., small diameter Type III collagen fibers. Examples include the framework of spleen, lymph nodes, bone marrow.)
 - Fibroblast (synthesis of the Type III collagen)
 - Reticular cell (macrophage-like)

3. Loose Fibrous Tissue (Cells in semi-solid matrix comprising reticular and thicker collagen fibers. An example is stroma, the supporting tissue or matrix of an organ, distinguished from its functional element, or parenchyma.)
 - Fibroblast

4. Dense Fibrous Tissue (e.g., dermis, ligament, tendon)
 - Fibroblast

3. Adipose (Fat) Cell

6. Hyaline Cartilage and Fibrocartilage
 - Chondrocyte

7. Bone
 - a. Osteoblast

- b. Osteocyte
 - c. Osteoclast

- 8. Tooth
 - a. Odontoblast (synthesis of dentin)
 - b. Cementocyte (synthesis of cementum)

9. Other
 - a. Macrophage/Histiocyte
 - b. Mast cell
 - c. Pericyte

B. Epithelia (Cell-Continuous)

1. Simple
 - a. Squamous cell (e.g., lining of blood vessels)
 - b. Cuboidal cell (non-secretory and secretory)
 - c. Columnar cell (e.g., lining of organs; including ameloblasts that synthesize enamel)
2. Pseudostratified Columnar Ciliated Cell (respiratory passages)
3. Compound (Stratified)
 - a. Transitional cell (e.g., lining of urinary passages)
 - b. Columnar cell (relatively uncommon)
 - c. Squamous cell (uncornified and cornified, e.g., skin)

C. Muscle (Contractile Cells)

1. Smooth muscle cell
2. Cardiac muscle cell
3. Skeletal (striated) muscle cell
4. Myofibroblast

D. Nerve Tissue

Nerve Cell

2.4 UNIT CELL PROCESSES

TABLE 2.2

Sites and Times at Which Unit Cell Processes Occur in Certain Clinical Sequences

<u>Process/ (Protagonist Cell)</u>	<u>Site</u>	<u>Time</u>	<u>Clinical Sequence</u>
Clotting (Platelet)	Vascular Tissue	Acute and Chronic	Wound Healing Stroke (thrombosis)
Collagen Degradation (Fibroblast)	Connective Tissue	Acute	Childbirth Wound healing
		Chronic	Collagen turnover Development Tumor resolution
		Acute and Chronic	Neoplasia Metastasis Bacterial infection (e.g. pneumonia, periodontal disease)
Collagen Synthesis (Fibroblast)	Connective Tissue	Acute and Chronic	Tumor growth Scar formation Regeneration
Epithelialization (Epithelial Cell)	Skin and oral mucosa	Acute	Wound healing
		Chronic	Epithelioma

2.4 UNIT CELL PROCESSES

TABLE 2.3

**Substrates Involved in Unit Cell Processes:
Components of Extracellular Matrix**

Collagen

Elastin

Adhesion Proteins (e.g., fibronectin, laminin)

Glycosaminoglycans

Proteoglycans

Apatite (mineral)

2.4 UNIT CELL PROCESSES

TABLE 2.4

Products of Unit Cell Processes

PROCESS	PRODUCT
Mitosis	More cells/Cell proliferation
Synthesis	
Insoluble matrix proteins	Matrix
Enzymes	Soluble matrix fragments
Cytokines	Regulators
Exocytosis (of stored granules/packets of regulators)	Regulators
Endocytosis	Solubilized fragments
Migration	Translocation
Contraction	Stress/Strain

2.4 UNIT CELL PROCESSES

TABLE 2.5

Examples of Unit Cell Processes

1. Clotting

Platelets interacting with ("activated" by) collagen fibers (serving as an insoluble regulator) or reacting to injury/implants act on a collagen fiber to **exocytose** granules of pre-packaged regulators (process of degranulation) and produce a clot.

2. Endocytosis

Macrophages **endocytose** fragments of the substrate. The substrate can be ECM, bacteria, or synthetic or natural materials related to implants. The products are small molecular weight metabolites.

3. Collagen Degradation

Fibroblasts **synthesize** the enzyme, collagenase, to depolymerize a collagen fiber to produce soluble peptide fragments.

4. Collagen Synthesis

Fibroblasts attach to ECM components and **synthesize** collagen molecules.

5. Contraction

Myofibroblasts exert **contractile** forces on collagen fibers.

6. Epithelialization

Epithelial cells act on a basement membrane and undergo **mitosis** in order to produce a confluent layer.

7. Bone Formation

Osteoblasts attach to ECM components and **synthesize** bone matrix.

8. Bone Resorption

Osteoclasts attach to bone matrix and **synthesize** protons and collagenase in order to solubilize the matrix, thereby producing peptide fragments and components of the apatite mineral.

2.4 UNIT CELL PROCESSES

TABLE 2.6

Examples of Unit Cell Processes

<u>Unit Cell Process</u>	<u>Cell Protagonist</u>	<u>Substrate</u>	<u>Activity/Function</u>	<u>Product</u>
Clotting	Platelet	Collagen	Exocytosis (Degranulation)	Platelet Aggregation
Collagen Degradation	Fibroblast	Collagen Fiber	Synthesis: Collagenase	Soluble Collagen Fragments
Collagen Synthesis	Fibroblast	ECM Component	Synthesis: Collagen	Collagen

2.4 UNIT CELL PROCESSES

TABLE 2.7

Composite Unit Cell Processes

1. Collagen Remodeling

Collagen degradation + collagen synthesis

2. Neovascularization

Collagen synthesis + endothelialization

3. Scar Formation

Collagen synthesis + contraction

Supercomposite Unit Cell Processes

1. Tissue Remodeling Associated with Wound Healing

Collagen remodeling + neovascularization + scar formation

2. Bone Remodeling

Bone resorption + bone formation

3. Acute Inflammation

De-endothelialization + clotting + endocytosis + neovascularization

3. Granulation Tissue Formation

Neovascularization + collagen synthesis.+endocytosis

4. Chronic Inflammation

Endocytosis + neovascularization + collagen degradation + collagen synthesis.

2.4 UNIT CELL PROCESSES

TABLE 2.8

Regulators of Unit Cell Processes

Cytokines*

Interleukins

IL-1

IL-6

Tumor Necrosis Factor (TNF)

Platelet Derived Growth Factor (PDGF)

Insulin-like Growth Factor (IGF)

IGF-1

IGF-2

Fibroblast Growth Factor (FGF)

basic FGF

Transforming Growth Factor (TGF)

TGF- β

Eicosanoids**

Prostaglandins

PGE₂

Leukotrienes

LTB₄

Differentiation Factors

Bone Morphogenetic Protein (BMP)

* **Cytokines** are polypeptides (proteins) that regulate many cell functions. They act on a target cell by binding to specific high-affinity **receptors**. Cytokines that act on the same cell that produced them are called **autocrine** factors; those that act on other cells are called **paracrine** factors; those that act systemically (through the vascular system) are referred to as **endocrine** factors. Molecules that switch on (*i.e.*, regulate) mitosis are referred to as **growth factors**.

** **Eicosanoids** are chemically related signaling lipid molecules made primarily from arachidonic acid (fatty acid). Eicosanoids include prostaglandins, leukotrienes, thromboxanes, and lipoxins. Prostaglandins are continuously synthesized in membranes from precursors (20-carbon fatty acid chains that contain at least 3 double bonds, *e.g.*, arachidonic acid) cleaved from membrane phospholipids by phospholipases, membrane-bound enzymes. They are continuously released by the cell, and are degraded by enzymes in the extracellular fluids. The subscript of PGE₂ refers to the 2 double bonds outside the ring structure.

2.4 UNIT CELL PROCESSES

TABLE 2.9

Certain Cytokines (Growth Factors) as Regulators of Cell Activities*

<u>Cytokine</u>	<u>Mitosis</u>		<u>Migration</u> (Chemotaxis)			<u>Synthesis, FB</u>	
	<u>FB**</u>	<u>EN</u>	<u>FB</u>	<u>EN</u>	<u>MC</u>	<u>Collagen</u>	<u>Collagenase</u>
Platelet Derived Growth Factor (GF) (PDGF)	+	0	+	0	+	+	+
Fibroblast GF (FGF)	+	+	+	+	?	?	+
Transforming GF- β (TGF- β)	-/+	-	+	?	+	+	+
Transforming GF- α and Epidermal GF (EGF)	+	+	0	+	?	?	+
Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF)	+	0/-	?	?	+	+	+

+ - Stimulates
 - - Inhibits
 0 - No effect

* Adapted from R. Cotran lectures and Sprugel, et al, Am. J. Pathol., 129:601, 1987.

** FB- Fibroblast; EN-Endothelial Cell; MC - Monocyte

2.4 UNIT CELL PROCESSES

TABLE 2.10

Regulators in Acute Inflammation

<u>Cell Regulator</u>	<u>Source</u>	<u>Vascular Leakage/ Endoth. Cell Contraction</u>	<u>Leukocyte Migration/ Chemotaxis</u>
Eisoanoid			
Leukotriene B ₄ (LTB ₄)	Leukocyte	0	+
Cytokines			
Platelet Act. Factor (PAF)	Leukocyte	+	+
IL-1	Macrophage	0	+
TNF	Macrophage	0	+
Amino Acid Derivatives			
Histamine Platelet	Mast Cell	+	0
Serotonin Platelet	Mast Cell	+	0

2.4 UNIT CELL PROCESSES

TABLE 2.11

Regulators for Bone Cells

<u>Regulator</u>	<u>Cell Source (Regulator)</u>	<u>Osteoblast, OB</u>		<u>Osteoclast, OC Precursor Cell</u>	
		<u>Mitosis</u>	<u>Synthesis</u>	<u>Mitosis</u>	<u>Synthesis*</u>
TGF- β	M ϕ , OB, OC	+ -	+	0	0
bFGF	M ϕ , OB	+	-	0	0
PDGF	M ϕ , OB	+	+	0	0
IGF	OB	+	+	0	0
BMP	OB	+	0	0	0
IL-1	M ϕ	+	+?	+	0
PGE ₂	M ϕ , OB	+ -	+ -	?	+
TNF α	M ϕ	+	?PGE ₂	?	+
CSF-GM	M ϕ , OB	0	0	+	0
Calcitonin (S)**		0	0	0	+
PTH (S)		0	PGE ₂ , CSF-GM	0	0
EGF (S)		+	-	0	0

* Osteoclast activity relates to synthesis of enzymes and hydrogen ions.

** Systemic factors not yet found to be produced in bone.

TGF: Transforming Growth Factor

FGF: Fibroblast Growth Factor

PDGF: Platelet Derived Growth Factor

IGF: Insulin-like Growth Factor

BMP: Bone Morphogenetic Protein

IL: Interleukin

TNF: Tumor Necrosis Factor

CSF-GM: Colony Stimulating Factor-Granulocyte/Monocyte

PTH: Parathyroid Hormone

EGF: Epidermal Growth Factor

2.5 Examples of Unit Cell Processes

Content not available.

2.6 References

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