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) prophases-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 cytoplasms.

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 difuse 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.

(Continued on next page.)

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, as distinguisheded from its functional element, or parenchyma.)
   Fibroblast

4. Dense Fibrous Tissue (e.g., dermis, ligiment, 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)

(Continued on next page.)

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

TABLE 2.2

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

Process/ (Protagonist Cell)	Site	Time	Clinical Sequence
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

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)

(Continued on next page.)

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

(Continued on next page.)

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.

TABLE 2.6

Examples of Unit Cell Processes

Unit Cell Process	Cell Protagonist	Substrate	Activity/Function	Product
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

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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.

(Continued on next page.)

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
  - PGE_2
- Leukotrienes
  - LTB_4

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 PGE_2 refers to the 2 double bonds outside the ring structure.

(Continued on next page.)

TABLE 2.9

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

	Mitosis		**Migration** (Chemotaxis)			**Synthesis**, FB	
Cytokine	FB**	EN	FB	EN	MC	Collagen	Collagenase
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

TABLE 2.10

Regulators in Acute Inflammation

Cell Regulator	Source	Vascular Leakage/ Endoth. Cell **Contraction**	Leukocyte **Migration**/ Chemotaxis
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	Mast Cell Platelet	+	0
Seratonin	Mast Cell Platelet	+	0

TABLE 2.11

Regulators for Bone Cells

Regulator	Cell Source (Regulator)	Osteoblast, OB		Osteoclast, OC Precursor Cell	
		Mitosis	**Synthesis**	**Mitosis**	**Synthesis***
TGF-β	Mϕ, OB, OC	+-	+	0	0
bFGF	Mϕ, OB	+	-	0	0
PDGF	Mϕ, OB	+	+	0	0
IGF	OB	+	+	0	0
BMP	OB	+	0	0	0
IL-1	Mϕ	+	+?	+	0
PGE_2	Mϕ, OB	+-	+-	?	+
TNF α	Mϕ	+	?PGE_2	?	+
CSF-GM	Mϕ, 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