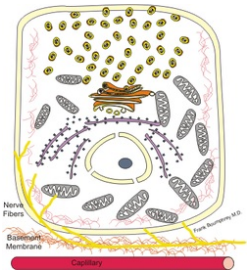


Epithelium (Pathobiochemistry)

Epithelial cells form continuous *leaves* (areas), called epithelia, lining the inner and outer surfaces of the body, or *form beams, glandular acins or tubules*. Their plasma membrane is organized into at least two different sections that perform their specialized functions - we say it is polarized. One side of its surface is firmly adjacent to the neighboring cell. There are a number of specialized types of epithelium:



- **Secretory** epithelial cells are found in most epithelia. They specialize in the excretion of various substances on the surface of epithelial layers. They are the main component of glands with external (exocrine) and internal (endocrine) secretion.
- **Absorbent** epithelium, on the other hand, absorbs the substances needed by the body. Their surface is therefore magnified many times by protruding small villi, called "microvilli". The individual epithelial cells are bound to each other by strong intercellular connections, which maintain a mechanically continuous layer of epithelium and at the same time prevent the passage of small molecules between the cells. The entire epithelial layer rests on the so-called basement membrane (*lamina basalis*). An example is intestinal epithelium.
- **Ciliary** epithelia (ciliary epithelium) have fine hairs on their surface, synchronously fluttering and thus displacing surface mucus with trapped dust or bacteria, which thus remove e.g. from the surface of the bronchial epithelium.

Enterocytes

The intestinal epithelial cell (enterocyte) lines the lumen small intestine. It has two main functions

1. absorb small molecules from the intestinal lumen created by digesting food;
 2. then transfer them to the bloodstream.
- The luminal (apical) part of the plasma membrane is specialized for absorption. This area is called the **brush border**. This is because thin finger-shaped protrusions with a diameter of 100 nm protrude from the surface, which are called "microvilli". The absorption area is thus increased many times over. Bundles actin filaments provide strength to microvilli. The exoplasmic membrane of microvilli contains hydrolytic enzymes:
- di- and tripeptidases, which cleave oligopeptides into individual amino acids;
 - disaccharides (sucrose, maltase, isomaltase, lactase, trehalase), which break down disaccharides into the corresponding monosaccharides and thus allow their absorption.

These hydrolytic enzymes are components of the glycocalyx. The molecules absorbed into the enterocyte are transferred and excreted by the "" basolateral membrane "" into the bloodstream. The transport proteins located in the basolateral membrane are different from those that realize absorption at the apical end. There are other protein molecules on the basement membrane that mediate anchorage to the basal lamina.

Classification

Enterocytes can be classified into three cell types.

Absorption cells Absorbent cells (*columnar absorptive cells*) are lined on the luminal surface by a dense row of microvilli (so-called brush border), which rest on a network of intracellular microfilaments below the cell membrane. Microvilli (or absorption cells) are the place of final digestion and absorption of food components. Each absorbent cell has up to *3000 microcolls* (1 x 0.1 μm), so that the total area of the microvilli is about 2 · 10⁸ cm² . On their surface is an apical envelope - glycocalyx, which is home to hydrolytic enzymes such as disaccharidases (lactase, sucrose-isomaltase, maltase, trehalase), dipeptidases and alkaline phosphatase. Absorption cells are rich in mitochondria, Golgi apparatus and endoplasmic reticulum. *Transport across the luminal membrane* proceeds as follows: Glucose is transposed from the intestinal lumen into the cell interior across the apical membrane using the glucose / Na⁺ symport transporter **facilitated diffusion**. Na⁺ ions are expelled from the enterocyte on the basolateral membrane by the action of Na⁺ / K⁺ ATPase pumps. A similar absorption mechanism (as a symport) exists for amino acids. Note: Disaccharide deficiency (congenital or acquired) is accompanied by diarrhea and a number of other symptoms. The most common is lactase deficiency.

Cup cells

Cup cells secrete mucin (acid glycoproteins) and are stored regularly between absorption cells. This protects the intestinal lining and provides it with a lubricating effect.

Enteroendocrine cells They are divided into a number of subtypes according to the hormones they produce

+ Division of enteroendocrine cells

Cell type	hormone	-	IG	gastrin	-	TG	tetrin	-	S	secretary	-	I	cholecystokinin	-	K	gastric inhibitory peptide	-	Mo	motilin	-	N	neurotensin	-	L	enteroglucagon	-	EC1	5-hydroxytryptamine, substance P, leu-enkephalin	-	P	bombesin-like
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M-cells M cells (membrane epithelial cells) are specialized as antigen presenting cells that phagocytose various antigen γ. They are passed on after processing immunocompetent cells lying beneath them in lymph follicles.

Parietal (covering) cells of the gastric mucosa

These cells have microvilli on the luminal side of the membrane, the basal side is very well supplied with blood from the blood capillaries. They also contain very numerous mitochondria, which indicates their high energy turnover. Their main task is the "acidification" of the gastric contents by HCl secretion to a concentration of 0.1 mol / l ('pH = 1.0). This is done by the activity of H⁺ / K⁺ ATPase on the apical side of the membrane. It resembles the Na⁺ / K⁺ ATPase erythrocyte membrane, but unlike it, its activity is electroneutral: it expels 1 ion H⁺ < / sup> and transfers 1 ion K⁺ to the cell during one cycle of hydrolysis ATP (at Na⁺ / K⁺ to expel / exchange 3No⁺ for 2K⁺). The proton concentration gradient between the gastric lumen and the cytosol of the parietal cell is 10⁶, a million times higher (pH 1.0 vs. pH 7.0). The concentration of OH⁻ in the cytosol would be expected to increase proportionally (based on the equation: [H⁺] x [OH⁻] = 10⁻¹⁴ < / sup> mol²). This is not the case (the pH of the cytosol remains neutral) is due to the fact that excess OH⁻ reacts with CO₂ , which diffuses into the cytosol from the bloodstream; this produces HCO₃⁻ catalyzed by carbonic anhydrase. The HCO anion ₃⁻ is transported across the basolateral membrane via the "anion exchange protein" (similar to the erythrocyte lane 3 protein, see also Hamburger effect) in exchange for Cl⁻ into the bloodstream. Cl⁻ - and K⁺ antiport are also involved.

Therapeutic blockade of H⁺ / K⁺ ATPases in parietal cells significantly reduces gastric secretion acidity, which is used in the treatment of esophageal reflux, peptic ulcer and other conditions with excessive acid gastric secretion. This is done by the application of "omeprazole", which is the so-called suicidal substrate of this enzyme, i.e. it binds irreversibly to enzyme, which then cannot continue to function. The gradual recovery of gastric acid secretion occurs in about 24-48 hours, when new (unblocked) parietal cells form during their regular recovery from basal cells.

🔗 For more information see *Determination of gastric secretion, acidity.*

Acinar pancreatic cell

Like an enterocyte (they have a common embryonic basis), it has two functional areas:

1. One part synthesizes and stores the hydrolytic enzymes needed to digest food in the gut.
2. The apical part, where clusters of secretory vesicles congregate, is the site of zymogen secretion.

The basolateral part of the membrane is surrounded by blood capillaries and is the place where nutrients come from. On the surface, it has numerous peptide hormone receptors that regulate the production and excretion of zymogens according to the food intake. These hormones come from the epithelium of the stomach and small intestine. Pancreatic cells form (with about a dozen identical cells) a small spherical formation - '*pancreatic acinus*'. The central cavity of the acinus is lined with ductal cells (centroacinar cells). Acinar cells contain zymogenic granules in which pancreatic hydrolytic enzymes are stored in an inactive form: trypsin ogen, chymotrypsinogen, elastase, procarboxypeptidases, aminopeptidases, ribonucleases, amylase and lipase.

Renal tubule cells

The main function of renal tubular cells is to transport water and glomerular filtered substances into the "primary" urine. Transport across tubular cells is an example of epithelial transport that occurs through multiple, polarized mechanisms across multiple biological membranes. Renal tubule cells can be classified into the following categories according to their location in nephron:

Proximal tubule cells

They line the first part of the twisted channels of the 1st order. There are so-called [tight junction]], they contain numerous mitochondria that supply energy Active transport, on the luminal side they are endowed with a brush border, which passes into the basolateral membrane. They have a number of water channels, the reabsorption of water and electrolytes is proportional, the filtrate in the lumen is isotonic. Reabsorption occurs first by equalization osmotic pressure. The basolateral membrane contains:

- Na⁺ / K⁺ ATPase that reabsorbs Na⁺ in exchange for K⁺ < / sup>.
- There is also passive reabsorption of Na⁺ with HCO₃⁻ and passive reabsorption of K⁺ via K⁺ channels.

In the brush border is located:

- cotransport for reabsorption of Na⁺ -solute and Na⁺ / H⁺ antiport (reabsorbs Na⁺ and secretes H⁺);
- an anion exchange transport that reabsorbs Cl⁻ in exchange for formate.

- Osmotic reabsorption of H₂O, secretion of organic cations in exchange for H⁺ and exchange of urate anions (proximal reabsorption and distal secretion) also take place here.

Henle loop descending arm (thin section)

It is highly permeable to water and slightly permeable to most solutes. It contains few mitochondria (little or no active transport). The lumen of the tubules leaves more water than solutes (the filtrate is *hypertonic*). Reassorption of filtered water Osmosis and minimal passive reabsorption of solutes take place here.

Henle loop ascending arm (thick part)

It is impermeable to H₂O. Passive reabsorption of solutes occurs in the thin ascending segment. The thick ascending segment contains mitochondria (for active transport). The output of solutes from the lumens rises more as the filtrate progresses through the ascending segment and therefore the filtrate becomes "hypotonic." On the basolateral membrane is located Na⁺ / K⁺ ATPase and channels for passive reabsorption Cl⁻ and channels for passive reabsorption K⁺ < / sup>. In the brush border there is a reabsorption cotransporter Na⁺ / K⁺ / 2 Cl⁻ and a secretory channel for K⁺.

Distal tubule cells (closer dilution segment)

They are impermeable to water and urea, and contain mitochondria to promote active transport. There is a macula densa for feedback secretion control renin. The solutes leave the lumen as the filtrate progresses, making it hypotonic. It contains the same channels as the thick ascending arm of Henle's loop.

Distal tubule cells (distal segment)

There are 2 cell types: *principal* and *intercalary*. Permeability to water and urea varies according to the secretion of antidiuretic hormone (ADH). In the absence of ADH, NaCl reabsorption causes the filtrate in the lumen to become progressively more hypotonic; in the presence of ADH, water is reabsorbed along the medullary gradient and the filtrate gradually becomes hypertonic. The basolateral membrane contains Na⁺ / K⁺ ATPase (in principal cells) and H⁺ ATPase in intercalated cells - this is responsible for the formation of acidic urine secretion H⁺. There are also reabsorption K⁺ and Cl⁻ channels.

Collecting duct cells

The antidiuretic effect of ADH is to increase the permeability of the apical membrane of the cells of the lower segment of the nephron to water. The mechanism is as follows: In the absence of ADH, aquaporins 2 (AQP2) are found outside the plasma membrane, but in its vicinity in specific vesicles - "aquaphores". Stimulation of the ADH cell induces a fusion of aquaphores with the adjacent apical membrane by signal transduction and creates water channels therein; this makes the apical membrane permeable to water molecules. In the absence of ADH, water channels from the membrane are withdrawn back to the vesicles by endocytosis. This whole process is repeated during the next stimulation. Intracellular transduction of the ADH signal occurs via a specific vasopressin (V2) receptor, which is part of the G-protein family, producing a second messenger - cAMP - and protein kinase A (PAK) activation. Another aquaporin (AQP3) is located on the basolateral membrane, which in turn facilitates the exit of water from the cell.

Clinical notes

Renal tubular epithelium lines the lumen of the renal tubules. The human kidney is made up of about 1.2 million tubules, which must maintain their tubular structure in order to function properly.

Polycystic kidneys In autosomal dominant polycystic kidney disease, cysts in the kidneys develop through disordered tubule enlargement. The disease is caused by mutation gene in PKD 1 or PKD 2. PKD 1 encodes a membrane protein called polycystin 1, which is required for cell-cell or cell-extracellular matrix interaction. The PKD 2 gene encodes polycystin 2, a membrane channel protein (non-selective cation channel regulated by Ca²⁺ - permeable to Ca²⁺, Na⁺ and K⁺). Polycystin 1 and polycystin 2 together form a heterodimer, which is necessary for the translocation of polycystin 2 from within the cell where it is formed to the cell membrane, where it performs its function. Both are necessary for proper morphology and function of the renal tubules.

 For more information see *Polycystic kidney disease / autosomal dominant*.

Bartter's syndrome Bartter's syndrome is characterized by hypokalemia caused by significant loss of K⁺ in the urine, metabolic alkalosis, and low or normal blood pressure; at the same time, the production of renin (hyperplasia of the juxtaglomerular apparatus) and aldosterone is increased; furthermore, the responsiveness of pressor effects to angiotensin II infusion is reduced. The production of prostaglandin E2, prostacyclin, kallikrein and bradykinin is often increased. Mg2⁺ levels tend to be reduced for hypermagnesiuria. The inheritance of the disease is autosomal recessive. Mutations in the renal Na⁺ -K⁺ -Cl⁻ - cotransporter gene (rarer) and chloride channel mutations (more common) have been demonstrated. In contrast, Gitelman's syndrome, which is a clinically milder variant with hypercalciuria and elevated plasma Ca (but Ca-ionized is normal), with normal prostaglandin production; is caused by a mutation in the renal thiazide-sensitive Na⁺ -Cl⁻ cotransporter gene. In the treatment of Bartter's syndrome, an increased supply of K⁺ and Na⁺ is recommended, in hypomagnesemia for hypermagnesiuria also Mg. Spironolactone reduces urinary K⁺ losses. In some patients, it is useful to administer prostaglandin synthetase inhibitors as well as angiotensin-converting enzyme inhibitors.

Familial diabetes insipidus A relatively rare mutation in the AVPR2 gene, which encodes the production of the V2 antidiuretic receptor, or a more frequent mutation in the AQP2 gene, causes familial nephrogenic diabetes insipidus. AQP2 mutations have been classified into 3 types: 1. the type of mutated receptor does not reach the membrane surface; in type 2, the receptor is on the membrane but does not have the ability to bind AVP; Type 3 is either inactive at all or degraded rapidly after formation. The result is impaired renal concentration, polyuria, polydypsyp, hyposthenuria, which does not improve after vasopressin application. There is a drug nephrogenic diabetes insipidus: Demeclocycline inhibits non-competitive adenylate cyclase activity; lithium salts cause vasopressin resistance by inhibiting adenylate cyclase by stimulating Gi-protein inhibitory activity.

Skin epithelium

After gastrulation, the surface of the embryo is covered by a simple layer of pluripotent ectoderm. Soon after the mesenchymal cells settle under the ectoderm, the epidermis and its appendages begin to form. Ectoderm changes into the skin. The cutaneous epithelia are separated from the mesenchyme by the underlying basal lamina of the extracellular matrix. The mesenchyme determines what type of epithelium and their accessory structures are formed. This means that when whole skin with hair follicles is transplanted into a hairless area of the skin (eg in the palm or soles), hair follicles are also formed at this point. So the skin knows what pendants to make, and the mesenchyme provides the appropriate stimuli.

Epidermal cells

The epidermis (skin) is a constantly regenerating multilayered organ whose cells are in *constant differentiation*¹. The viscous part has 2 main zones of cells (keratinocytes):

- inner life cell zone (stratum germinativum);
- outer layer of stratum corneum.

In the stratum germinative, 3 more layers can be distinguished: (i) basal, (ii) spinous and (iii) granular; each represents advanced stages of differentiation and keratinization. The final stage is dead, compressed *stratum corneum* cells on the surface skin. Epidermal cells are derived by mitotic division from basal cells, consisting of a single layer of cubic cells on the basal lamina. As they differentiate towards the surface, they become polyhedral as they synthesize increasing amounts of cytokeratin. Desmosomes containing several intracellular proteins maintain mutual adherence of epidermal cells:

- **desmoplakin** - causing as a paraneoplastic autoantigen pemfigus vulgaris;
- transmembrane **desmoglein**, which can become an autoantigen in both pemphigus foliaceus and pemphigus vulgaris.

With continued differentiation, keratohyalin granules (granular layer of keratocytes) appear in the cells. These granules form the protein filaggrin, which induces aggregation of cytokeratin fibers into parallel layers, making the cells "chemically resistant". The insolubility and protective properties of the stratum corneum are given by:

- the amount of keratin fibers coated with keratohyalin in cornocytes;
- thickening of cornocyte membranes or their stratum corneum;
- deposition of glucosylceramide and acylceramines in the intercellular space of cornocytes.

This mastic substance forms a very important barrier that prevents water from escaping from the body's surface. It was a prerequisite for life on land. In the "stratum lucidum", the cytokeratin filaments are encapsulated in a mass containing "eleidine". The basal layer of the epidermis has a stable population of germ cells. New keratinocytes need about 14 days to develop into stratum granulosum cells and another 14 days to reach the surface of the stratum corneum and peel off.

Melanocytes

Melanocytes are round cells with irregular, very long protrusions that penetrate between the stratum basale and stratum spinosum cells. Their ends interfere with invaginations on the surface of keratinocytes. Melanocytes are connected to the basal lamina by a system of hemidesmosomes. Desmosomes are not developed between melanocytes and neighboring keratinocytes. The function of melanocytes is the synthesis of melanin u, a pigment formed from tyrosin u oxidized by tyrosine oxidase to dihydroxyphenylalanine (DOPA) and further metabolised to melanin. It gets into the granules, where it goes through several developmental stages. The final stage is the development of melanosome. Mature melanosomes are transmitted by cytoplasmic protrusions to keratinocytes in the stratum basal and stratum spinosum (cytokrine secretions). In the cytoplasm of keratinocytes, the melanin granule settles in the area above the nucleus; thus protects them (during cell division) from the harmful effect of UV - radiation (290-320 nm). The cells in which the melanin has been placed are called **melanophores**.

The number of melanocytes varies in different areas skin of the body. There is about 1000 per 1 mm² on the back, and 2000 per 1 mm² on the scrotum. The number of melanocytes *'is not'* (!) Influenced by gender or race; skin color is determined by the amount of melanin granules in the keratocytes. Darkening of the skin (tan) after UV exposure is the result of a two-step process:

- physico-chemical reaction - darkening of already existing melanin and its rapid transport to keratinocytes;
- increase melanin synthesis in melanocytes, thereby increasing its total amount.

Deficiency cortisol e.g. u Addison's disease (adrenal cortex insufficiency) leads to increased secretion ACTH and increased skin pigmentation due to lack of feedback. Epidermal cell turnover decreases with age (decreases to 50% between 30 and 70). The loss of elastin and collagen fibers in the skin contributes to the appearance of thin paper, transparency and greater brittleness of blood vessels. The increase in cross-links between collagen and elastin chains causes greater skin rigidity ("Old" skin returns to its original position, if summarized,

only very slowly). Qualitative changes in dermal collagen (its replacement for amorphous basophils) are caused by wrinkles of the skin, especially on the face and neck. Every decade, the number of enzymatically active melanocytes decreases by 10-20%, which leads to the formation of irregular pigment spots and graying of the hair.

Other cell types

Langerhans dendritic cells are in the stratum spinosum; belongs to the monocyto macrophage system, to the group of antigen-presenting cells. They have a star shape and are usually in the epidermis (possibly in the dermis) 400-1000 per 1 mm². Merkel cells occur in thick-skinned skin (*planta pedis* or *manus*). It is close in shape to keratinocytes. These are probably mechanoreceptors, although other authors believe that they belong to the group of neuroendocrine cells. The boundary between the epidermis and the dermis is not equal; the dermis (papillae) interdigitate with the evagination of the epidermis (epidermal laths), which thus strengthens the dermo-epidermal connections. The basal cells are connected to the basal lamina of the hemidesmosome, the anchoring intermediate filaments, and in the dermis of the collagen VII fibril. The elastic fibers are attached to the basal lamina by fibriline microfibrils; fibronectin is also involved in the association. With age, the number of Langerhans cells decreases by 50% (reduction of immunoreactivity).

Clinical notes

Psoriasis is a chronic skin disease with a genetic predisposition (HLA antigens BW17, B13, BW37; the candidate predisposition gene is about chromosome 3q21 locus PSORS5, gene gene / SLC12A8 SLC12A8 (<https://ghr.nlm.nih.gov/>)) manifested by erythematous papules and plaques with silvery thick scales, easily removed and localized mainly above the skin protrusions (elbow, knee) but also elsewhere. The etiology is unknown. There is a significant proliferation of epidermal cells in the pathogenesis (7 times higher acceleration of the cell division cycle). The time when keratinocytes get from the basal layer to the surface of the stratum corneum lasts only 3-4 days (normally 28 days); there is increased keratinization, which leads to thickening of the epidermis (papules, plaques) and parakeratinous changes of the 'stratum corneum' '(silvery scales). A glycoprotein, called "corneodesmosin", has been identified in cells with advanced differentiation, which is probably involved in keratinocyte adhesion and is probably a factor in susceptibility to psoriasis. It is much more pronounced in skin lesions.



Psoriasis is currently considered to be an inflammatory dermatosis arising from abnormal homeostasis of the epidermis and characterized by hyperproliferation and abnormal differentiation of keratinocytes with prior activation of the cutaneous immune system. It is a multifactorial disease with hereditary and environmental pathogenetic mechanisms. There are two types: familial and sporadic. Psoriasis is thought to be a autoimmune disease with a share of T-lymphocytes, releasing a number of cytokines (IL-8, INFγ) that induce abnormal keratinocyte activation and differentiation. The goal of therapy is to suppress keratinocyte proliferation and inflammatory skin reactions. Steroids, tar and anthraniline ointments, UVB or UVA irradiation and combinations are applied topically. Psoralen, more recently calcipotriene ointment (derivative vitamin D - reduces proliferation) is used orally. Antimetabolites and antimitotics (methotrexate, azathioprine, hydroxyurea), and etretinate (retinoid) are used systemically (in resistant cases).

Links

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