REVIEW

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Short histological kaleidoscope – recent findings in histology. Part III

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Abstract

The paper provides an overview of the current understanding of different cells' biology (*e.g.*, keratinocytes, Paneth cells, myoepithelial cells, myofibroblasts, chondroclasts, monocytes, atrial cardiomyocytes), including their origin, structure, function, and role in disease pathogenesis, and of the latest findings in the medical literature concerning the brown adipose tissue and the juxtaoral organ of Chievitz.

Keywords: keratinocytes, myoepithelial cells, myofibroblasts, monocytes, chondroclasts, brown adipose tissue.

Introduction

Due to modern technology, new information about histological structures and their functions is published each year in various medical literature papers. As seen in parts one and two, this short kaleidoscope emphasizes the review of less common histological aspects regarding the biology and function of certain cells (keratinocytes, Paneth cells, myoepithelial cells (MECs), myofibroblasts, chondroclasts, monocytes, atrial cardiomyocytes), tissular elements, such as brown adipose tissue (BAT), or bizarre assembly as the juxtaoral organ of Chievitz.

Keratinocytes

The skin encompasses a whole unique summation of functions, including protection from ultraviolet light, vitamin D synthesis, body temperature regulation, sebaceous and sweat glands balanced secretion, largest sensory organ; by far, the most important function is yet represented by the barrier the tegument provides against water loss, pathogens assault, chemical, and mechanical injuries.

Keratinocytes constitute the most abundant resident cell population of the epidermis, the skin's outermost layer. The epidermis is a stratified squamous keratinized epithelium in which keratinocytes are organized into five layers in the thick skin, and four layers in the thin skin (*stratum lucidum* is absent here). Conventional concepts in characterizing the epidermis structure describe, from the basement membrane (BM) towards the surface, the following layers (or *stratum*): *stratum basale*, *stratum spinosum*, *stratum granulosum*, *stratum lucidum*, and *stratum corneum* [1].

During the human embryonic development stages, the keratinocytes differentiate from the surface ectodermal cells; these cells embrace an epidermal fate and form a single-layered epithelium that covers the embryo after gastrulation. Thus, the embryonic epidermis is initially represented only by a basal layer of cells. The basal keratinocytes will bring forth the cells of the periderm, a transiently overlying cell layer, that will coat the evolving epidermis until cornification emerges. At approximately eight weeks of estimated gestational age (GA), the embryonic epidermis commences stratification by generating an intermediate layer of cells between the basal layer and periderm. In contrast to the suprabasal keratinocytes in the postnatal epidermis, the intermediate layer of keratinocytes maintains their capacity to proliferate, thus ensuring the capacity to adapt to the rapid development of the embryo and to generate, over the following weeks, supplemental new cells. Intermediate cells will withdraw their highly proliferative potential by the beginning of the second trimester, leaving the cell cycle and undergoing differentiation into spinous and granular keratinocytes. By the end of the second trimester, the cornified cell layer of the epidermis

is present and the periderm undergoes apoptosis and will be sloughed off into the amniotic fluid, contributing to the *vernix caseosa* formation. In the third trimester, the number of cell layers in the *stratum corneum* increases, as do the keratohyalin granules and lamellar bodies. At the end of the pregnancy timeline, the epidermis is morphologically similar to the adult epidermis, but the complete barrier function will be attained only a few weeks after birth [2].

This complex process to reach an epidermal fate and achieve stratification and terminal differentiation of keratinocytes is enabled by the intracytoplasmic presence of the intermediate filaments of keratin. In overall epithelial cells these intermediate filaments twist around the nucleus, form the cytoskeletal system and attach to the desmosomes plaques, thus ensuring cell-to-cell connection and tissue resilience and stability.

In keratinocytes, the keratins (Ks), a comprehensive group of proteins in the structure of the intermediate filaments, sustain proper growth, progression towards the surface, and maintain the barrier function. Both type I keratin molecules (K9–K28, K31–K40) and type II (K1–K8, K71–K86), assemble in various molecular heteropolymers, resulting in these long, unbranched, 10 nm diameter intermediate filaments [3].

During embryogenesis, in the developing epidermis, there is a specific succession of Ks expression in the keratinocytes. At first, the initial basal layer of multipotent epithelial cells expresses K8/K18 keratins. Under the p53 protein inductive influence, before stratification, K8/K18 expression will be replaced by K5/K14 expression. The K5/K14 primary keratin pair is of crucial importance for the epidermis strength and basal keratinocyte adhesion to the BM. Missense mutations or deletions in the structure of the genes that encode especially the helix initiation or termination motifs, lead to dysfunctional K4 or K14, which will translate into increased skin fragility, with blister occurrence in response to minor physical injuries [4]. This group of inherited blistering diseases, namely *epidermolysis bullosa* (EB) and its subtypes have either autosomal dominant or a recessive pattern of transmission; they include a wide spectrum of skin lesions (from mild to severe), with localized to widespread blisters, hemorrhagic blisters or bruises, that can be, depending on the EB subtype, associated with hyper and hypopigmentation, atrophic scars, dystrophic nails, onychogryphosis, and palmoplantar keratoderma [5].

To accomplish stratification, basal cells tend to escape from the BM and modify their mitotic axis direction; thus, the capacity to maintain both the self-renewal capacity to restore the basal undifferentiated cell population, as well as to generate a suprabasal cell, that will further divide (forming the intermediate layer of cells), is granted [6]. The Notch signaling pathway will trigger K1 expression in these cells, and in the mature postnatal spinous layer' keratinocytes (after the intermediate cell layer's dissolution in the embryo's development). Depending on the variation of the Ca^{2+} concentrations on both sides of the cytoplasmic membrane, mature spinous keratinocytes will further begin the terminal differentiation process and migrate towards the surface, generating the granular and the cornified layers [7].

Attaining the barrier properties starts during embryogenesis and the process continues in the mature epidermis through a self-maintained renewing program. Keratinization, the step-by-step process of keratinocyte cornification, is dependent on the presence of keratohyalin granules in the granular layer (some of these granules also exist in small numbers in the superficial cells of the spinous layer). Keratohyalin granules in the epidermis, generally, are stellate structures (except those with globular form in the oral mucosa) that contain loricrin, trichohyalin, and profilaggrin; these several cross-linking proteins interact with the keratin filaments and promote their assembly, thus forming the epidermal cornified cell envelope. Profilaggrin is the inactive form of filaggrin, the main protein involved in keratin filaments aggregation and disposition within keratinocytes' cytoskeleton. A high complexity sequence of events, through the intervention of various proteases and phosphatases, triggers the dissolution of keratohyalin granules and the release of profilaggrin, promptly transformed into filaggrin monomers. Filaggrin will determine the thickening of the cytoskeleton and the flattening of the definitive differentiated granular cells before their conversion into corneal squames. Filaggrin will finally decompose into a natural humectant, the natural moisturizing factor, an insoluble protein material, deposited on the cytoplasmic surface of the plasma membrane (as a cell envelope), that will endow epidermis water barrier sustenance [8].

Keratinocytes in the spinous layer also produce small, round to ovoid-shaped structures called the lamellar granules (the lamellar bodies, or the Odland bodies). These specialized organelles are membrane-coated granules filled with a pile of lipid lamellae, progressively accumulated in the cytoplasm of the granular layer' keratinocytes. Alongside their ascension towards the *stratum corneum*, there is a deposition of the granules' lipid content, which will also be deposited in the intercellular spaces at this level, while the bordering membrane will fuse to one of the keratinocytes. Various studies investigating the structure of these granules reported an assembly of pro-barrier lipidic components, represented by phosphoglycerides, sphingomyelin, and glucosylceramides, in association with acid hydrolases, proteolytic enzymes, and antimicrobial peptides (AMPs); the complex composition prevents the transepidermal water loss [9]. Morphological and functional alterations in lamellar granules' secretory cargo determine a defective epidermic barrier formation. Mutations in the set of genes that encode essential proteins involved in skin water barrier integrity, lipid processing enzymes, or lipid transporters, will generate impaired keratinocyte differentiation and improper barrier formation. The *"collodion baby"* results from this aberrant embryofetal epidermic development, which clinically translates into a newborn wrapped up into a tight, polished, translucent membrane, formed by an abnormal *stratum corneum*. The collodion membrane once shed, may leave an entirely normal skin surface, or may translate as an autosomal recessive *ichthyosis* (lamellar ichthyosis or *congenital ichthyosiform erythroderma*), with extensive layered brown scales [10] or erythroderma with mild faint scales [11].

The *harlequin ichthyosis*, the extreme impairment in premature terminal cornification process [due to mutations in the adenosine triphosphate (ATP)-binding cassette, subfamily A member 12 (*ABCA12*) gene], manifests as a rough, rigid cuirass of hyperkeratosis, spaced by profound

crevices; it is a syndrome that presents itself in association with nose and ears malformations, important *eclabium* and *ectropion* and, recently reported, severe involvement of both large and small joints with a chronic progression [12].

Insufficient maturation of *stratum corneum* is of crucial importance in premature infants because it leads to compromised skin barrier function, associating substantial risk of dehydration, aggravated infections, and significant transcutaneous assimilation of toxic drugs or chemicals. Autopsy skin tissue sample analysis from liveborn preterm infants revealed age-dependent, an increased presence of basket weave disposition of keratin in the keratinocytes of the corneous layer, thus conferring a more appropriate barrier accretion [13]. Considerable variation in water incorporation in the skin was observed, relative to both GA and prematurity interval. Water content decreases progressively from 92% to 83% in the interval 13 weeks embryo to term, with a marked continued decrease over the first few days after birth, but with a compensatory increase for the next three weeks of life [2].

Paneth cells in the small intestine, colon, and appendix

Paneth cells are part of the intestinal epithelial cells and research related to them is continuously expanding due to their particularly important role in the small intestine's homeostasis. In the late 19th century, Gustav Schwalbe and Josef Paneth described firstly, at the base of the small intestine' crypts of Lieberkühn, columnar epithelial cells with a cytoplasm rich in granules [14]. These granules contain different AMPs and proteins with multiple immunological functions: (*i*) they regulate the intestinal flora (*e.g.*, modulating the microbiome); (*ii*) they play an important role in the response to intestinal inflammation; (*iii*) they are involved in the mechanisms of injury and repair of the intestinal mucosa. The mucosa' process of repair is based on the capability of Paneth cells to secrete epidermal growth factor (EGF), Wnt, and Notch; therefore, they support the local stem cells (SCs) in the regeneration process of the intestinal epithelium [15, 16].

Although Paneth cells are mostly found in the distal small intestine, they can also exist in other regions, such as the colon or appendix. However, at this level, most of them are metaplastic, appearing in response to mucosa inflammation [14]. Metaplasia is defined as the presence of differentiated cells in a morphological location (where they would not be physiologically present), in response to various intestinal injuries. Paneth cell metaplasia often occurs in different segments of the digestive tract too, including the esophagus, stomach, or colon, but it can also exist outside the gastrointestinal (GI) tract [17].

The small intestine, the main location of Paneth cells, has particular importance considering that the absorption of nutrients takes place here. Its epithelium is represented by several populations of cells, such as enterocytes, goblet, Paneth, enteroendocrine, tuft and intestinal stem cells (ISCs) [18]. Paneth cells are found at the base of the Lieberkühn crypts. Unlike other cells in the intestinal epithelium, with a lifespan of 3–5 days before undergoing apoptosis (intestinal epithelium is the tissue with the fastest regeneration), Paneth cells have a lifespan of approximately 30 days [19]. The process of proliferation of the intestinal epithelial cells begins in the region above the Paneth cells; from here, the cells migrate along the villi, to their tips (the so-called "rolling carpet" phenomenon). During this process, the cells differentiate into goblet cells, tuft cells, enteroendocrine cells, and enterocytes. Unlike these cells, Paneth cells do not migrate upwards, but downwards, towards the base of the crypt; at this level, they will reside for several weeks before undergoing cell fragmentation and phagocytosis by macrophages from the *lamina propria* [20]. The development of Paneth cells is complex; it has been shown that they originate from ISCs which will transform and proliferate in the presence of juxtacrine signaling of growth factors (GFs), Wnt and Notch, produced by the nearby Paneth cells [21].

From a histological point of view, Paneth cells are cone-shaped cells with an apical pole towards the lumen of the Lieberkühn crypt. The basal pole of the cell is adjacent to the BM, and the nucleus is also located at this level. The apical cytoplasm contains numerous acidophilic granules with antimicrobial substances [22].

The ultrastructure of a Paneth cell indicates a nucleated cell, with a nucleolated basal nucleus. Both rough endoplasmic reticulum (ER) and Golgi apparatus, as well as a few lysosome-like bodies, are observed in the perinuclear region [22].

Several secretory granules containing AMPs and proteins [*e.g.*, alpha-defensins, lysozyme, secretory phospholipase A2, tumor necrosis factor (TNF), matrix metalloproteinase-7 (MMP-7), xanthine oxidase, alpha-1-antitrypsin, interleukin (IL)-17A, IL-1β, and lipokines] can be observed in the cytoplasm of the Paneth cells by immunohistochemistry (IHC) techniques; the granules are being excreted into the crypts through exocytosis [23]. Paneth cell secretion (once it reaches the surface of the mucosa in response to exposure to bacterial antigens and cholinergic stimulation), intervenes in maintaining intestinal homeostasis. The main product of the cytoplasmic granules is represented by the epithelial-derived AMPs, divided into two classes: cathelicidins and defensins [24]. Under electron microscopy (EM), they appear as having high electron density [22].

Numerous research studies have been carried out about the activity of the Paneth cells in the intestine of premature newborns. In the small intestine, Paneth cells occur around the GA of 22–24 weeks. At this GA, they do not possess granular constituents, so they are not completely functional. Thus, in the event of a premature birth, the intestinal mucosa of the newborn will be exposed to foreign antigens in the presence of functionally incompletely matured Paneth cells. A dysbiotic microbiome will appear, due to the damage of the defense barrier against pathogenic bacteria, followed by the development of an inflammatory environment; that will affect the ISCs, with impaired cell growth and regeneration [25].

The distribution of Paneth cells in the digestive tract has been intensively studied, being established that in the small intestine, there is an equal number of Paneth cells both in the Lieberkühn crypts of the jejunum and in those of the ileum. In the large intestine, Paneth cells are physiologically found in only a quarter of the population, especially in the cecum and ascending colon. Much more

frequently, in 75% of cases, they are found in the appendix, but in a very reduced number [17].

Regarding the presence of Paneth cells in the colon, most of them are metaplastic because of persistent inflammation. Some studies suggest that in this context, responsible for the metaplastic phenomenon is the Wnt activity in the secretory granules of Paneth cells. Additional factors and signaling mechanisms are still being researched [19]. The role of metaplastic Paneth cells has not yet been precisely established; considering the function of normal Paneth cells in modulating the immunity of the small intestine, it may be concluded that metaplastic cells also represent a colonic epithelium's adaptive immune response (in the context of an intestinal injury) to the microbial population [16]. Foci of Paneth cell metaplasia can be observed in inflammatory intestinal pathologies, such as Crohn's disease or ulcerative colitis (UC). Generally, in intestinal diseases, the number of Paneth cells can be altered by a decrease, with one exception, UC, where the number of Paneth cells increases [17]. Tanaka *et al.* conducted an experimental study to see the frequency of the colonic metaplastic Paneth cells in two important intestinal pathologies: Crohn's disease and UC. Finally, they concluded that, like in normal mucosa, metaplastic Paneth cells, with rich content in phospholipase A2 and lysosomes, are more frequently in the cecum and ascending colon. At the level of the descending colon and rectum, the researchers found a reduced number of Paneth cells, similar to the absence of these cells in physiological conditions. Also, this study suggested that the presence of metaplastic Paneth cells in the colon occurs in the context of regeneration and repair of the damaged mucosa [26]. The location of metastatic Paneth cells in the appendix was described by Kooij *et al.*, in 2016. The presence of these cells was especially noted in the lower part of the Lieberkühn crypts, in the context of UC [17].

Myoepithelial cells

MECs originate from the ectoderm; they are cells with a dual phenotype, displaying both smooth muscle cells (containing myofilament proteins, dense bodies, and caveolae) and epithelial cells features [*e.g.*, the presence of desmosomes junctions and intermediate filaments with cytokeratin (CK)] [27, 28].

MECs are localized in the secretory units and ducts of many glandular structures (*e.g.*, the lacrimal, salivary, sweat, mammary, and prostate glands [27, 29, 30]), and are disposed between the basal pole of the secretory epithelial cells and the BM [27, 31].

Histologically, MECs appear as slender, stellate-shaped cells, surrounding the adenomere and the ducts of the different glands, in the form of a basket-like network [27, 29, 30, 32]. There have been described five different morphological types of MECs: (*1*) angulate/basaloid-like cells, with tiny dark stained nuclei and pale eosinophilic cytoplasm; (*2*) epithelioid cells, presenting polygonal shape, pale stained nuclei, with abundant cytoplasm; (*3*) clear cells, having pale cytoplasm; (*4*) spindle cells with cigarette-like shape and faint cytoplasm; (5) hyaline cells with intense pink cytoplasm and peripheric nuclei [27, 30]. Furthermore, MECs can exhibit squamous, chondroid, or oncocytic metaplasia [27, 33, 34].

Ultrastructurally, MECs present a small, dense (10–15 μm) cellular body with 4–8 thin, elongated, branched cytoplasmic processes; these processes are occupied by longitudinally arranged, delicate filaments, around 4–6 nm thick [27, 29, 32]. The nucleus is flattened, parallel to the BM, and could present an irregular outline [30]. The cytoplasmic organelles are found in the perinuclear region: the Golgi apparatus and protuberant centrioles; mitochondria are few, with an equal disposition in the cellular body and the cytoplasmic processes [30]; the ER is represented by rare little cisternae [30]. On their apical pole, MECs present micro-pinocytic vesicles [27, 32].

Several histological methods have been used to identify MECs [27, 35–37]. The standard Hematoxylin–Eosin (HE) staining, which highlights only the flattened nuclei [27] is not specific enough, so these cells are poorly visible in light microscopy; special stains [*e.g.*, alkaline phosphatase (AP) reaction, iron hematoxylin, Levanol fast cyanine (Coomassie Blue), silver impregnations and phosphotungstic acid hematoxylin (PTAH)] or enzyme histochemistry, immunoperoxidase stain and IHC markers [27, 29, 36, 37] are of much greater value and accuracy.

Currently, because these cells can express numerous markers (some of them of smooth muscle cell differentiation, others with epithelial origin, and few with neurogenic origin), IHC techniques are more frequently used in the MECs identification [27, 30, 38–40].

IHC markers of smooth muscle cell differentiation

The main marker of myogenic differentiation is alpha-smooth muscle actin (α-SMA). This marker stains the cytoplasm of MECs and is responsible for cell contractility [27, 29, 30, 40].

Another marker of myogenic origin is α-actinin [41]. α-Actinin represents an actin-connecting protein involved in various functions of several cell types of many tissues. In MECs, α-actinin is disposed of adjacent to microfilament bundles, perhaps being implicated in the connection of actin to the cellular membrane [29, 41].

One more characteristic marker expressed by MECs is calponin [42]. Calponin is a fine cytoplasmic filament-associated protein [42], that has the property to connect to actin, calmodulin, and others; this finding supports the role of calponin in the regulation of smooth muscle contraction [43].

Markers of epithelial origin

MECs contain in their cytoplasm intermediate filaments with CK [27, 29, 44]. They exhibit CK 4, 5, 6, and CK 14 [44, 45]. In the cells, the CK creates a compact network spreading from the nucleus to the plasma membrane. In addition, they behave as cytoplasmic support that assures MECs the capacity to maintain mechanical and non-mechanical tension [44, 45].

Another specific epithelial marker is p63 [46]. P63 acts as an oncogene, controlling several signaling pathways, mandatory for ectodermal organogenesis and differentiation, and influences cell development and persistence [47, 48]. P63 stains the nuclei of MECs [46–48].

Markers of neurogenic origin

MECs express S100, a neurogenic cell-related protein that stains the cytoplasm and nucleus of these cells [49].

Other neurogenic markers exhibited by these cells are nestin and neurotrophin receptors (p75) [29]. Nestin represents a category of VI intermediate filament protein [50]. Even if it's mainly expressed in SCs with neurogenic origin, is additionally detected in many tumoral cells [50, 51]. P57 has crucial functions in the development, growth, preservation, and death of various cell types [52–54].

Other MECs markers

MECs also display vimentin, laminin, fibronectin, and paired box 6 (Pax6) protein [27, 29, 40].

Vimentin represents an intermediate filament with mesenchymal origin. It is directly associated with myofilaments and cell junctions [27, 40].

Fibronectin and laminin are glycoproteins located in the cytoplasm and the cell membranes of MECs [27, 29, 30].

Pax6 is a transcription factor expressed in the nuclei of MECs [55].

Growth factors

MECs exhibit several GFs that regulate their morphogenesis and differentiation [27, 29].

The cluster of differentiation (CD)109 is expressed in MEC and has a negative effect on transforming growth factor-beta (TGF-β) signaling [56, 57]. Furthermore, MECs express fibroblast growth factors (FGFs) and their receptors (FGFRs), mainly FGF2, obviously liberated into the basal membrane (positive for FGF2) [29, 58]. FGF2 communicates *via* FGFR1c isoform, exhibited by cells with mesenchymal origin [29].

Recent findings have revealed the multiple roles of the MECs, such as glandular development, homeostasis, maintenance of the glandular normal structure, secretion of BM material, contractility, metabolic and electrolyte exchanges between the luminal epithelial cells and stroma, the transmission of neural stimuli, and promotion of tumor suppression [27, 29, 30, 59–62].

MECs have key roles in glandular morphogenesis, promoting glandular epithelial cell development and differentiation, due to their GFs, like CD109 and FGF2 [27, 29, 59].

MECs also secrete a high amount of BM proteins, like laminin, fibronectin, and elastin, and function as a framework for the proliferation and differentiation of these types of proteins [27, 29, 30, 35].

Furthermore, they preserve the normal architecture of glandular epithelium and sustain acinar cell polarity, due to their secretion of BM components [27, 29, 59–62].

MECs have contractile properties, regulated by hormonal and neural mediators, helping the elimination of the secretion material from the lumen of the acini and ducts [27, 29, 30, 35]. They avoid over-expansion, as the secretory material collects in the cytoplasm of acinar cells [27]. Also, they contract and enlarge the diameter of the intercalated ducts, therefore allowing drainage. On the other hand, they contribute to the rift of material over field secretory cells [27, 30].

Due to their strategic position, between the acinar epithelial cells and the subjacent connective tissue, they control the metabolic and electrolyte exchange [27, 29, 30, 35, 37]. Thus, they have a key role in the epithelial–mesenchymal crosstalk *via* the extracellular matrix (ECM) [27, 29]. In addition, other features that support their involvement in metabolic and electrolyte transport are represented by the presence of basal infoldings, pinocytotic vesicles, an enhanced AP, and magnesium-dependent adenosine triphosphatase (ATPase) activity [30, 35].

It seems that MECs can propagate nervous stimuli [43]. The hypothesis is supported by the occurrence of cytochemical cholinesterase and gap junctions in EM [63].

Recent data have shown that MECs are considered natural tumor suppressors; they have anti-invasive function in a paracrine fashion, *via* stimulating epithelial transformation, producing BM material, and generating suppressors for the proteinases, that inhibit neoangiogenesis, invasion, and metastasis [27, 29, 30, 59, 64, 65].

All these findings highlight MEC's multipotent capacity. Their morphofunctional integrity and their tumor suppression capacity straighten out the fact of being considered as a prognostic marker in cancer. Furthermore, MECs represent the hallmarks of glandular epithelia development, morphogenesis, and conservation. Still, there is data regarding the MEC's line and the functional connection between them and other glandular cell types. Thus, future improved technological research is required in MEC's analysis.

Myofibroblasts

Myofibroblasts are contractile cells that are known to play a key role in wound healing, fibrosis, tissue repair, and regeneration, possessing the ability to generate and transmit force. They are specialized cells with a unique combination of fibroblast and smooth muscle cell properties (by the presence of α-SMA filaments) [66, 67].

Myofibroblasts are thought to arise from a variety of cell types, including resident fibroblasts, pericytes, bone marrow-derived cells, and even epithelial cells [68]. In the context of wound healing, myofibroblasts are believed to primarily originate from resident fibroblast precursors. Yet, a variety of other tissue-resident mesenchymal cells, such as pericytes, and adipocytes, can be activated following tissue injury or in the context of tissue repair, and undergo a reversible conversion to the myofibroblast state [69]. The process is known as *fibroblast-to-myofibroblast differentiation* and is characterized by the upregulation of SMA and the acquisition of contractile properties. Yet, there is also heterogeneity when fibroblasts transform into myofibroblasts. Recent studies using single-cell ribonucleic acid (RNA) sequencing combined with cluster analysis of gene expression show that tissues may harbor different cell populations ranging from fibroblasts to myofibroblasts. For example, the term 'primitive fibroblast' was used to denote an intermediate state in which α-SMA can be expressed, but the cell cannot contract. Thus, while useful conceptually, the terms 'fibroblast' and 'myofibroblast' fail to capture the true complexity of these cell populations' roles, and there is a possibility that these populations may change with disease [70]. In renal interstitial fibrosis, one of the origins of myofibroblasts is the *epithelial–mesenchymal transition* (EMT). Mesenchymal stem cells (MSCs) have been shown to alleviate this process, but the specific mechanism is unknown [71].

Myofibroblasts are spindle-shaped cells, that can contract, mediated by their expression of smooth muscle-

specific proteins, such as α-SMA, calponin, and the smooth muscle myosin heavy chains [66, 67].

These cells also have a high nuclear-to-cytoplasmic ratio and an abundant ER, reflecting their fusion capacity [66, 67].

Myofibroblasts play an essential role in tissue repair and regeneration by producing and depositing ECM proteins, such as collagen and fibronectin. They are recruited to sites of injury or inflammation by a variety of signaling pathways, including TGF-β, platelet-derived growth factor (PDGF), and mechanical stretching. Once activated, myofibroblasts secrete a variety of cytokines and GFs that regulate immune responses, angiogenesis, and fibrosis.

Myofibroblasts are associated with a wide range of medical conditions: fibrosis, cardiovascular disease, and cancer [72].

They are the primary cells responsible for pathogenic fibrosis. Myofibroblasts with high α-SMA expression can express high levels of mature collagen I, overproducing ECM proteins, and fibrotic and inflammatory cytokines [73]. The persistence of myofibroblasts in fibrosis and the excessive deposition of ECM are leading to conjunctive tissue hardening, loss of the conjunctive tissue' structure and function, impaired organ function, and finally, organ failure. Therefore, targeting myofibroblast activation and function is an important therapeutic strategy for the treatment of fibrotic diseases.

Myofibroblast-derived leucine-rich alpha-2-glycoprotein 1 (LRG1) may contribute to vascular eye dysfunction by stimulating *retinal fibrosis*. In support of this hypothesis, it was recently observed that LRG1 is expressed by human myofibroblasts with high α-SMA expression, due to mechanical stretching, during the healing of hypertrophic wounds [74].

Cardiac fibrosis is mediated by activation of resident cardiac fibroblasts that differentiate into myofibroblasts in response to lesions, stress, inflammation, and cytokines. Cardiac myofibroblasts are characterized by increased ECM production and contractile capacity. These cells may also secrete GFs that cause cardiomyocyte hypertrophy [75]. Myofibroblast formation is a physiological response to acute injury, such as myocardial infarction. However, myofibroblast persistence contributes to maladaptive regeneration and progressive cardiac dysfunction, as seen in heart failure. Although the classical activation pathways [including TGF-β and angiotensin II (AngII)] are well characterized, alterations in mitochondrial (MT) function and cellular metabolism of these cells can appear. The cells required to initiate and maintain myofibroblasts formation and function are still poorly understood [76].

Although EMT is a common feature of pulmonary fibrosis, the role of EMT in the fibrotic process remains controversial. Recently, abnormal basal cells in fibrotic lung tissue were identified as a novel epithelial cell type that partially expresses the EMT phenotype. The origin of development of these cells is still unknown [77].

Idiopathic pulmonary fibrosis begins with chronic epithelial lung injury, followed by BM disruption that promotes myofibroblast activation and excessive synthesis of ECM proteins and epithelial–mesenchymal junctions [78].

Several studies have shown that myofibroblasts play a role in *cancer*. They create a supportive microenvironment that promotes the formation of new blood vessels, essential for cancer cells' survival and multiplication [79]. Myofibroblasts promote tumor growth and invasion by secreting cytokines and GFs. This includes producing TGF-β and hepatocyte growth factor (HGF), that can impact cancer cell development and migration, as well as remodeling the ECM to allow an easier invasion. A recent study found that myofibroblast-derived HGF was essential for the development of *pancreatic cancer* in mice and that targeting HGF signaling in myofibroblasts could be a potential therapeutic strategy [80, 81]. Also, myofibroblasts are involved in the development and progression of *lung cancer*. They are activated in response to injury and inflammation and are responsible for ECM generation and remodeling in the lung tissue. Therefore, recent studies indicate that targeting myofibroblasts could be a promising therapeutic approach to treat this type of cancer [82]. Moreover, inhibition of specific cytokine secretion by myofibroblasts has been shown to reduce tumor growth and metastasis in animal models of lung cancer.

Myofibroblasts are also known to promote the EMT of cancer cells, a key step in the development of metastasis. During EMT, cancer cells lose epithelial properties and take mesenchymal properties; the mesenchymal properties allow them to become more aggressive, by invading the surrounding tissues and migrating to distant organs [72]. This is thought to occur through the secretion of factors, like TGF-β, which can activate signaling pathways that promote EMT. A recent study showed that myofibroblasts could induce EMT in *breast cancer* cells through the secretion of IL-6 and that targeting IL-6 signaling could inhibit this process [72, 83].

Myofibroblasts can also have *immunosuppressive effects* that contribute to tumor progression. For example, they can secrete factors like TGF-β and IL-10 that inhibit immune cell function and promote immune cell exhaustion. A recent study found that myofibroblast-derived TGF-β was responsible for inhibiting the function of CD8+ T-cells in the tumor microenvironment and that blocking TGF-β signaling could improve the efficacy of immunotherapy in mouse models of cancer [84].

Myofibroblasts play an essential role in the process and progress of *lung cancer*. They are activated in response to injury and inflammation and are responsible for ECM generation and remodeling in lung tissue [82].

Chondrocyte and chondroclast. Different or not? Are chondroclasts identical to osteoclasts?

The cartilage distributes mechanical loads by lining the joints and lubricating the joint movements. It contains isolated cells embedded in an ECM, called chondrocytes. Chondrocytes are mature cells that sustain the matrix due to the detection and reaction to shifting mechanical loads. Mechanosensitive ion channels are involved in chondrocyte mechanical transduction, giving them the ability to distinguish between specific stimuli operating in complex mechanical environments. Both PIEZO1 and transient receptor potential vanilloid 4 (TRPV4) ion channels are activated by the mechanical stimulation of these cells. PIEZO1 is activated

by both stretch and substrate deflection, and TRPV4 responds only to substrate deflection [85].

Chondrocytes play an important role in long bone growth and fracture repair but surviving in an avascular environment and maintaining their highly anabolic activity need specific metabolic requirements. Thus, they are closely related to glutamine metabolism in a continuing process [86]. The chondrogenic master transcription factor sex-determining region Y (SRY) box transcription factor 9 (SOX9) increases the levels of glutaminase 1 (GLS1) and glutamine consumption thus increasing its metabolism. As a result, the action of GLS1 (a rate-limiting enzyme) influences the function and properties of chondrocyte *via* a three-way mechanism. It starts with the synthesis of acetyl-CoA dependent of glutamate dehydrogenase under chondrogenic gene expression regulated by glutamine, which is required for histone acetylation. Then, chondrocytes proliferate, and matrix is being produced due to the synthesis of aspartate mediated by transaminase. And, due to the synthesis of glutathione from glutamine, the accumulation of reactive oxygen species (ROS) is avoided, thus chondrocytes can survive in the avascular growth plates [87].

GFs made by chondrocytes, such as bone morphogenetic protein-2 and -7 (BMP-2/-7), cartilage-derived morphogenetic protein (CDMP), insulin-like growth factor-1 (IGF-1), and TGF promote the formation of the matrix while preventing the production of proteolytic enzymes. When the matrix is degraded, many of these are released from the matrix protein bonds. This allows them to act locally to stop the degradation [88]. Aged chondrocytes, however, do not respond as well to growth stimulation factors, which causes the imbalanced catabolic and anabolic activity that continues destroying the matrix [89].

Intercellular adhesion molecule-1 (ICAM-1), a leukocyte adhesion receptor, was expressed more frequently by injured chondrocytes, which continue to produce hazardous ROS and allow leukocytes to release ROS. This is important in cases of acute trauma, where blood enters the joint, or in rheumatoid arthritis, where there would be an increase in leukocytes [88, 90].

Macrophages, natural killer (NK) cells, B cells, T cells, dendritic cells (DCs) and osteoclasts are involved in cartilage damage and repair [91]. The first immune cells to be drawn in upon damage are neutrophils, which also have the capacity to draw in, macrophages, DCs, and NK cells. Neutrophils also release elastase and proinflammatory mediators and cause ECM breakdown and chondrocyte death. After NK cells are activated, interferon-γ (IFN-γ) is released, and T-helper 1 (Th1) cells polarize invading macrophages into M1 macrophages. Next, the M1 macrophages influence the chondrogenic differentiation of MSCs by secreting proinflammatory factors. Mast cells encourage ECM breakdown, whereas DCs cause Th1 and Th17 activation, which results in the degeneration of cartilage. IL-4 produced by Th2 cells polarizes macrophages into M2 macrophages during the repair of the matrix. M2 macrophages can suppress inflammation and stimulate cartilage repair by secreting chondrogenic cytokines and anti-inflammatory factors. M1 macrophages promote tissue fibrosis. DCs encourage MSC chondrogenic development by secreting IL-10, and they also encourage regulatory T cells (Tregs) to proliferate. Inhibiting inflammation and stimulating chondrogenesis, IL-10 and TGF-β1 are expressed more abundantly when Tregs are present. NK cells also promote osteoclast differentiation and MSC recruitment. Vesicles produced by neutrophils can potentially cause anti-inflammatory reactions [92].

According to ancient literature data, chondroclasts appear on the mineralized cartilage matrix, and resorb it during endochondral bone formation. More recently, the "clasts" are presented in processes like fracture repair, arthritis, or tumor metastasis. Osteoclasts, chondroclasts, and septoclasts are three cell types that break down and eliminate skeletal structures during growth, healing, or disease. The unnamed and less well-understood fourth type removes non-mineralized cartilage when secondary ossification centers develop.

"Septoclasts" are less well-known and valued. They are cathepsin B-rich mononuclear perivascular cells. To allow capillaries to bud into the transverse cartilage septum in the growth plate, they extend a cytoplasmic process with a ruffled membrane. For achieving this, vascular trophic factors, primarily vascular endothelial growth factor (VEGF), must override antiangiogenic signals in cartilage. Numerous findings indicate that hypertrophic chondrocytes are crucial for supplying VEGF and receptor activator of nuclear factor kappa-B ligand (RANKL) to signal septoclasts and chondroclasts or osteoclasts [93].

Multinucleated chondroclasts began to resorb the mineralized cartilage matrix (with ruffled borders at the initial ossification site) during the development of the malleus from the Meckel's cartilage, but numerous tartrate-resistant acid phosphatase (TRAP)-positive mononuclear cells also invaded the zone [94]. These fibroblast-like cartilage-resorbing mononuclear cells have dense bodies and many phagolysosomes, and they extend lengthy cytoplasmic processes toward opening lacunae. They phagocytose the degenerated, hypertrophic chondrocytes and remove transverse septa from hypertrophic cartilage. Contrary to the longitudinal septa dividing chondrocyte columns, transverse septa are not calcified. Mononuclear cells only superficially resorb longitudinal septa, whose calcified matrix persists, and these septa are then covered by osteoblasts, which secrete osteoid that calcifies and generates the primary bone trabeculae [95].

Due to their multinucleation and similar ultrastructural characteristics, such as their comparable nuclear profiles, their abundance of MT profiles, and the presence of intra-cytoplasmic vesicles, chondroclasts resemble osteoclasts; moreover, they express TRAP, released in the ruffled border zone of osteoclasts and chondroclasts [96], CD14-, CD45+, CD51+, CD68+, MMP9+, human leukocyte antigen (HLA)-DR- and cathepsin K+ [86]. The ruffled border and clear zone are smaller, and chondroclasts accumulate more TRAP than osteoclasts do. These are some of the specific variations. Genetic animal models in which RANK or RANKL were inhibited provided proof that osteoclasts and chondroclasts originate from the same myeloid progenitors. Where chondroclasts and osteoclasts were formed there was also noted the RANKL expression [97]. The theory is supported by the discovery of osteopetrotic humans that exhibit chondroclast and osteoclast abnormalities [98].

The same elements that control osteoclastogenesis also control chondroclastogenesis. In-depth research by Ota *et*

al. (2009) indicates that chondrocytes play a part in the development of chondroclasts. Osteoprotegerin (OPG), a decoy receptor for RANK, the primary regulator of osteoclast development, is produced by chondrocytes. Factors that regulate RANKL expression [1,25-dihydroxyvitamin D, prostaglandin E_2 (PGE_2), parathyroid hormone-related peptide (PTHrP), TNF-α, IL-1] in chondrocytes increased RANKL and decreased OPG, leading to activation of chondroclastogenesis. These factors control how multinucleated cells develop from mononuclear cells, which leads to the resorption of both calcified cartilage and bone [99].

Previous research has only offered weak support for the hypothesis that the only difference between osteoclasts and chondroclasts is their substrate. Another study hypothesized that chondrocytes and osteoclasts may express MMPs differently [100]. These studies, however, ignored the large genome transcriptome pool and the molecular distinctions between chondroclasts and osteoclasts, in favor of morphological, ultrastructural, and rudimentary expression evaluations. The understanding of how surrounding substrates (cartilage or bone) influence the activity and function of chondroclasts and osteoclasts is very limited. It has been proposed that osteoclasts and chondroclasts may form a transcriptionally different population because the nearby substrate affects the levels of gene expression in several regulatory pathways and biological processes. Therefore, to visualize specific chondroclast and osteoclast gene signatures or molecular processes and pathways, genome-wide profiling of transcriptional changes is necessary [101]. Prior to Khan *et al.*'s discussion of the genetic similarities and differences between osteoclasts and chondroclasts in 2020, which identified distinct molecular signatures, functional grouping, and interaction network, no information was known. They isolated from murine femoral fracture callus sections cell populations that were TRAP-positive and were homogeneous populations of TRAP-positive cells, that were in relation with bone (osteoclasts) and mineralized cartilage (chondroclasts) in the same section view. Using a mouse genome Agilent GE 4X44K V2 microarray platform, they carried out a global transcriptome profiling of chondroclasts and osteoclasts. The transcriptome landscape of osteoclasts and chondroclasts was examined using a variety of computational methods and interaction networks. Multiple tests regarding the transcriptomic signature reveal differences between osteoclasts and chondroclasts with different molecular pathways and Gene Ontology terms suggesting the existence of chondroclast specific genes. ETV6 (member of the ETV transcription factors family), sirtuin 1 (SIRT1), and activating transcription factor 1 (ATF1) had chondroclast-specific gene signatures at the regulatory network assessment [101].

New insights about monocytes – macrophages origin & heterogeneity and function

The cells of the mononuclear phagocyte system (MPS) are represented by a family of bone marrow-derived myeloid cells; they engender the monocytes in the blood, the macrophages in the tissues, and the DCs [102, 103]. The proliferation and maintenance of the MPS are mainly regulated by IL-34 and the macrophage colony-stimulating factor [M-CSF, also known as colony stimulating factor 1 (CSF1)] GF [103].

In the bone marrow, from the common myeloid progenitors are deriving two progenitor populations: the granulocyte-monocyte progenitors (GMPs) and the monocyte-dendritic cell progenitors (MDPs), both producing monocytes during steady-state homeostasis and inflammatory responses (studies in mouse) [104].

From the progenitor populations, monoblasts, promonocytes, and monocytes are generated as stages of monocyte development [105]. After differentiation, monocytes are moving into the bloodstream, where they account for an average of 5% (between 2–8%) of the blood total leukocytes [106, 107].

The monocytes are circulating in the blood, bone marrow, and spleen, and do not proliferate in a steady state [108]. Monocytes, the largest leukocytes, have a 12–20 μm diameter; they are easy to identify in the peripheral blood smear by their size and bilobed kidney-shaped nuclei [106].

The monocytes have a short intracirculatory transit; the circulating monocyte pool has three subtypes (classical, intermediate, and nonclassical) in an active equilibrium, depending on both steady-state homeostasis and inflammatory responses. The first generation (postmitotic interval of 1.6 days) is the classical subset of monocytes, that circulates for a day. Intermediate and nonclassical monocytes are following in a sequential transition and have longer circulating lifespans (~4 and ~7 days, respectively) [109]. The classical subset can be identified by its high and low $CD14^{hi}CD16^{low}$ expression, the nonclassical or patrolling subset expresses $CD14^{low}CD16^{hi}$ and the intermediate subset of monocytes expresses high and middle $CD14^{hi/mid}CD16^{+}$ [110, 111]. These dynamics of monocyte subsets during homeostasis and following infection are controlled by the balance between differentiation of GMPs and MDPs [74]. Another study defined the three distinct subsets of monocytes by the expression of C-X-C motif chemokine receptor type 4 ($CXCR4^{hi}$) enriched in bone marrow, C-C motif chemokine receptor 2 (CCR2), presents in the bone marrow and peripheral organs, and IL-1β^{hi}, enriched in peripheral organs [112].

Actually, by transcriptomic analysis at a single-cell level, nine subsets of monocytes were differentiated: five distinct monocyte populations of the classical subset (profile connected to inflammatory, neutrophil-like, IFN-related, and platelet-related pathways), two distinct populations of the nonclassical subset (one with a high expression of complement components), one monocyte population of the intermediate subtype, with a high level of *HLA* genes and one monocyte population appertaining to both classical and nonclassical subset, which has a strong cytotoxic signature [113].

The circulating monocytes are passing into tissues within 12 to 24 hours, being attracted by a series of chemotactic factors. Activation and maturation of these cells occur at the tissular level and monocytes mostly arise from the tissue-resident macrophage populations. However, it has been suggested that in some tissue-resident macrophage populations, the *central nervous system* (CNS)-associated macrophages (as brain' microglia and meningeal macrophages) are forming from the yolk sac during early embryogenesis, and can be maintained for long periods, even throughout life [104, 114].

Long-time monocytes have been considered only as precursors of tissular macrophages or DCs, but new research has highlighted them as critical cells of the immune system, with an effector role, still poorly understood [113].

The two main roles of the monocytes are surveillance of microbial cells and participation in the inflammatory response [106]. Monocytes have a Toll-like receptor (TLR), potentiated by the CXCR4, which will initiate signaling cascades [115]. Thus, monocytes can phagocytose and present antigens, produce a cytokine storm that will recruit additional cells, and proliferate in response to infection and injury, engaging a significant immune response [116]. They are also able to produce anti-inflammatory cytokines, to restore homeostasis [106].

The classical monocyte subtype has a proinflammatory phenotype and can respond to fungi and bacteria by the production of ROS and cytokine secretion. The intermediate subset has high levels of major histocompatibility complex (MHC) class II cell surface receptor (HLA-DR) molecules but is still poorly functionally described. The nonclassical subtype remains and surveys the vasculature [113]. Under physiological conditions, the brain cannot be infiltrated by circulating monocytes, but when the blood–brain barrier (BBB) is compromised in some diseases, the monocytes expressing chemokine receptors – CCR2, C-X3-C motif chemokine receptor 1 ($CX3CR1^{low}$), Ly6C (glycoprotein expressed during mid-stage development), programmed death-ligand 1 (PD-L1) ($CX3CR1^{low}/CCR2^{+}/Ly6C^{hi}$/PD-L1) – can penetrate the brain and become macrophages [107].

Physiologically, the primary monocytes enter the tissue and transdifferentiate to M0 macrophages, through transient families of transcription factors [*e.g.*, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the transcription factor activator protein-1 (AP-1), and oligodendrocyte transcription factor 2 (OLIG2)], expressed in a complex, dynamic pattern. These transcription factors may represent potential therapeutic targets for initiating pathological responses [117]. In response to inflammatory signaling, the monocytes will activate, undergoing phenotypic and functional changes. The transition to immature macrophages begins within the vasculature and will depend on CCR2, in circulating cells and TNF receptor type II (TNFR2) in parenchymal cells [118]. During the activation of monocytes *in vivo*, they change from a non-adherent state to an adherent state [117]. The initiation of the inflammatory process will accelerate the monocyte activation, their entering into the tissues, and their trans-differentiation into M1 or M2 macrophages, where they will contribute, next to the tissue-resident macrophages, to the immune response [117]. During the activation process, it may be established an autocrine CCR2 – a loop that will amplify the inflammatory process [118].

The M0 macrophages, derived from bone marrow, are in a resting state and are considered precursors of polarized macrophages [119]. The classically activated phenotypes of the bone marrow-derived macrophages are M1 and M2 and they are induced by interactions of the cytokines secreted by CD4+ Th. The M1 phenotype has high levels of MHC II and is induced by IFN alone and TLR ligands [*e.g.*, lipopolysaccharide, or granulocyte-macrophage colony-stimulating factor (GM-CSF)]. The M2 phenotype is induced by IL-4, IL-13, and IL-10 [120]. The M1 anti-tumorigenic phenotype ($CD68^{+}CD80^{-}$) can enhance antitumoral immune responses through antigen presentation toward adaptive immune cells, and through proinflammatory cytokines and nitric oxide (NO) and ROS production, being able to phagocytose tumor cells, and play an antitumor role in the early stages of tumor progression [121–123]. The M2 pro-tumorigenic phenotype ($CD68^{+}CD163^{+}$) can polarize into tumor-associated macrophages (TAMs), by upregulating cytokine secretion and protein expression to stimulate tumor growth [120, 122].

Another category of macrophages is the tissue-resident macrophages [120]. Their diversity has been recently highlighted; they have distinct immunophenotypes, shaped by individual microenvironmental niches [124]. These macrophages populations are derived from the yolk sac and vary between organs; the "closed" sites (*e.g.*, brain) receive an early population and maintain it through local proliferation, whereas "open" sites (*e.g.*, gut) receive a continuing resupplying from circulating monocytes [110].

Based on their transcriptome profile, eight macrophage subtypes were mentioned: "osteoclasts", "Kupffer-like", "microglia-like triggering receptor expressed on myeloid cells 2, high expression ($TREM2^{hi}$)", "MHC class II^{hi}", "lymphatic vessel endothelial hyaluronan receptor 1, high expression ($LYVE1^{hi}$)", "iron-recycling", and "proliferating" macrophages. Across organs, the macrophages from the yolk sac and the $LYVE1^{hi}$ subset have an increased self-renewal potential [112].

The macrophages' plasticity responds to internal and environmental challenges, maintaining homeostatic or generating inflammatory states. Under homeostatic conditions, macrophages secrete immunomodulating cytokines (*e.g.*, IL-10) and can phagocytize apoptotic cells; also, macrophages are the first responders to microbes [125]. Certain studies in humans and mice for the alveolar macrophage could highlight to some point, age-related changes of the macrophage transcriptome, as resistance to proliferation during viral infection.

Moreover, repeated injuries that affect the lifespan of the tissue-resident macrophages, determine their replacement by bone marrow-derived macrophages, and monocyte-derived; the differences between these distinct cells might alter the response to environmental challenges [126].

A viral infection or co-infections [*e.g.*, with cytomegalovirus (CMV) or human immunodeficiency virus (HIV)] could change the macrophage' phenotype and functionality by exceeding the established limits of macrophage plasticity and niche adaptation; the site-specific immunity against bacteria will be affected, and the reprogrammed macrophages could be implicated in cancer, promoting tumor growth and de-differentiation [125].

Unraveling the macrophage anti-inflammatory and reparative functions could develop new therapeutic interventions to reduce the destructive inflammatory response that eventually led to chronic and/or autoimmune diseases. Differentiation of developmental stages of monocyte is important in the differential diagnosis of neoplastic processes, such as leukemias. Mapping the human immune system enhances our understanding and facilitates cell engineering and regenerative medicine.

Atrial *versus* ventricular cardiomyocyte

The myocardium consists of an association of cardiomyocytes, interstitial connective tissue, blood vessels, and nerves [127].

In the adult human heart, the distribution of cardiomyocytes and other types of cells, including fibroblasts, the cells in the wall of blood vessels (endothelial cells, pericytes, and smooth muscle cells), adipose cells and neuronal cells are different in the atrial and ventricular myocardium. The atrial tissues contain a lower proportion of cardiomyocytes compared to ventricles, whereas fibroblasts are more abundant [128].

During embryogenesis, the differentiation of atrial and ventricular cardiomyocytes and the cell-specific features are regulated by gene expression. Both atrial and ventricular cardiomyocytes express genes essential for the excitation–contraction coupling, but also, exhibit distinct gene profiles, associated with the different embryonic origins and the functional particularities, caused by the intensity of hemodynamic forces [98].

Atrial cardiomyocytes express higher levels of aldehyde dehydrogenase 1 family member A2 (ALDH1A2), receptor tyrosine kinase-like orphan receptor 2 (ROR2), synaptoporin (SYNPR), synaptophysin, and calcitonin gene-related peptide (CGRP). The product of the *ALDH1A2* gene is an enzyme implicated in the synthesis of retinoic acid from retinaldehyde. ROR2 plays a role in Wnt-signaling during cardiovascular development [129]. Synaptophysin is a marker of synaptic vesicles in the sensory nerve endings, which are mechanosensory receptors for atrial volume [130]. SYNPR is a protein associated with synaptic vesicles, which plays a role in the function of transient receptor potential (TRP) channels; cationic TRP channels act as signal transducers by regulating the Ca^{2+} influx [131]. CGRP induces vasodilation and acts as a chronotropic and inotropic agent [132]. Ventricular cardiomyocytes mainly express genes that encode proteins involved in the activity of the sarcomere: myosin heavy chain 7 (MYH7) and myosin light chain 2 (MYL2), and transcription factors, including Iroquois homeobox 3 (IRX3), Iroquois homeobox 5 (IRX5), Iroquois homeobox 6 (IRX6), mannan-binding lectin serine protease 1 (MASP1), hairy/enhancer-of-split related with YRPW motif protein 2 (HEY2) and PR domain containing 16 (PRDM16) [133].

Atrial and ventricular cardiomyocytes have different structural and molecular profiles, which underlie distinct functional characteristics. Atrial cardiomyocytes exhibit particular morphological features, different from the ventricular cells: (*i*) the transverse T-tubules are fewer; (*ii*) the Golgi apparatus, well developed in the perinuclear sarcoplasm, is associated with dense secretory granules; (*iii*) mitochondria are very numerous in the axial sarcoplasmic cones and also aligned in longitudinal rows, densely packed among the myofibrils; (*iv*) the cisterns of the peripheral sarcoplasmic reticulum come in contact with the sarcolemma [134].

Cardiomyocytes are cylindrical or brick-shaped, with distinct specializations of the different sarcolemma regions, associated with the physiological functions.

The extremities, representing the transverse, short surface of the cardiomyocytes, are interconnected by specialized intercellular junctions – the intercalated discs – to form a three-dimensional (3D) arrangement [127]. The intercalated discs consist of a complex association of intercellular junctions: gap junctions, *fascia adherens*, desmosomes, and ion channels: Na^+ and K^+ channels. Gap junctions comprise a variety of connexins with specific distribution in atria and ventricles: connexin 43 (Cx43), connexin 40 (Cx40), connexin 45 (Cx45), and connexin 31.9 (Cx31.9). Connexins form complex interactions and play important roles in modulating conduction and cell-to-cell communication. In the atrial cardiomyocytes, gap junctions consist mainly of Cx43 and Cx40; these two connexins chemically aggregate to form mixed Cx43/Cx40 channels, which reduces the unitary conductance of the gap junctions [135]. Moreover, in the human atrial myocardium, Cx43/Cx40 levels of expression and their coordinated regulation are of functional importance: high levels of Cx40 relative to Cx43 are associated with lower propagation velocity, whereas high levels of Cx43 relative to Cx40 result in increased velocity [136]. Ventricular cardiomyocytes and Purkinje cells contain Cx43, which ensures a high velocity of impulse propagation. The atrioventricular nodes and the sinus are characterized by Cx45 and Cx31.9 and have a low velocity [137].

The lateral, longitudinal surface of the sarcolemma exhibit invaginations represented by the caveolae and the T-tubules. Caveolae are microdomains of the sarcolemma demonstrated in EM as flask-shaped or omega-shaped invaginations of the plasma membrane with large neck openings onto the surface. Occasionally, several caveolae can be grouped in a pinwheel shape and open into a common neck [134]. Characteristically, atrial caveolae express caveolin-3 (Cav-3), the prominent isoform in cardiomyocytes. Cav-3 determines the caveolae formation by enabling the interaction of multiple signaling molecules, thus modulating the signal transduction. Recent studies demonstrated that Cav-3 is a promising therapeutic target in various cardiac diseases. Increased expression of Cav-3 has a protective role in myocardium exposed to ischemia–reperfusion injuries and in cardiomyopathy induced by cirrhosis [138, 139]. Moreover, caveolae and Cav-3 are associated with natriuretic peptides, which have diuretic, natriuretic, and vasodilatory effects, thus protecting the myocardium from the hypertrophy induced by dynamic overload [140].

A particular feature of mammalian atrial cardiomyocytes is the phenotype common to both contractile muscle fibers and endocrine cells. The specific secretory granules are mainly located in the perinuclear cones among the Golgi complexes but can also be found distributed in the entire sarcoplasm, between the myofibrils, and beneath the sarcolemma, separated by caveolae [134].

The endocrine secretion of atrial cardiomyocytes is represented by two hormones: the atrial natriuretic factor (ANF) and the brain natriuretic peptide (BNP); they are crucial for extracellular fluid homeostasis and maintenance of blood pressure, but also play multiple other roles, as recently described. Later, C-type natriuretic peptide was demonstrated in the atrial-specific granules; collectively, these hormones were named cardiac natriuretic peptides (cNPs) [141]. Additionally, cardiomyocytes secrete other polypeptide hormones with paracrine and autocrine effects, including adrenomedullin, pro-adrenomedullin *N*-terminal peptide (PAMP) [142], and endothelin-1 (ET-1) [143]. Increased blood levels of ANF and BNP are associated with

various cardiovascular diseases, and these markers can be used for diagnosis and prognostic purposes.

The morphological and functional complexity of atrial cardiomyocytes provides a shift from the classical paradigm describing the heart as a muscular pump and brings new insights regarding the endocrine roles of this organ, capable to self-regulate its workload, and influencing the activity of other organs, both under normal and pathological conditions.

Brown adipose tissue

According to classical histology, BAT, a multilocular adipose tissue, is the thermogenic component of the adipose organ, better developed in fetuses and newborns and absent in adults under physiological conditions [144, 145]. BAT is a thermogenic organ that is believed to be crucial for maintaining the energy homeostasis of humans [146, 147]. The primary function of BAT, which is specialized in heat production through no shivering thermogenesis, is to prevent hypothermia in small mammals, including neonates of humans [148, 149].

The dermomyotome, which has the same cell lineage as myocytes, produces brown adipocytes that express myogenic factor 5 (Myf5) and engrailed 1 (EN1) [150]. Pluripotent MSCs primarily develop from the mesoderm and give rise to adipocyte precursors. Pluripotent MSCs can also differentiate into adipocytes, myocytes, chondrocytes, and osteoclasts [151]. These cells are delivered to the adipogenic pathway and produce preadipocytes and adipomyocytes. After clonal expansion and differentiation, preadipocytes and adipomyocytes form adipocytes [152]. Based on their origin, location, and function, adipocytes are divided into three distinct cell types: white, brown, and beige adipocytes [153, 154]. These cells become committed to the adipogenic pathway, producing preadipocytes and adipomyocytes. After clonal expansion and differentiation, preadipocytes and adipomyocytes form adipocytes [152].

Based on their origin, location, and function, adipocytes are divided into three distinct cell types: white, brown, and beige adipocytes [153]. Occasionally found in white adipose tissue (WAT) depots, beige adipocytes are an inducible variety of thermogenic adipocytes. The inducible brown adipocytes represent the third type of adipocyte. Structurally and functionally, these adipocytes resemble brown adipocytes but have different molecular characteristics [155]. They also express MT uncoupling protein 1 (UCP1) [154]. The inducible brown adipocytes have a morphological appearance similar to that of brown adipocytes (the cytosol contains numerous mitochondria with cristae-dense expressing UCP1 and lipid droplets – multilocular), and have a thermogenic function [154, 156]. The transcriptional characteristic of inducible brown adipocytes differs from that of classical brown adipocytes [157]. It is known that cold exposure or chemical stimulation with β_3-adrenergic agonists will encourage the development of beige adipocytes [151].

BAT is typically found in designated BAT depots (such as the interscapular regions and the area surrounding the kidney), during the neonatal period in humans [154, 158]. The polygonal brown adipocytes contain many small lipid droplets and numerous large, spherical mitochondria that are densely packed with laminar cristae. BAT has a lot of blood vessels. The high MT density and vascularization confer BAT its brown color [151, 152].

BAT is a highly metabolic organ that, when fully engaged, can release a significant amount of energy by creating heat, while WAT stores the extra-energy as triglycerides [151]. Human brown adipocytes consume oxygen at a rate that is two times higher than white adipocytes, even in the unstimulated state [157]. Brown adipocytes express the MT UCP1, whose activation by cold, results in the production of heat [155, 157]. UCP1 resides within the inner MT membrane of brown and beige adipocytes and mediates the no-shivering thermogenesis process [155]. The internal MT membrane's H^+ gradient is dissipated by UCP1, which causes the electron transport chain and ATP synthase activity to become decoupled. This speeds up respiration and produces heat instead of ATP from the energy of substrate oxidation [157, 159, 160].

BAT represents the main site of adaptative thermogenesis and for this reason it has positive metabolic effects on obesity and insulin resistance. Before, it was thought that the brown adipocyte population in BAT was uniform. Recently, using multiple mouse models, single cell RNA sequencing and using 3D tissue models, a new subpopulation of brown adipocytes with reduced thermogenic activity was discovered. This new category of adipocytes coexists with the classical population of brown adipocytes that have high thermogenic activity [161]. These low-thermogenic brown adipocytes had larger lipid droplets, lower MT content, and significantly lower UCP1 and Adipoq expression when compared to the high-thermogenic brown adipocytes. Functional analyses revealed that low thermogenic brown adipocytes specialized in fatty acid uptake and have significantly lower basal MT respiration than high thermogenic brown adipocytes [161]. Due to the positive regulation of MT biogenesis and activity by adiponectin, high-thermogenic brown adipocytes express Adipoq at higher levels. In the very early stages of life, BAT represents the principal site of adiponectin secretion. In adult life, as the WAT depot' development begins, these tissues take over as the main locations for adiponectin production [162, 163]. Low-thermogenic brown adipocytes were transformed into high-thermogenic cells by exposure to cold. The opposite result was seen in a thermoneutral environment. High-fat diet feeding does not affect the recruitment by cold stimulation of high-thermogenic brown adipocytes. Recent 3D adipose tissue imaging reveals that the amount of sympathetic innervation determines how many brown adipocytes are produced when it is cold in the subcutaneous adipose tissue [164, 165]. The sympathetic nervous system, which becomes active during exposure to cold, is the main activator of BAT [157, 166]. Additionally, to the *UCP1* gene's transcriptional upregulation, noradrenaline released by sympathetic nerves near brown adipocytes causes lipolysis [167]. Both α- and β-adrenergic nerve fibers are heavily present in the innervation of brown adipocytes [161]. Although β_3-adrenergic fibers are primarily responsible for the thermogenic response to adrenergic stimulation, β_1 and β_2 stimulation in humans also have a similar effect [155]. Brown adipocytes are stimulated by adrenaline, which upregulates the expression of the *UCP1* gene and boosts lipolysis and oxygen consumption. When exposed to cold, brown adipocytes receive more sympathetic signals, which activate no shivering thermogenesis [168].

The discovery that adipose tissue is an active neuroendocrine organ and that adipocytes can send and receive

neural and chemical signals that regulate the body's energy balance and metabolism has shed light on the role of adipocytes in normal tissue biology over the past 50 years [152]. Brown adipocytes are efficient energy absorbers by burning and discarding excess lipids and glucose [169, 170]. Studies conducted over the past two decades have demonstrated that BAT plays a metabolic role in maintaining body weight as well as in thermogenesis [144, 145]. Some metabolic disorders or dyslipidemias that may occur in obese individuals can be prevented by inducing and triggering BAT [171, 172]. BAT activation promotes fat burning in laboratory animals, which reduces both diet-induced and genetic obesity [173]. BAT activation causes the increase of *UCP1* expression, the proliferation of brown adipocytes, and the phenotype modification of some white adipocytes located in distinct fatty deposits into cells similar to multilocular adipocytes [174]. WAT and BAT have different anatomy and physiology, but they work together to perform different functions [172]. Chronic exposure to cold leads to the conversion of WAT to BAT (the browning phenomenon of fat), and prolonged overeating habits, lead to the conversion of BAT to WAT (the lightening phenomenon of fat) [175, 176]. Recent research has demonstrated that body fat represents the adipose organ. In mice and humans, the adipose organ is the largest endocrine organ [172]. This idea is based on the distinct secretory capacities of subcutaneous and visceral fat, and the interchangeable properties of WAT and BAT. It was shown by Giordano *et al.* (2022) that WAT and BAT are contained in the same depots in both subcutaneous and visceral compartments, as distinct entities, but in continuity with one another [172]. Most fat depots in mice and humans are arranged to form a single unitary organ, according to the first 3D reconstructions. This information is crucial for creating future therapeutic strategies for obesity and related disorders based on the browning of visceral fat [177]. Numerous hormones are secreted by white and brown adipocytes, many of which have an impact on eating habits and energy expenditure [178]. The nutritional system, suggested by anatomical and functional data, represents a new system in the mammalian body. In this system, the adipose organ cooperates with the digestive organs, thus distributing energy between thermogenesis and metabolism [172].

The juxtaoral organ of Chievitz

The juxtaoral organ of Chievitz is a normal anatomical structure located within the oral soft tissue, bilateral to the walls of the oral cavity. It is described to be a neuro-epithelial formation, containing islands of epithelium and nerve fibers. Despite all the research, the function of this organ has not been established precisely. One of the most discussed situations refers to the risk of erroneous interpretation of an oral squamous cell carcinoma (OSCC) with perineural invasion, this misdiagnosed having an important impact on therapeutic management [179, 180].

In 1885, Johan Henrik Chievitz, a Danish histologist was conducting a study on the organogenesis of the parotid salivary glands in human embryos, when he observed a transient rudimentary epithelial formation near the glandular duct. In the first years, he described this formation as being present only in embryos, but 50 years later, in 1935, Wolfgang Zenker, proved the persistence of this structure in adults as well. Also, the team led by Zenker described the histological structure of the Chievitz organ as consisting of a mass of nerve fibers and epithelial cells with sensory receptors role, having an abundant innervation from the buccal nerve. Around the 2000s, some authors suggested that the juxtaoral organ of Chievitz could have the role of a mechanoreceptor involved in receiving sensory information from the side wall of the oral cavity [180]. Over time, further investigations focused both on the description of the histological structure and on establishing the role of this organ. However, despite 138 years of research, the real functions of the juxtaoral organ of Chievitz are only speculative [181].

The embryological origin of the juxtaoral organ of Chievitz has been intensively studied, the first description is made by Chievitz, who suggests that this organ originates from the ectoderm of the oral cavity around the oral commissure, which invaginates into the underlying mesenchyme during intrauterine life and subsequently disappears after birth [182]. Finally, Chievitz stated that the organ that bears his name is a transitory and rudimentary structure associated with the embryological development of the parotid glands, but Zenker contradicts this demonstration, stating that the parotid glands develop later [181].

Another team of researchers (Kleiss & Kleiss, 1985) described the development of the Chievitz organ in three periods: the condensation and invagination of the oral epithelium, the detachment of the formed structure from the epithelium and the acquisition of innervation by the oral nerve and the third stage, encapsulation with connective tissue [180].

D'Andrea and his research team (2015) summarized the embryological development according to the component anatomical structures: the oral part descends caudally towards the intersection between the parotid duct and the buccinator muscle (this part disappears during embryonic development), the middle part of the organ intersects the buccal nerve, and the dorsal part correlates with the pterygoid muscle [183].

The juxtaoral organ of Chievitz presents a wide variety of locations, being discovered at different levels by several researchers during the autopsy, being a microscopic organ. The presence of this structure was reported in the buco-temporal space in the depth of the soft tissue, right in front of the buccal nerve that innervates it [184, 185]. Other authors describe the Chievitz organ as located in the pterygomandibular space, deep in the side wall of the oral cavity covering the mandibular angle, in the submucosa of the pterygomandibular raphe, in the temporal region or less often, at the level of the posterior portion of the tongue, associated with the nerve plexus of the taste buds. In any case, regardless of location, this organ does not communicate with the oral cavity or the duct of the parotid gland [181].

The juxtaoral organ of Chievitz is generally defined as an elongate, flat, bilateral neuroepithelial structure, with millimeter dimensions, not being considered an organ with macroscopic relevance [180]. The juxtaoral organ is described by Palazzolo *et al.* as a structure formed by nests of non-keratinized stratified squamous epithelium and nerve

fibers originating from the subepithelial nerve plexus of the taste buds [185].

From a histological point of view, the juxtaoral organ consists of three concentric layers surrounding the parenchyma (an inner core – epithelial islands). The internal connective layer is called *stratum fibrosum internum* and is made of collagen fibers. The middle layer is characterized by loose connective tissue, in the thickness of which there are myelinated and unmyelinated nerve fibers and is called the *stratum nervosum*. The external layer, which connects the organ with the fascia of the bucotemporal muscle, is called *stratum fibrosum externum* [182, 186]. The parenchyma (the inner core) contains two cell types: type I is the most numerous and contains granular vesicles and type II, cells with cytoplasmic processes, scattered among the other cells [181].

Numerous types of research have focused on immunohistochemical studies of epithelial cells and thus it was discovered that these cells present immunoreactivity for p63 and the CK10, CK14, CK19, KL-1. Also, nerve fibers were positive for S100 protein and protein gene product 9.5 (PGP 9.5). Other authors demonstrated immunoreactivity for epidermal growth factor receptor (EGFR), TGF, or nerve growth factor (NGF), which led to the hypothesis that the juxtaoral organ, through immunohistochemically positive granules in close relation with blood vessels, could have a neurosecretory role [164]. The *fibrosum internum* and *fibrosum externum* layers showed immunohistochemical positivity for glucose transporter 1 (GLUT1), so these layers show perineurial characteristics. The *stratum nervosum* consists of nerve fibers and sensory corpuscles (Pacinian, Ruffini's, glomerular or lamellar corpuscles), being described as a mechanosensory structure. Also, in 2015, Kobayashi *et al.* demonstrated the presence of a ring of sensory endings between the parenchyma and *stratum fibrosum internum* [187]. Suarez-Quintanilla and the research team discovered that the connective layers showed intense immunoreactivity for a blood vessel marker (CD34), and thus suggested the presence at this level of structures resembling capillaries [182, 184]. Also, the presence of increased enzymatic activity at the level of parenchymal cells, demonstrated by IHC, may suggest intense metabolic activity at this level [180].

Regarding the functions performed by the juxtaoral organ of Chievitz, they remain unknown, but with each study that has been carried out, numerous hypotheses have been raised. Thus, approximately 50 years ago, due to the sensory corpuscles contained, it was assumed that the Chievitz organ would have a mechanosensory function for sucking, swallowing, mastication, speech, reflexes, and muscular tone for the lateral wall of the oral cavity. Twenty years ago, the presence of intracellular granules was described, which is why the neurosecretory role of these structures was affirmed. The content of the secretory granules demonstrated by IHC to be rich in chromogranin A and neuron-specific enolase (NSE) led to the conclusion that the Chievitz organ has a nerve receptor function and neurosecretory activity [181].

Understanding the morphology of the juxtaoral organ of Chievitz is particularly important in maxillofacial surgical pathology because the presence of nests of squamous epithelial cells together with nerve structures can be misinterpreted as perineural invasion in OSCCs [181].

Conclusions

Revisiting the key functions of the filaggrin and the lamellar granules in keratinocytes homeostasis can help in understanding the skin's barrier malfunctions and can lead to the discovery of a curative treatment of skin ichthyosis and more successful methods to treat dry and atopic skin.

The Paneth cells have antibacterial and inflammatory roles and are emerging as mediators of intestinal mucosal immunity. As host and microbiota factors regulate Paneth cell functions, these cells are involved in the pathogenesis of inflammatory bowel diseases and their metaplasia can represent an adaptive immune response.

Studying the expression of differentiation markers in the myofibroblasts and MECs could help to a better understanding of development and progression of neoplasms as those of salivary or mammary glands.

The resorptive cells as osteoclasts, odontoclasts and chondroclasts derive from a monocyte-cell lineage, adhere and fuse to mineralized surfaces, exerting their resorbing activity. The analysis of transcription factors identifies their specific gene signature, allowing a further exploration of their function *in vivo*, with possible therapeutical applications in rheumatic and osteo-articular diseases.

The monocyte-macrophages phagocytes' populations have numerous functions that contribute to homeostasis and to infectious defense (trophic, regulatory, regenerative roles, clearance of senescent/dead cells, antigen presenting cells). Their large phenotypic heterogeneity expresses in organ-specific environments, drawing to particular functions and can lead to an improvement of differential diagnosis in neoplastic processes.

A comprehensive understanding of differences between atrial and ventricular cardiomyocytes can be useful in cardiac-disease modeling and can have therapeutical applications.

BAT is a fascinating tissue, part of the new nutritional system of the mammalian body. It is involved in controlling eating habits, metabolic homeostasis, thermogenic response, obesity-induced inflammation and, through its endocrine functions, communicates with other organs. Its deeper study can lead to new therapeutic approaches of human cardiometabolic diseases.

The juxtaoral organ of Chievitz can be important in squamous cell cancers and oral surgical pathology.

Conflict of interests

The authors declare that they have no conflict of interests.

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