ELECTRON MICROSCOPIC INVESTIGATIONS OF THE TUMOR-STROMA INTERFACE DURING SKIN BASAL CELL CARCINOMA DEVELOPMENT

ANA-MARIA MOROȘANU[*], LEON DĂNĂILĂ[**], GABRIEL-VALERIU MIRANCEA[***], DANIEL FLORIN JURAVLE[****], VLAD DENIS CONSTANTIN[***], NICOLAE MIRANCEA[*]

The aim of this paper is to know subtle infrastructural alterations of cancer cells *per se* as well as associated tumor stroma of basal cell carcinoma (BCC). From the external part of the tumor mass towards the associated stroma a gradually alteration of histoarchitecture is remarkable. Basement membrane and hemidesmosomes are severely altered or totally abolished. Tumor cells affronted to the stromal microenvironment shed extracellular microvesicles. Because of high fragility of tumor associated microvasculature, extravasated inflammatory cells become intermingled with tumor cells. Inside of tumor mass, particular conduit systems delimited by tumor cells can be detected. A recently described cell phenotype termed telocyte is present inside of peritumoral stroma of all our investigated cases of BCC. These peculiar stromal cells establish both homo- and heterocellular junctions.

Keywords: Basal cell carcinoma, tumor-stroma interface, defective hemidesmosomes, shedding membrane vesicles, tumor microvasculature, conduit system, telocytes.

INTRODUCTION

Cancer is considered an irreversible disease mainly due to gradually accumulation of one or some mutations and/or deregulation of oncogenes and tumor suppressor genes and chromosomal abnormalities. This model corresponds to the so called somatic mutation theory (SMT) of cancer (Sonnenschein & Soto, 2000, 2014). SMT posits that cancer begin with a single mutation in a somatic cell followed by successive mutations (Baker % Kramer, 2007). Because many authors reported conflictual data *versus* the SMT, an alternative theory was elaborated termed tissue organization field theory (TOFT). TOFT states cancer arises and maintain as a result of defective cell-cell and cell-extracellular matrix communication (Soto & Sonnenschein, 2004; Baker & Kramer, 2007; Bizzari *et al*., 2014; Monti *et al*., 2022). Some infrastructural aspects observed in this study may contribute to sustain also the second theory. The large majority of human cancers have an epithelial origin accounting for circa 80% of all malignancies.

Like any other type of cancer, skin tumours occur when damaged DNA of some epidermal cells is unrepaired and mutations are installed so that affected epidermal epithelial cells proliferate uncontrolled. Stratified epithelial epidermal cells mainly represented by keratinocytes become in direct contact with the hostile environment. Cancer (a malignant tumor) develops as a progressive multi-step process in which involved cells undergo consecutive genetic alterations and in cooperation with stromal cells gradually acquire phenotypic changes so that transformed cells will grow rapidly and uncontroled. Mention must be made that there is a body of evidence that alterations in the tumor cells themselves are not sufficient to generate a tumor so that an adequate stromal microenvironment is a necessary condition (Fusenig *et al.*, 2002; Mueller & Fusenig, 2004; Mirancea & Mirancea, 2010a,b). Indeed, a malignant tumor is a complex ecosystem: (1) genetically altered neoplastic cells and (2) the associated tumor stroma represented by (a) connective tissue cells, imported cells plus (b) extracellular matrix and (3) the embedded microvasculature (Fusenig *et al*., 2002; Mirancea *et al*., 2013; Moroşanu *et al.*, 2013).

There are two main categories of skin cancer: (1) melanoma and (2) non melanoma. Non melanoma skin cancers are mainly comprised of (a) basal cell carcinoma (BCC) which accounts for about 80% of all non melanoma skin cancers and (b) squamous cell carcinoma (SCC) (Mirancea *et al*., 2013; Căruntu *et al.*, 2014). In terms of classification of BCCs, Reiter *et al.* (2021) showed that the most common dermoscopic features of BCC were arborizing vessels (59%), shiny white structures (49%), and large blue-gray ovoid nests (34%), which allow the systematic classification of BCC histopathologic subtypes. More than 26 different subtypes of BCC are known, but the more common types include: nodular, micronodular, superficial, morpheaform, infiltrative and fibroepithelial (Basset-Seguin & Herms, 2020; McDaniel *et al*., 2021). Because approximately 29% of patients with a primary BCC lesion will develop at least one such lesion in their lifetime, it is necessary to pay more attention to the profile of risk factors specific to each patient in order to have a better view of the differential diagnosis and long-term prognosis (Bartos, 2019). Taking into account the histopathological aspects and the molecular alterations, it can be stated that the probability of developing BCC is the result of a complex cumulation of factors that interact with each other: genetic, phenotypic and environmental factors (Dika *et al*., 2020).

A tumor is a complex ecosystem formed by neoplastic genetic altered cells and associated tumor stroma represented by different cell phenotypes and extracellular matrix represented by soluble mater and fibrils. There was a great interest to know morphologic aspects of tumor cells *per se*, so that a growing body of results was accumulated (Cheville, 2009; Mirancea & Mirancea, 2010a,b; Mirancea *et al*., 2010, 2014; Moroşanu *et al.*, 2013). Nevertheless, there are still unknown subtle infrastructural alterations of both tumor and extracellular microenvironment which compose the tumour ecosystem. The aim of this paper is to know such peculiar abnormalities which accompany tumor development and tumor cell behaviour.

Here we report about some original observations obtained by electron microscopic investigations of different tumoral specimens from human skin involved in BCC development. Our electron microscopic investigation of the basal cell carcinoma tumors from all investigated cases provide relevant aspects concerning ultrastructure of both tumor cell *per se* as well as associated tumor stroma, including tumor microvasculature and a recently identified cell phenotype termed telocyte.

MATERIAL AND METHODS

In order to perform transmission electron microscopic investigations, small tissue fragments about 2–3 mm^3 from the skin tumors resulted by surgery for diagnostic and curative therapy from the patients with clinic diagnostic for Basal Cell Carcinoma (surgeon got patients' consent) were processed following the routine TEM protocol (Mirancea *et al*., 2007; Mirancea & Mirancea, 2010a). Semithin sections of Epon-embedded tissue fragments were stained with 1% toluidine blue for light microscopy. Ultrathin sections were cut using a diamond knife and collected on 200 mesh grids and double counterstained with uranyl acetate and subsequently lead citrate. The grids were examined by a transmission electron microscope JEOL JEM-1400 operated at an acceleration voltage of 80kV. Several electron microscopic images were digitally colored.

RESULTS

Light microscopy examination

In spite of the fact that histopathological subtypes diagnosis is very important in view of planning patient management, so far, there is no unified and generally accepted classification of BCCs (Saldanha *et al*., 2015). In order to get an accurately diagnosis is very important the modality of biological material excision. It seems that the whole excision of the presumed malign cutaneous lesion is recommended comparing with shave and biopsy specimens because only the whole specimen offers the possibility to detect the biological transformation of BCC which tends to be much evident at the base and edges of the growing neoplasm (Crowson, 2006; Tanese, 2019). Indeed, in almost our investigated BCC cases, there is a clear difference in both light and electron microscopic aspects, depending on the level of the place we focus microscopic the section: from the external region of the tumor mass towards the associated stroma, a gradually alteration of histoarchitecture is detectable (Figs. 1–5) (Moroşanu, 2019, PhD thesis). This aspect is better visible by electron microscopic examination (Figs. 6–10) (Moroşanu, 2019, PhD thesis).

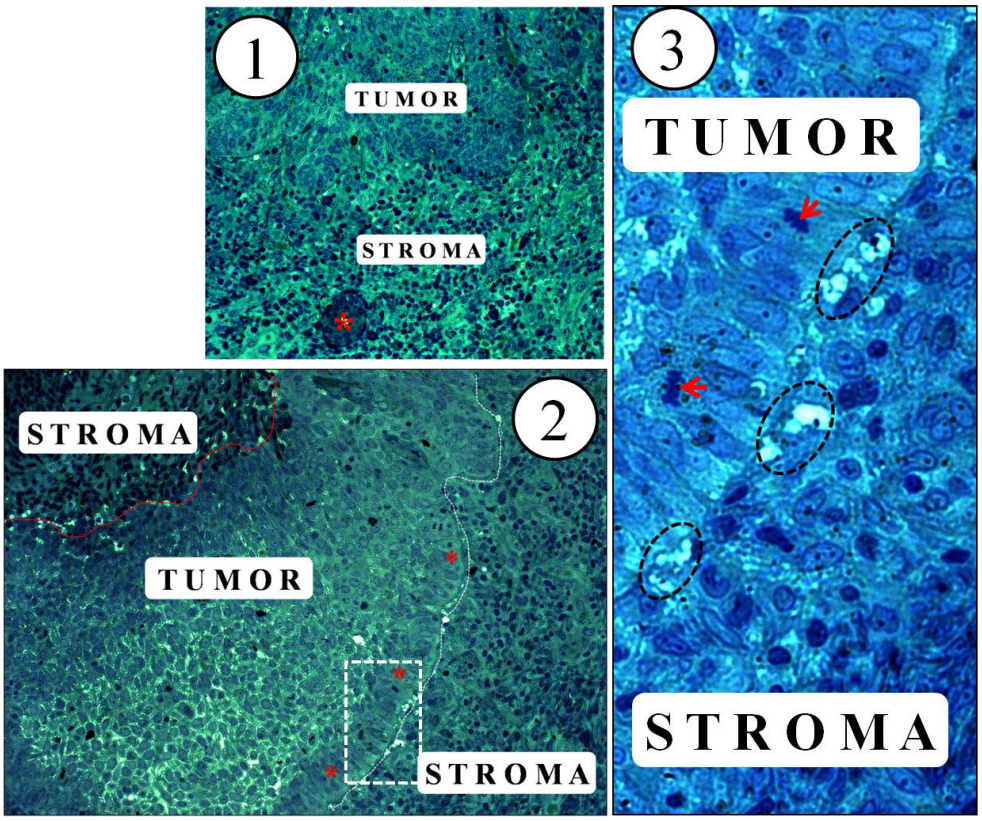

Fig. 1. An overview shows few tumor strands which penetrate inside of the rich epithelioid phenotype stroma (see details in Fig. 2 and Fig. 3). An islet of tumor cells can be detected deeply inside of the stroma (asterisk) (ob. 20x).

Fig. 2 and Fig. 3. A massive mass of tumor at the tumor-stroma interface shows at one side large columnar cells (asterisks), some of them being in mitosis (framed area detailed in Fig. 3, arrows; ob. 20x). Many lacunae can be seen between palisaded basal cells and adjacent stroma (elliptic areas) (ob. 40x).

At the tumor stroma interface, many lacunae can be detected (Fig. 3) (Moroşanu, 2019, PhD thesis). Such kind of lacunae fused and slit-like (cleft-like) spaces are formed (Fig. 4) (Moroşanu, 2019, PhD thesis). Crowson (2006) also reports about slit-like (cleft-like) spaces between palisaded basal cells and adjacent stroma in different morphological subtypes of BCC. Saldanha *et al.* (2015) consider that presence of lacunae or cleft-like between tumor cells and adjacent stroma contributes to differentiate BCC from other tumors.

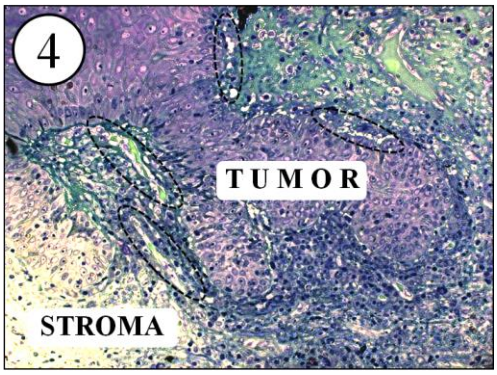

Fig. 4. A very extensive strand o tumor cells penetrates deeply inside of a fibrotic stroma. Clefts-like are formed by adjacent lacunae fusion at the tumor-stroma interface (elliptic areas) (ob. 20x).

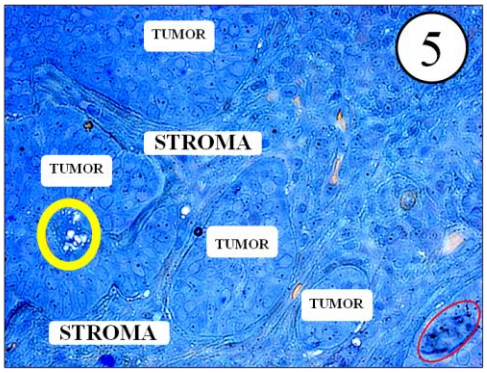

Fig. 5. Overview from a very large tumor showing many cords of tumor cells intermingled with restraint strands of stromal tissue. Yellow elliptic area indicates a primitive lumen formed by coalescence of small lacunae inside of a tumor with adenoid (pseudoglandular) while red elliptic area indicates necrotic cells inside of the tumor strand (ob. 40x).

Electron microscopic investigation

In all investigated skin basal cell carcinoma tumors, an overview from the external part of the tumor mass towards the associated stroma shows a gradually alteration of histoarchitecture. Large nuclei are almost euchromatic and nucleolated. Tumor cells still express some of characteristic but impaired infrastructures of the normal epidermis: limited as number and impaired as ultrastructure desmosomes, totally absence or defective hemidesmososmes, reduced amount of kerain intermedium filaments. Some intercellular spaces can be detected (Fig. 6) (Moroşanu, 2019, PhD thesis). In the middle of the tumor mass, the paucity of both keratin intermedium filaments and desmosomes are remarkable. Moreover, intercellular spaces are much numerous and larger (Fig. 7) (Moroşanu, 2019, PhD thesis).

Inside of the tumor mass much close to the tumor stroma, by hard the epidermal cell phenotype as origin of tumor cells can be identified. Very scanty keratin intermedium filaments and illusive desmosomes can be detected. In such circumstances, numerous and large wide intercellular spaces are formed (Fig. 8) (Moroşanu, 2019, PhD thesis).

At the tumor stroma interface, no basement membrane can be detected but an amorphous material is interposed. Hemidesmosomes are missing or defective hemidesmosomes can be detected (not shown). Ultrastructurally, two tumor cell phenotypes can be distinguished: cells with euchromatic nuclei and cells with heterochromatic nuclei. Some tumor cell exhibit cell projected towards the stroma suggesting an invasive behavior, but also exhibits some remnants of keratin intermedium filaments. Large apparently vide spaces or filled with amorphous material are visible at the tumor stroma border (Fig. 9) (Moroşanu, 2019, PhD thesis).

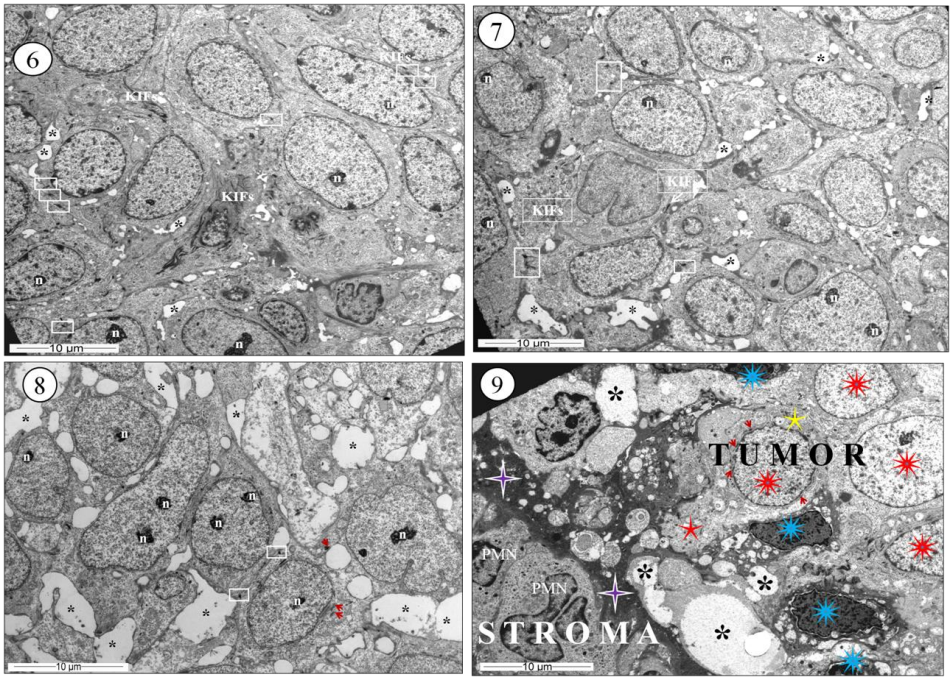

Fig. 6. An overview from the external part of the tumor mass shows an altered histoarchitecture. Large nuclei are almost euchromatic and some nucleols (n) can be seen. Tumor cells still express some of characteristic but impaired infrastructures of the normal epidermis: limited as number and impaired as ultrastructure desmosomes (framed areas), reduced amount of keratin intermedium filaments (IFs). Some intercellular spaces can be detected (asterisks).

Fig. 7. A successive overview towards the middle of the tumor mass shows a similar aspect from the Fig. 6, but the paucity of both keratin intermedium filaments (KIFs) and desmosomes (framed areas) are remarkable. Intercellular spaces (asterisks) are much numerous and larger. n = nucleols.

Fig. 8. A succesive image from the middle of the tumor mass towards of the tumor stroma. By hard the epidermal cell phenotype as origin of tumor cells can be identified. Very scanty keratin intermedium filaments (red arrows) and illusive desmosomes (framed areas) can be detected. Intercellular spaces are very numerous and some are very large (asterisks). n = nucleols.

Fig. 9. At the tumor stroma interface, no basement membrane can be detected but an amorphous material is interposed (4-point stars). Ultrastructurally, two tumor cell phenotypes can be distinguished: cells with euchromatic nuclei (red ten point stars) and cells with heterochromatic nuclei (blue ten point stars). One tumor cell with euchromatic nucleus exhibits uropodial cell extension towards the stroma (five point red arrow) while the the rest of cytoplasm (five point yellow star) exhibits some remnants of keratin intermedium filaments (red arrows) around the nucleus. Large apparently vide spaces or filled with amorphous material (asterisks) are visible at the tumor stroma border. Inflammatory stromal cells (PMN) in close vicinity to tumor cells can be seen.

Inflammatory stromal cells in close vicinity to tumor cells can be seen. In some areas, extravasated blood cells become intermingled with invasive tumor cells (Fig. 9 and Fig. 10) (Moroşanu, 2019, PhD thesis).

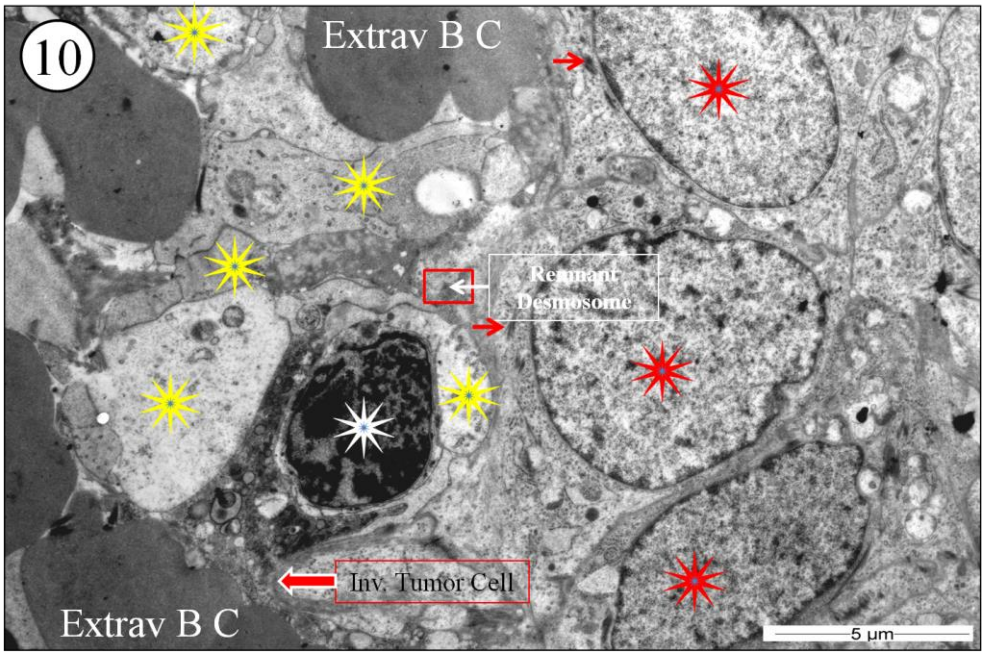

Fig. 10. An intermingled of tumor cells with extravasated blood cells (Extrav B C). Some tumor cells have euchromatic nuclei (ten point stars) with very scanty keratin intermedium filaments (red arrows) and remnant desmosome. One tumor cell has a nucleus with large blocks of condensed chromatin (white ten point star) while some others are in advanced stage of degradation (yellow ten point stars). A tumor cell extension deeply penetrates into adjacent stroma (large arrow).

Very often, small tumor blood vessels are very fragile with large gaps between adjacent endothelial cells so that leukocytes and red blood cells will extravasate. Moreover, some blood vessels are defective for basement membrane and pericytes (Fig. 11 and Fig. 12) (Moroşanu, 2019, PhD thesis).

Interestingly, inside of tumor mass, particular conduit systems delimited by tumor cells still preserving some keratin intermedium filaments and desmosomal junctions can be detected. The central part of the conduits is represented by collagen fibrils cross sctioned (Fig. 13) (Moroşanu, 2019, PhD thesis).

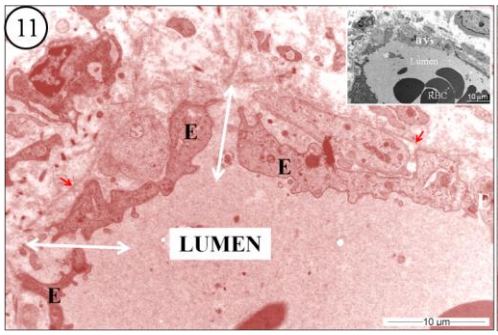

Fig. 11. Between the tumor cells facing tumor stroma, desmosomal junctions are missing (white elliptic area). A tumor cell exhibit microvesicles (red elliptic area). Delivered membrane vesicles (red asterisks) can be seen. Basement membrane is missing but dense amorphous material is deposited (yellow asterisks). No hemidesmosome can be detected. A gap in plasma membrane of the tumor cell is visible (large arrow). For overview see inset **a.** Tumor cell still express keratin intermedium filaments (inset **b**, KIFs).

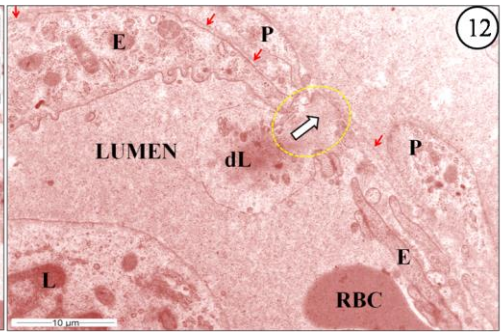

Fig. 12. A very fragile small blood vessel (for larger view, see the insert) exhibits endothelial cells (E) missing interendothelial junctions so that large gaps can be seen (double arrows). Small red arrows indicate fragments of basement membrane. BVs = blood vessel. RBC = red blood cells.

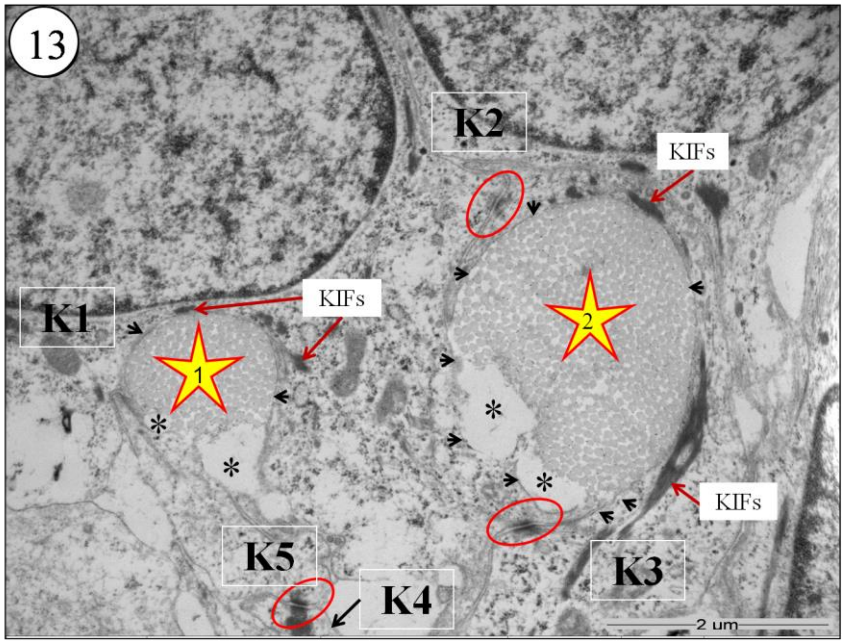

Fig. 13. A tumor blood vessel exhibits a large gap between two adjacent endothelial cells (E) so that a leukocyte (dL) is engaged in diapedesis. An interrupted basement membrane facing endothelial cells can be detected (red small arrows). Pericytes (P) are devoid of any basement membrane.

When present, nucleated telocytes with telopods can be detected inside of the tumor stroma but mention must be made, they are relative far from the tumor cells. Telocytes esthablish homo- and/or heterocellular junctions (Fig. 14) (Moroşanu, 2019, PhD thesis). Fig. 15 (Moroşanu, 2019, PhD thesis) depicts plasma cell membrane recombination between a telocyte and a tumor stromal cell. Moreover, at this level, microvesicles of different size can be seen but is difficult to know if these originate from the stromal cell or are delivered by the telocyte. Fig. 16 depicts a homotypic junction between two telopodes located inside of a fibrotic tumor stroma (detailed in Fig. 17) (Moroşanu, 2019, PhD thesis).

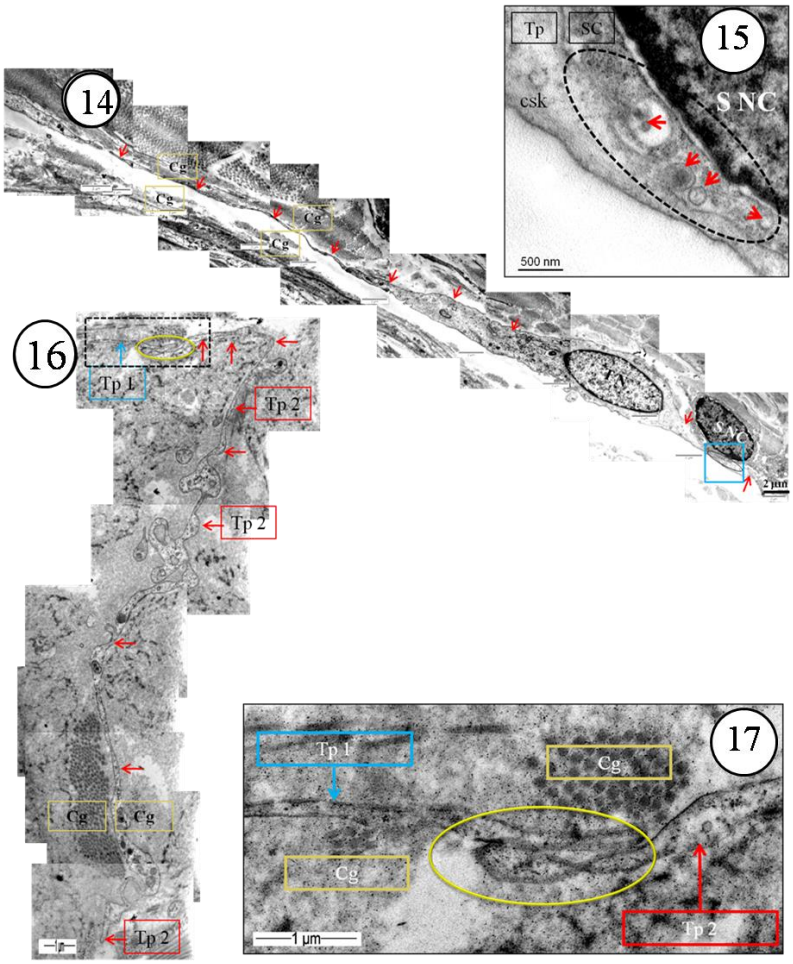

Fig. 14. Inside of tumor mass, there are particular conduit systems (big stars 1 and 2) delimited by tumor cells (K1-K5) still preserving some keratin intermedium filaments (KIFs) and desmosomal junctions (elliptic areas). The conduits with a core represented by collagen fibrils cross sectioned are delimited by plasma membranes of tumor cells (arrows). Empty spaces inside of each conduit system can be seen (asterisks).

Fig. 15. A nucleated telocyte exhibiting two telopods (red arrows) were detected inside of the tumor stroma but relative far from the tumor cells. A stromal nucleated cell (SNC) become in direct contact with one telopode.
Fig. 16. Detail of the framed area in Fig. 15 shows a plasma cell membrane recombination (elliptic area) established between telopode (Tp) and tumor stromal cell (SC). Microvesicles of different sizes can be seen (red head arrows) but is difficult to know if these originate from the stromal nucleated cell (SNC) or are delivered by the telocyte. Csk=cytoskeleton.
Fig. 17 and Fig. 18 depict a homotypic junction (elliptic areas) between two telopodes (TP 1 and TP 2) located inside of a fibrotic tumor stroma. Cg = collagen fibers.

DISCUSSIONS

Tumor-stroma interactions. The tumor microenvironment

Normal human skin (NHS) represented by (1) a pavimentous stratified epithelium termed epidermis of ectodermal origin attached to (2) the dermis of mesenchymal origin and, more profound, (3) the hypodermis is considered the second larger organ of the human body. Skin is a vital organ. The epidermis is the first defense line or barrier against environmental injuries for the skin, resting on the dermis underneath. In the NHS between epidermis and subjacent dermis there is a so called dermal-epidermal junctional zone (DEJZ). At the dermal-epidermal interface, a specialized extracellular matrix (ECM) highly organized at the molecular level composed of glycoproteins and proteoglycans appears as a continuous anhist infrastructure known as the basement membrane (BM) which separates and also connects epidermis to the dermis (Hashmi and Marinkovich, 2015). Depletion or functional deficiencies of any BM component may be lethal at some stage of development or around birth or may induce impairment in the skin function late in the life. Skin may be involved in inborn or acquired skin diseases.

Because ECM functions as a reservoir of various types of growth factors, cytokines and chemokines, the intense remodeling process it undergoes in cancer affects the processes of angiogenesis, proliferation or cell mobility, by specifically regulating signaling pathways (Jarvelainen *et al.*, 2009; Chen and Nunez, 2010; Kavasi *et al*., 2022).

Histoarchitecture and ultrastructure of the epithelial tumor. Cell-cell relationships inside of tumor

During normal skin morphogenesis as well as in *in vitro* reconstructed skin equivalents a permanent interplay exists between epithelial cells and adjacent fibroblast cells (Mackenzie, 1994; Stark *et al*., 2001; Marionnet *et al*., 2006). Now days appears more clearly that associated stroma to the tumor plays a major role in tumor initiation, tumor growth and invasive behaviour of malignant cells during

metastasis (Mueller & Fusenig, 2004; Mirancea *et al*., 2010, 2014). That is the reason why we focus our electron microscopic investigations also on the tumor stroma. Interestingly, in this context electron microscopic examination showed that inside of tumor mass there is a gradually change of tumor cell phenotype so that, cells located at the tumor-stroma interface are ultrastructurally very different from the tumor cell located at the tumor external surface (opposite and far from the stromal tissue).

This study related to some peculiar ultrastructural alterations detected in some histiotypic human skin basal carcinoma both inside of tumoral mass as well as associated tumor stroma. In all investigated cases a severe histoarchitecture disarrangement of the epidermal tumor cells is remarkable (Figs. 6–7) (Moroşanu, 2019, PhD thesis). The paucity of desmosomal junctions and associated keratin filaments may partially explain this aspect (Fig. 8) (Moroşanu, 2019, PhD thesis). In fact, loss of adhesive regulation is a hallmark of almost invasive carcinoma types, a prerequisite to dissemination in ectopic places to form secondary tumors (Kimura *et al*., 2007; Mirancea *et al*., 2013, 2014; Moroșanu *et al*., 2013).

Basement membrane at the tumor stroma interface

In normal human skin the DEJZ is represented by specific type molecules arranged in particular infrastructures: hemidesmosomes ($\alpha 6\beta 4$ integrin, bullous pemphigoid 180 kDa and 230 kDa, HD 1/plectin, basement membrane (laminin and type IV collagen) and anchoring fibrils (type VII collagen) (Mirancea *et al*., 2001, 2010; Mirancea & Mirancea, 2010a; Neve *et al*., 2014; Hashmi & Marinkovich, 2015). Basement membrane is a potential source and bifunctional for pro- and antiangiogenic molecules (McDonald & Baluk, 2002; Neve *et al*., 2014).

DEJZ is severely altered during epidermal carcinogenesis so that, accordingly with the tumor progression BM becomes illusive or even totally disappearing (Figs. 9, 10) (Moroşanu, 2019, PhD thesis). When present, it appears as redundant patches of basement membrane. In fact, DEJZ alteration is a hallmark of a bad evolution of skin BCC.

Alteration of hemidesmosomal junctions

BM alteration is associated with another important abnormality, namely absence of hemidesmosomal junctions or presence of defective hemidesmosomes. Either absence or defective hemidesmosomes were also reported in BCC and SCC (Mirancea *et al*., 2010; Moroşanu *et al*., 2013).

Absence of hemidesmosomes, BM and anchoring fibrils may explain the lacunae ad slit-like stromal retraction characteristic in BCC (Crowson, 2006).

The tumor microenvironment and inflammatory cells inside of the tumor stroma

A solid tumor is a site of chronic inflammation. Inflammatory cells are coming from the blood flow in response to the pro-angiogenic factors delivered from the tumor cells and their accomplices from the tumor microenvironment (Mueller & Fusenig, 2004). In all our investigated cases of BCC, especially at the tumor-stroma interface we detected altered (fragile) microvasculature and, consequently extravasated free inflammatory bold cells become in close contact with tumor cells, as is depicted in Fig. 9 and Fig. 10 (Moroşanu, 2019, PhD thesis). Similar aspects were reported by Mirancea *et al*. (2014) and Constantin *et al*. (2015) in both neuroendocrine and exocrine pancreatic tumors. In an elegant experimentally study, Arwert *et al.* (2010) demonstrated that differentiated epidermal cells triggered by inflammatory infiltrate can initiate tumor formation without reacquiring the ability to divide, by recruiting undifferentiated cells to become incorporated into the tumor and form its proliferative compartment.

Shedding membrane vesicles

There are many players involved in cell-cell and cell-extracellular matrix communications. Very tightly mechanisms of control represented by autocrine and paracrine factors maintain normal local tissue homeostasia. Now is well stated that bioelectric signals play a major role in cell-cell communications (Lobikin *et al*., 2012). Moreover, small lipoprotein sacks termed extracellular vesicles (ECVs) produced by all body cells and a special cell phenotype called telocytes present and described in almost all organs (Popescu *et al*., 2005, 2010; Rusu *et al*., 2012a; Mirancea *et al*., 2013) are added to the list of mediators involved in cell-cell and cell-extracellular matrix. Almost eukaryotic cell phenotypes release into their microenvironment, including blood and body fluids, a heterogeneous mixture of vesicular (infra)structures organelle-like, often termed extracellular (micro)vesicles (ECMVs) or extracellular organelles (Mathivanan *et al*., 2010). ECMVs which include (1) exosomes, (2) shedding membrane vesicles, (3) apoptotic blebs are spherical bilayered proteolipids vesicles with a mean diameter of 20-1.000 nm. Exososmes are formed inside the cell in multivesicular bodies, whereas the other two types bud off from the plasma membrane (Smythies, 2015). These are generated *via* diverse biological mechanisms triggered by diverse pathways involved in different cellular activities: intercellular communications, pathogenesis including oncogenic transformation etc. Now is well documented that EMCVs contain bioactive molecules as growth factors and their receptors, adhesion molecules, signaling molecules, DNA, mRNA, microRNA sequences, proteases, lipids so that ECMVs appear as bioactive cargoes which play important roles in patho-physiology, including facilitation of tumor growth (Hendrix & Hume, 2011; Lee *et al*., 2011; Cismașiu & Popescu, 2015; Kok and Yu, 2020).

In almost all our investigated cases of BCCs as well as SCCs we detected shedded microvesicles by tumor cells (Mirancea *et al.*, 2010, 2013). Cancer cells release or deliver large amounts of ECMVs which can be transferred also to non-transformed cells (stromal cells as fibroblasts, endothelial cells and to the inflammatory infiltrated cells). Such events may contribute to tumor angiogenesis as well as to tumor migration, invasion and ectopic dissemination in order to develop secondary tumor (metastasis), drug resistance, and cancer stem cell hierarchy (Lee *et al*., 2011).

Microvasculature

Like in many other tumor types, in our investigated patients diagnosed with basal cell carcinoma in different degrees, we observed leakiness of tumor vessels (Fig. 11 and Fig. 12) (Moroşanu, 2019, PhD thesis). There is a general agreement that tumor blood vessels are abnormal, namely (1) defective and leaky endothelium, (2) impaired associated basement membrane or redundant layers of basement membrane as a continuous vascular remodeling and (3) dissociation of pericytes (McDonald & Baluk, 2002; Stratman *et al*., 2009; Stratman & Davis, 2012). Low-molecular-weight vascular-disrupting agents induce severe damage of the tumor associated microvasculature causing an extensive tumor necrosis while the blood vessels in normal tissues remain relatively intact (Tozer *et al.*, 2005). The evaluation of the microvasculature and its status is even a tool in establishing the differential diagnosis, the subtypes of BCC and their aggressiveness, namely by the dermoscopic evaluation of the vascular model (Lupu *et al*., 2019).

Tumor microvasculature is abnormal in their constitution as is depicted in Fig. 11 and Fig. 12 (Moroşanu, 2019, PhD thesis). That appears leaky with remarkable increased vascular permeability, so that, both red and white blood cells disseminate inside or in peritumoral spaces (Mirancea *et al*., 2010; Stratman & Davis, 2012; Mirancea *et al*., 2014; Constantin *et al*., 2015). Consequently, delivered inflammatory blood cells become rich sources of pro-inflammatory agents, a prerequisite for the well known tumor status as a disease that do not heal (Dvorak, 1986).

Conduit system

In one of the skin BCC case we investigated, a special structure termed conduit system was detectable. Such kind of conduits has been described for lymph nodes, spleen and thymus (Sixt *et al*., 2005; Drumea-Mirancea *et al*., 2005; Roozendaal *et al.*, 2008, 2009; Mirancea & Mirancea, 2010a). A conduit of lymph nodes and spleen is composed of a network of collagen fibers with periodicity enwrapped by fibroblastic reticular cells (Drumea-Mirancea *et al.*, 2005). Immune electron microscopic examination of a conduit system detected inside of the human thymus showed that such kind of 3-D tubes are represented by fibrillar collagens surrounded by a laminin-5-containing membrane (Drumea-Mirancea *et al*., 2005). Moreover, desmosomal junctions were detected (Drumea-Mirancea *et al*., 2005;

Mirancea & Mirancea, 2010a). Different from the above more complex conduit system, in our skin BCC case we investigated, a conduit system also exhibit a core of fibrillar collagens, but the basement membrane is missing, so that, only plasma membranes of tumor cells surround fibrillary collagen and, associated soluble extracellular micromedium. One the other hand, also epithelial cells namely tumor keratinocytes exhibit defective desmosomes and some intermedium filaments but no hemidesmosome or hemidesmosome-like junction is detectable. Inside of a conduit some apparently wide spaces can be seen (Fig. 13) (Moroșanu, 2019, PhD thesis). Mention must be made that, from our best knowledge, so far, this is for the first time when such particular structure is detected and described in a case of BCC. These unique structures seem to play an important role for the transport of fluids and some low weight soluble molecules as cytokines, chemokines (Sixt *et al.*, 2005; Drumea-Mirancea *et al*., 2005; Roozendaal *et al*., 2008; Roozendaal *et al*., 2009; Morgado *et al*., 2020; Novkovic *et al*., 2020).

Telocytes

Recently, a new interstitial/stromal cell phenotype termed telocyte presents inside of almost all tissue type gain a lot of interest. Telocytes (TCs) have been described in the interstitium of many normal tissues as heart (Popescu *et al*., 2005; Popescu & Faussone-Pellegrini, 2010; Rusu *et al*., 2012b), skin (Rusu *et al*., 2012 a), esophagus (Rusu *et al*., 2012c), trachea (Rusu *et al*., 2012d), uterus (Roatesi *et al*., 2015) or tissues involved in different diseases as heart failure (Richter & Kostin, 2015), oviduct disease (Yang *et al*., 2015a,b), skin diseases (Mirancea *et al*., 2013; Manole *et al.*, 2015), human brain tumor (Mirancea *et al.*, 2022). So far, ultrastructural characteristics remain the modality for precisely identification of TCs (Popescu *et al*., 2010; Mirancea *et al.*, 2013). A specific Immuno Histo Chemical (IHC) marker has not yet been found, but several IHC markers have been found that have variable expression in TCs from different tissues (Roatesi *et al.*, 2015). The immunophenotype of TC includes double immunostaining with CD34/CD117/Kit (mainly for cell body) or CD34/vimentin (mainly for telopodes). TC may also express caveolin -1, CD44, NOS-2, desmin, cadherin-11 and PDGF-R beta (Popescu & Nicolescu, 2013). *In vitro*, in primary culture, cardiac TCs were positive for CD34/c-kit, CD34/vimentin, and CD34/PDGFR- as well as for mesenchymal maker CD29 (Bei *et al*., 2015 b).

We also detected this special cell phenotype, namely telocyte, inside of tumor stroma in our investigated cases of BCC (Figs. 14-17) (Moroşanu, 2019, PhD thesis). TCs were detected relative far from the tumor cells. There is a body of evidence that TCs might be involved in many physiological and pathological processes. By their homocellular junctions TCs connect each other (Fig. 16 detailed in Fig. 17 – Moroşanu, 2019, PhD thesis) while *via* hetero-cellular junctions TCs can be connected with other stromal cells (Fig. 14 detalied in Fig. 15 – Moroşanu, 2019, PhD thesis) as endothelial cells, nerve ending, putative stem cells, mast cells,

macrophages, fibroblasts etc. By homo- and heterocellular junctions, TCs can form an interstitial 3D network able to modulate tissue homeostasis and development as well as pathogenesis of some disorders. Moreover, owing to their close relationship with stem cells and or/progenitor cells in almost all tissue types as was reported in heart (Popescu, 2011), skin (Ceafalan *et al*., 2012). TCs influence/support tissue regeneration (Mirancea *et al*., 2013; Manole *et al*., 2015; Smythies, 2015; Bei *et al.*, 2015a; Cismașiu & Popescu, 2015). Smythies & Edelstein (2014), consider that TCs network might be well regarded as a very primitive nervous system. TCs may be involved in morphogenetic bioelectrical signalling (Edelstein & Smythies, 2014). Mention must be made that TCs damages, reduced number of telocytes *per se* as well as the 3-D interstitial architectural alteration by reduced number of telocytes homo- and heterocellular junctions have been reported in different pathologies as cardiac diseases, skin cancers etc. (Mirancea *et al*., 2013; Moroșanu *et al*., 2013; Manetti *et al.*, 2014; Yang *et al*., 2015a,b; Richter & Kostin, 2015; Díaz-Flores *et al*., 2021).

TCs are able to release extracellular vesicles which may play a role in intercellular communications, cell signaling, maintaining tissue homeostasis (Mirancea *et al.*, 2013; Cretoiu & Popescu, 2014). Fig. 15 (Moroșanu, 2019, PhD thesis) depicted a heteocellular junction between a telocyte and a stromal cell where plasma cell membranes recombinate and microvesicles are present in way to be delivered. Such kind of extracellular organelles are considered to be involved in paracrine long distance signaling (Popescu, 2011; Cretoiu *et al.*, 2012; Mirancea *et al*., 2013).

There are many reports which emphasize that telocytes play a major role as integrators of many intercellular functions in normal tissue (Smythies, 2015), as well as in tissues involved in different pathologies, including tumor development (Mirancea *et al*., 2013; Moroşanu *et al.*, 2013; Manetti *et al.*, 2014, 2015). In a very recently published paper Mirancea *et al.*, (2022) emphasize that inside of the human severely altered brain tumor stroma many telocytes still keeping their homocellular junctions are visible, suggesting a kind of mechanically protection against aggressive growth of the tumor brain.

CONCLUSIONS

Our study pointed out some original relevant dynamics alterations of the tumor stroma interface. Basement membrane and hemidesmosomes are severely altered or totally abolished. Vesicular (infra)structures organelle-like termed extracellular (micro)vesicles are released by tumor cells at the tumor-stroma interface. Tumor associated capillary are often devoid of basement membrane and pericytes so that extravasated inflammatory cells become intermingled with tumor cells. Inside of tumor mass, particular conduit systems delimited by tumor cells can be detected. A recently described interstitial/stromal cell phenotype termed telocyte

is present inside of peritumoral stroma of all our investigated cases of BCC. These peculiar stromal cells, mostly located far from the tumor cells, establish both homo- and heterocellular junctions.

Acknowledgements. The authors acknowledge for financing support done to perform and to write the paper coming from project No. RO1567- IBB07/2011 from the Institute of Biology Bucharest of Romanian Academy. Electron microscopic investigations were performed by a transmission electron microscope JEOL JEM 1400, supported by DIBIOCLIM Project. The authors thank to A. Brînzan and V. Stan for technical assistance.

REFERENCES

ARWERT N.E., LAL R., QUIST S., ROSEWELL I., VAN ROOIJEN N., WATT M.F., 2010, *Tumor formation initiated by nondividing epidermal cells via an inflammatory infiltrate.* Proceedings of National Academy of Sciences of the United States of America, **107** (46): 19903–19908.

BAKER S.G., KRAMER B.S., 2007, *Paradoxes in carcinogenesis: New opportunities for research directions.* BMC Cancer, **7**: 151.

BARTOS V., 2019, *Development of multiple-lesion basal cell carcinoma of the skin: A comprehensive review*. The Medical Buletin of Sisli Etfal Hospital, **53** (4): 323–328.

BASSET-SEGUIN N., HERMS F., 2020, *Update in the management of basal cell carcinoma*. Acta Dermato-Venereologica, **100** (11): adv00140.

BEI Y., WANG F., YANG C., XIAO J., 2015a, *Telocytes in regenerative medicine*. Journal of Cellular and Molecular Medicine, **20** (10): 1–14.

BEI Y., ZHOU Q., FU S., LV D., CHEN P., CHEN Y., WANG F., XIAO J., 2015b, *Cardiac telocytes and fibroblasts in primary culture: different morphologies and immunophenotypes*. Plos One, **10** (2): e0115991.

BIZZARI M., CUCINA A., PROIETTI S., 2014, *The tumor microenvironment as a target for anticancer treatment.* Oncobiology & Targets, **1** (1): 3–9.

CĂRUNTU C., BODA D., GUȚU E.D., CĂRUNTU A., 2014, *In vivo reflectance confocal microscopy of basal cell carcinoma with cystic degeneration.* Romanian Journal of Morphology and Embryology, **55** (4): 1437–1441.

CEAFALAN L., GHERGHICEANU M., POPESCU L.M., SIMIONESCU O., 2012, *Telocytes in human skin – are they involved in skin regeneration*. Journal of Cellular and Molecular Medicine, **6** (7): 1405–1420.

CHEN G.Y., NUNEZ G., 2010, *Sterile inflammation: sensing and reacting to damage*. Nature Reviews Immunology, **10**: 826-837.

CHEVILLE N.F., 2009, *Ultrastructural pathology: the comparative cellular basis of disease*. Second Edition, John Willey & Sons, Hong Kong, Singapore, 1000 pp.

CIȘMASIU V., POPESCU L.M., 2015, *Telocytes transfer extracellular vesicles loaded with microRNAs to stem cells*. Journal of Cellular and Molecular Medicine, **19** (2): 351–358.

CONSTANTIN V.D., MIRANCEA G.V., MOROȘANU A.M., MIRANCEA N., 2015, *Relevant infrastructural alterations in invasive pancreatic ductal adenocarcinoma.* Romanian Journal of Morphology and Embryology, **56** (1): 207–222.

CRETOIU S.M., POPESCU L.M., 2014, *Telocytes revisited.* BioMolecular Concepts, **5** (5): 353-368.

CRETOIU S.M., CRETOIU D., POPESCU L.M., 2012, *Human myometrum – the ultrastructural 3D network of telocytes*. Journal of Cellular Molecular Medicine, **41** (6): 949–956.

CROWSON A.N., 2006, *Basal cell carcinoma: biology, morphology and clinical implications.* Modern Pathology, **19**: S127–S157.

DÍAZ-FLORES L., GUTIÉRREZ R., GARCÍA M.P., GONZÁLEZ-GÓMEZ M., RODRÍGUEZ-RODRIGUEZ R., HERNÁNDEZ-LEÓN N., DÍAZ-FLORES L. JR., CARRASCO J.L., 2021, Cd34+ *Stromal cells/telocytes in normal and pathological skin*. International Journal of Molecular Science, **22** (14): 7342.

DIKA E., SCARFÌ F., FERRACIN M., BROSEGHINI E., MARCELLI E., BORTOLANI B., CAMPIONE E., RIEFOLO M., RICCI C., LAMBERTINI M., 2020, *Basal cell carcinoma: A comprehensive review*. International Journal of Molecular Sciences, **21** (15): 5572.

DRUMEA-MIRANCEA M., WESSELS J.T., MUELLER C.A., ESSL M., EBLE J.A., TOLOSA E., KOCH M., REINHARDT D.E., SIXT M., SOROKIN L., STIERHOF Y.-D., SCHWARZ H., KLEIN G., 2005, *Characterization of a conduit system containing laminin-5 in the human thymus: a potential transport system for small molecules*. Journal of Cell Science, **119**: 1396–145.

DVORAK H.F., 1986, *Tumors: wounds that do not heal*. New England Journal of Medicine, **315**: 1650–1659.

EDELSTEIN L., SMYTHIES J., 2014, *The role of telocytes in morhogenetic bioelectrical signaling: once more unto the breach*. Frontiers in Molecular Neuroscience, **7** (41): 1–3.

FUSENIG N.E., SKOBE M., VOSSELER S., HANSEN M., LEDERLEE W., TOMAKIDI P., STARK H.-J., MIRANCEA N., BOUKAMP P., BREITKREUTZ D., 2002, *Proteases and their inhibitors in cancer metastasis, Tissue models to study tumor-stroma interactions*. *In*: Ruth J. & Foidart J.-M. Eds.), Kluwer Academic Publishers, Dordrecht, The Netherlands, New York, 256 pp.

HASHMI S., MARINKOVICH M.P., 2015, *Blistering diseases: clinical features, pathogenesis, treatment, Biology of the basement membrane zone*, Springer-Verlag Berlin Heidelberg, 773 pp.

HENDRIX A., HUME A.N., 2011, *Exosome signaling in mammary gland development and cancer*. International Journal of Developmental Biology, **55**: 879–887.

JARVELAINEN H., SAINIO A., KOULU M., WIGHT T.N., PENTTINEN R., 2009, *Extracellular matrix molecules: potential targets in pharmacotherapy*. Pharmacology Reviews, **61**: 198–223.

KAVASI R.M., NEAGU M., CONSTANTIN C., MUNTEANU A., SURCEL M., TSATSAKIS A., TZANAKAKIS G.N., NIKITOVIC D., 2022, *Matrix Effectors in the Pathogenesis of Keratinocyte-Derived Carcinomas*. Frontiers in Medicine (Lausanne), **9**: 879500.

KIMURA T.E., MERRIT A.J., GARROD D.R., 2007, *Calcium-independent desmosomes of keratinocytes are hyper-adhesive*. Journal of Investigative Dermatology, **127**: 775–781.

KOK V.C., YU C.C., 2020, *Cancer-derived exosomes: Their role in cancer biology and biomarker development*. International Journal of Nanomedicine, **15**: 8019–8036.

LEE T.H., D'ASTI E., MAGNUS N., AL-NEDAWI K., MEEHAN B., RAK J., 2011, *Microvesicles as mediators of intercellular communication in cancer – the emerging science of celluar debris*. Seminars in Immunopathology, **33**: 355–467.

LOBIKIN M., CHERNET B., LOBO D., LEVIN M., 2012, *Resting potential, Oncogene-induced tumorigenesis, and metastasis: the bioelectric basis of cancer in vivo*. Physical Biology, **9** (6): 065002.

LUPU M., CARUNTU C., POPA M.I., VOICULESCU V.M., ZURAC S., BODA D., 2019, *Vascular patterns in basal cell carcinoma: Dermoscopic, confocal and histopathological perspectives.* Oncology Letters, **17** (5): 4112–4125.

MACKENZIE I.C., 1994, *The keratinocyte handbook, Epithelial-mesenchymal interactions in the development and maintenance of epithelial tissue.* Cambridge University Press, 584 pp.

MANETTI M., ROSA I., MESSERINI L., GUIDUCCI S., MATUCCI-CERINIC M., IBBA-MANNESCHI L., 2014, *A loss of telocytes accompanies fibrosis of multiple organs in systemic sclerosis*. Journal of Cellular and Molecular Medicine, **18** (2): 253–262.

MANETTI M., ROSA I., MESSERINI L., IBBA-MANNESCHI L., 2015, *Telocytes are reduced during fibrotic remodelling of the colonic wall in ulcerative colitis*. Journal of Cellular and Molecular Medicine, **19** (1): 62–73.

MANOLE C.G., GHERGHICEANU M., SIMIONESCU O., 2015, *Telocyte dynamics in psoriasis*. Journal of Cellular and Molecular Medicine, **22** (10): 1504–1519.

MARIONNET C., PIERRARD C., VIOUX-CHAGNOLEAU C., SOK J., ASSELINEAU D., BERNERD F., 2006, *Interactions between fibroblasts and keratinocytes in morphogenesis of dermal epidermal junction in a model of reconstructed skin.* Journal of Investigative Dermatology, **126**: 971–979.

MATHIVANAN S., JI H., SIMPSON R.J., 2010, *Exosomes: extracellular important in intercellular communication*, Journal of Proteomics, **73** (10): 1907–1920.

MCDANIEL B., BADRI T., STEELE R.B., 2021, *Basal Cell Carcinoma*. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; PMID: 29494046.

McDONALD M.D., BALUK P., 2002, *Significance of blood vessel leakiness in cancer*. Cancer Research, **62**: 5381–5385.

MIRANCEA N., MIRANCEA D., FUSENIG N., BREITKREUTZ D., 2001, *Immunoelectron microscopic detection of the molecular components of the hemidesmosomal junction*. Proceedings of the Romanian Academy, **3** (2): 123–130.

MIRANCEA N., HAUSSER I., METZE D., STARK H.-J., BOUKAMP P., BREITKREUTZ D., 2007, *Junctional basement membrane anomalies of skin and mucosa in lipoid proteinosis (hyalinosis cutis et mucosae).* Journal of Dermatological Science, **45** (3): 175–185.

MIRANCEA N., MIRANCEA D., 2010a, Ultrastructura celulelor şi ţesuturilor, Editura Ars Docendi, Universitatea Bucureşti, 703 pp.

MIRANCEA N., MIRANCEA D., 2010b, *Rolul interacţiunilor gene-mediu în etiologia cancerului*. Pp. 241–247. *În*: *Impactul factorilor de mediu aupra biodiversităţii* (M. Enache, Ed.), Editura Academiei Române, Bucureşti, 304 pp.

MIRANCEA N., MIRANCEA G.-V., MOROȘANU A.-M., JURAVLE F.D., MIRANCEA D., 2010, *Infrastructural and molecular tumor-extracellular matrix interface alterations in the basocellular and squamous cell carcinoma development*. Romanian Journal of Biology-Zoology, **55** (1): 95–109.

MIRANCEA N., MOROȘANU A.-M., MIRANCEA G.-V., JURAVLE F.D., MANOIU V.S., 2013, *Infrastructure of the telocytes from tumor stroma in the skin basal and squamous cell carcinomas*. Romanian Journal of Morphology and Embryology, **54** (4): 1025–1037.

MIRANCEA G.V., MOROȘANU A.M., CARNICIU S., DIMA S., BACALBAȘA N., POPESCU I., IONESCU-TÎRGOVIȘTE C., MIRANCEA N., 2014, *Relevant infrastructural alterations in a pancreatic neuroendocrine tumor: an insulinoma case.* Romanian Journal of Morphology and Embryology, **55** (2 Suppl): 659–668.

MIRANCEA N., DĂNĂILĂ L., MIRANCEA G-V., MOROȘANU A-M., 2022, *Telocytes in the human brain tumor. Infrastructure and relationships of the telocytes inside of the brain tumor*. Proceedings of the Romanian Academy, Series B, 24 (2): 247–265.

MONTI N., VERNA R., PIOMBAROLO A., QUERQUI A., BIZZARRI M., FEDELI V., 2022, *Paradoxical behavior of oncogenes undermines the Somatic Mutation Theory. Biomolecules*. 12, 662. https://doi.org/10.3390/ biom12050662.

MORGADO F.N., DA SILVA A.V.A., PORROZZI R., 2020, *Infectious diseases and the lymphoid extracellular matrix remodeling: A focus on conduit system*. Cells, **9** (3): 725.

MOROȘANU A.-M., MIRANCEA G.-V., JURAVLE F.D., MIRANCEA N., 2013, *Cell-cell and cell-extracellular matrix junctions alteration are prerequisite for tumor progression in the human basal cell carcinoma*. Romanian Journal of Biology- Zoology, **58** (1): 67–83.

MOROȘANU A.-M., 2019, *Investigaţii privind alterările ultrastructurale şi moleculare ale interfeţei tumoră-stromă peritumorală în carcinomul bazocelular şi carcinomul scuamocelular. (Investigations on ultrastructural and molecular alterations of the tumor-peritumoral stroma interface in basal cell carcinoma and squamous cell carcinoma).* PhD Thesis, Romanian Academy, Institute of Biology Bucharest, 298 pp.

MUELLER M.M., FUSENIG N.E., 2004, *Friends or foes – bipolar effect of the tumor stroma in cancer*. Nature Reviews Cancer, **4**: 839–849.

NEVE A., CANTATORE F.P., MARUOTTI N., CORRADO A., RIBATTI D., 2014, *Extracellular matrix modulates angiogenesis in physiological and pathological conditions*. BioMed Research International, vol. 2014, article ID 756078, 10 pages, doi:10.1155/2014/756078.

NOVKOVIC M., ONDER L., BOCHAROV G., LUDEWIG B., 2020, *Topological structure and robustness of the lymph node conduit system.* Cell Reports, **30** (3): 893–904.

POPESCU L.M., GHERGHICEANU M., CREŢOIU D., RADU E., 2005, *The connective connection: interstitial cells of Cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells. Electron microscope study in situ*. Journal of Cellular and Molecular Medicine, **9** (3): 714–730.

POPESCU L.M., FAUSSONE-PELLEGRINI M.S., 2010, *Telocytes - a case of serendipity: the winding way from interstitial cells of Cajal (ICC), via interstitial Cajal-like cells (ICLC) to telocytes*. Journal of Cellular and Molecular Medicine, **14**: 729–740.

POPESCU L.M., MANOLE C.G., GHERGHICEANU M., ARDELEAN A., NICOLESCU M.I., HINESCU M.E., KOSTIN S., 2010, *Telocytes in human epicardium*. Journal of Cellular and Molecular Medicine, **14** (8): 2085–2093.

POPESCU L.M., 2011, *The tandem: telocytes-stem cells*. International Journal of Biology and Biomedical Engineering, **5** (2): 83-92.

POPESCU L.M., NICOLESCU M.I., 2013, *Resident stem cells and regenerative therapy, Telocytes and stem cells.* Academic Press, 270 pp.

REITER O., MIMOUNI I., DUSZA S., HALPERN A.C., LESHEM Y.A., MARGHOOB A.A., 2021, *Dermoscopic features of basal cell carcinoma and its subtypes: A systematic review*. Journal of American Academy of Dermatology, **85** (3): 653–664.

RICHTER M., KOSTIN S., 2015, *The failing human heart is characterized by decreased numbers of telocytes as result of apoptosis and altered extracellular matrix composition.* Journal of Cellular and Molecular Medicine, **20** (10): 1–10.

ROATESI I., RADU B.M., CRETOIU D., CRETOIU S.M., 2015, *Uterine telocytes: a review of current knowledge.* Biology of Reproduction, **93** (1): 1–13.

ROOZENDAAL R., MEBIUS R.E., KRAAL G., 2008, *The conduit system of the lymph node*. International Immunology, **20** (12): 1483–1487.

ROOZENDAAL R., MEMPEL T.R., PITCHER L.A., GONZALES S.F., VERSCHOOR A., MEBIUS R.E., VON ADRIAN U.H., CARROL M.C., 2009, *Conduits mediate transport of low-molecular-weight antigen to lymph node follicles.* Immunity, **30**: 264–276.

RUSU M.C., MIRANCEA N., MĂNOIU V.S., VÂLCU M., NICOLESCU M.I., PĂDURARU D., 2012a, *Skin telocytes*. Annals of Anatomy, **194** (4): 359–367.

RUSU M.C., POP F., HOSTIUC S., CURCA C.G., JIANU A.M., PĂDURARU D., 2012b, *Telocytes from networks in normal cardiac tissue*. Histology and Histopathology, **27** (6): 807-816.

RUSU M.C., NICOLESCU M.I., JIANU A.M., LIGHEZAN R., MĂNOIU V.S., PĂDURARU D., 2012c, *Esophageal telocytes and hybrid morphologies*. Cell Biology International, **36** (12): 1079-1088.

RUSU M.C., JIANU A.M., MIRANCEA N., DIDILESCU A.C., MĂNOIU V.S., PĂDURARU D., 2012d, *Tracheal telocytes*. Journal of Cellular and Molecular Medicine, **16** (2): 401–405.

SIXT M., KANAZAWA N., SELG M., SAMSON T., ROOS G., REINHARDT D.P., PABST R., LUTZ M.B., SOROKIN L., 2005, *The conduit system transport soluble antigen from the afferent lymph to resident dendritic cells in the T cell area of the lymph node*. Immunity, **22**: 19–29.

SALDANHA P., SHANTHALA P.R., UPADHAYA K., 2015, *Cutaneous basal cell carcinoma: a morphologic spectrum*. Archives of Medical Health Science, **3**: 24–28.

SMYTHIES J., 2015, *Intercellular signaling in cancer – the SMT ant TOFT hypotheses, exosomes, telocytes and metastases: is the messenger in the message?* Journal of Cancer, **6** (7): 604–609.

SMYTHIES J., EDELSTEIN L., 2014, *Telocytes, exosomes, gap junctions and the cytoskeleton: the makings of a primitive nervous system?* Frontiers in Cellular Neuroscience, **7** (278): 1–3.

SONNENSCHEIN C., SOTO A.M., 2000, *Somatic mutation theory of carcinogenesis: why it should be dropped and replaced*. Molecular Carcinogenesis, **29** (4): 205–211.

SONNENSCHEIN C., SOTO A.M., 2014, *Le cancer et ses genes insaisissables*. Medicine/Sciences, **30**: 688–692.

SOTO A.M., SONNENSCHEIN C., 2004, *Emergentism as a default: Cancer as a problem of tissue organization*. Journal of Biosciences, **30**: 103–181.

STARK H.-J., MAAS-SZABOVSKY N., SMOLA H., BREITKREUTZ D., MIRANCEA N., FUSENIG N.E., 2001, C*ultured human keratinocytes and tissue engineered skin substitutes, Organotypic keratinocyte-fibroblast cocultures*:*in vitro skin equivalents to study the molecular mechanisms of cutaneous regeneration.* Thieme Verlag, Stuttgart, New York, 363 pp.

STRATMAN N.A., MALOTTE M.K., MAHAN D.R., DAVIS J.M., DAVIS E.G., 2009, *Pericyte recruitment during vasculogenic tube assembly stimulates endothelial basement membrane matrix formation.* Blood, **114** (24): 5091–5101.

STRATMAN N.A., DAVIS E.G., 2012, *Endothelial cell-pericyte interactions stimulate basement membrane assembly: Influence on vascular tube remodeling, maturation and stabilization.* Microscopy and Microanalysis, **18** (1): 68–80.

TANESE K., 2019, *Diagnosis and management of basal cell carcinoma*. Current Treatment Options in Oncology, **20**: 13.

TOZER G.M., KANTHOU C., BAGULEY B.C., 2005, *Disrupting tumor blood vessels.* Nature Review Cancer, **5** (6): 423–435.

YANG J., CHI C., LIU Z., YANG G., SHEN Z.-J., YANG X.-J., 2015a, *Ultrastructure damage of oviduct telocytes in rat model of acute salpingitis*. Journal of Cellular and Molecular Medicine, **19** (7): 1720–1728.

YANG X.-J., YANG J., LIU Z., YANG G., SHEN Z.-J., 2015b, *Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility*. Journal of Cellular and Molecular Medicine, **19** (2): 252–462.

Received April 23, 2022

[*]*Institute of Biology Bucharest of Romanian Academy, 296 Splaiul Independenței, 060031 Bucharest, POBox 56-53*
[**]*Clinic of Neurosurgery, National Institute of Neurosurgery and Neurovascular Diseases, 10-12 Soseaua Berceni sector 4, Bucharest, Romania.*
[***]*"St Pantelimon" Emergency Hospital, Bucharest, Romania 340 – 342 Pantelimon St., Bucharest, Romania*
[****] *CMDTAMP, Department of Plastic Surgery, Bucharest, Romania.*
[*] e-mail: nick_mirancea@yahoo.com