Chapter 10
Presence of Telocytes in a Non-innervated Organ: The Placenta

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Abstract This chapter discusses the relationship between failure in placentation and the subsequent alterations in the normal structure of the placenta. Interstitial Cajal-like cells (ICLC) were observed for the first time in the human placenta in 2007 and later were named telocytes. Strong evidence confirms that in the placental chorionic villi, TC are located strategically between the smooth muscle cells (SMC) of the fetal blood vessel wall and the stromal myofibroblasts. As the placenta is a non-innervated organ and considering the strategic position of telocytes in chorionic villi, it has been postulated that their function would be related to signal transduction mechanisms involved in the regulation of the blood flow in the fetal vessels, as well as in the shortening/lengthening of the chorionic villi providing the necessary rhythmicity to the process of maternal/fetal metabolic exchange. In this context, telocytes represent part of a functional triad: "SMC of fetal blood vessel-telocyte-myofibroblast." This triad takes part in the regulation of fetal growth and development via transport of nutrients and gases. This chapter also discusses the alterations in the metabolic maternal–fetal exchange, leading to intrauterine growth retardation and preeclampsia. Additionally, the apoptosis undergoing in the preeclamptic hypoxic placenta affects all the chorionic villi cells, including telocytes and myofibroblast, and not only trophoblast, as it has been so far considered. In consequence, we proposed that apoptosis affects the triad structure and alters the placental function, subsequently affecting the normal fetal growth and development.

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Abbreviations

CTB	Cytotrophoblast
EVT	Extravillous trophoblast
ICC	Interstitial cells of Cajal
ICLC	Interstitial Cajal-like cells
IUGR	Intrauterine growth restriction
NO	Nitric oxide
PE	Preeclampsia
ROS	Reactive oxygen species
SMC	Smooth muscle cells
STB	Syncytiotrophoblast
TC	Telocytes
TP	Telopode
UL-vWF	Ultra-large vWB multimers
VEGF	Vascular endothelial growth factor

10.1 Telocytes

Ramón y Cajal, the eminent Spanish neuropathologist of the nineteenth century, discovered a particular cell type in the gut, which he named "interstitial neuron." In the early 1970s, electron microscopy studies established that this interstitial cell type did not correspond to neurons and, consequently, were renamed "interstitial cells of Cajal" (ICC) [1]. It is now widely accepted that in the gut, the ICC are pacemaker cells involved in the regulation of gastrointestinal motility [2, 3]. ICC were also found outside the gastrointestinal tract and were named "interstitial Cajal-like cells" (ICLC). An example of this is the mammary gland [4], where ICLC were found in the intralobular stroma and were identified by methylene blue vital staining and c-kit immunoreactivity [5]. Later, ICLC were also found in many other human organs such as in the fallopian tube [6], gallbladder [7], placenta [8, 9], etc. Due to all these confusing names, Popescu and Faussone-Pellegrini [10] proposed the term telocytes (TC) for these cells.

The most striking ultrastructural feature of TC is that they possess few and long cytoplasmic projections emerging from an elongated cell body, with small perinuclear cytoplasm and oval nucleus, presenting one or more nucleoli [10]. Cell-to-cell communication between TC occurs through the cytoplasmic's very long moniliform prolongations called telopodes (TP), frequently two to three per cell. The TP present thin fibrillar-like segments called podomers, and dilated cistern-like regions denoted as podoms. Mitochondria and endoplasmic reticulum cisternae are accumulated inside podoms [8, 9]. In addition, homocellular junctions correspond to TC communication established between telopodes, and heterocellular junctions to those established with other cell types. Additionally, these junctions could also be established with the surrounding connective tissue (stromal synapses), and metabolite signaling

can be released via microvesicles or exosomes [9]. Furthermore, the expression of c-kit/CD117 is commonly accepted as a specific marker for TC, while vimentin expression is considered as an alternative or supplementary marker [8].

10.2 Placental Telocytes

For the first time in 2007, Suciu et al. [8] reported that TC were present in the extra-embryonic mesoderm of the villi from the human term placenta. Placental TC were immunohistochemically positive for the following markers: vimentin, c-kit, CD34, VEGF, caveolin-1 and iNOS, αSMC, neuron-specific enolase, S-100, and nestin [9]. The light microscopy study of Suciu et al. [8] on semithin sections of human term placenta demonstrated that TC were easily identifiable as cells with long cellular processes (TP) that surround blood vessels, or extend into the connective tissue beneath the trophoblast, or were interposed between arterioles and the trophoblast basement membrane, in both large, peripheral stem villi and small stem villi. The authors also proposed that the presence of TP suggests a juxta- and/or paracrine activity with immunoreactive cells. These TP were connected by gap junctions forming a network extending into the placental stroma between SMC layers of large blood vessels and myofibroblasts [8, 9, 11]. The former authors considered "that these cells may be involved in tissue remodelling and, since the placenta is a non-innervated organ, they may also intervene in blood flow regulation." Regarding their disposition, myofibroblast are arranged in parallel to the longitudinal axis of the anchoring and stem villi [12, 13]. Even if no distinct junctions between TC and myofibroblasts are apparent, the close contact between them suggests some sort of communication. Based on the placental lack of innervation and the strategic position of TC in placental villi [8, 9], Bosco et al. [11] have proposed to consider TC as placental pacemakers. However, in order to avoid any possible misinterpretation, it seems advisable to reserve the pacemaker denomination for the gastrointestinal ICC [3] and consider placental TC related to cellular signaling [9, 14].

Studies from Nicolescu and Popescu [15] and Bosco et al. [16] in the pancreas, an organ where there is no presence of muscle layers, have suggested that TC may constitute the pancreatic pacemaker, considering the strategic position of these cells between neurons and pancreatic exocrine ducts, as well as between neurons and blood vessels, thus providing rhythmicity to the exocrine ducts and flow regulation in the pancreatic blood vessels.

10.3 Placental Telocytes Origin

It has been demonstrated that normal placental development ensures normal fetal development and growth [17]. All the events involved are highly related to each other and are susceptible to the effects of intra- and extraplacental environmental

factors, including the nutritional status of the mother and nutrient intake during pregnancy [18, 19].

As we previously described, the first fetal–placental villi develops as trophoblast sprouts, an epithelial tissue subsequently invaded by extraembryonic mesoderm, forming the secondary villi which are then transformed, by vasculogenesis, into tertiary villi [19]. Due to the fact that TC have mesodermal origin, which has been immunohistochemically evidenced by the presence of vimentin-positive cells [9, 14] have postulated that they probably differentiated from mesenchymal cells of the mesoderm present in the secondary and tertiary villi.

10.4 Placenta

The placenta is the site where the physiological exchange between the mother and the fetus occurs. Placental function is to transfers nutrients to the fetus, excrete waste products into the maternal blood, and modify maternal metabolism at different stages of pregnancy, via hormones [20]. Therefore, it is reasonable to assume that the placenta functions as a lung, gastrointestinal tract, kidney, liver, as well as an endocrine organ for the fetus [20, 21]. Additionally, the placenta constitutes an immunological barrier between the fetus and the mother and produces and secretes different hormones [21], as well as a variety of cytokines and signaling molecules [22]. The events that characterize normal placental growth are considered to be important determinants of fetal growth and development. All of these events are likely interrelated and susceptible to the effects of many environmental factors, including maternal food intake, both before and during pregnancy [18].

The blastocyst is an embryonic structure constituted by an inner cell mass, the embryoblast, formed at 4–5 days of gestation, surrounded by the external trophoblast. The cells of the trophoblast layer differentiate into two layers, an inner cytotrophoblast or epithelial stem cells (CTB) and an outer syncytiotrophoblast (STB), both of which contribute to the formation of the villi and ultimately the placenta [19]. The stem villi, which represent the central branches of the villous trees, are characterized by a loose connective tissue or stroma in which the fetal arteries and veins are embedded [19].

Human placenta development depends critically on the differentiation of CTB [23], process for which two differentiation pathways exist. In one, CTB remains in the fetal compartment and fuse themselves to form multinucleate STB that cover the floating chorionic villi. These villi, which are in direct contact with the maternal blood in the intervillous space, perform the nutrient and gas exchange for the fetus [24, 25]. In the other pathway, a subset of CTB in anchoring chorionic villi aggregate into cell columns that attach to the uterine wall [26]. From there, CTB differentiated to extravillous trophoblasts (EVT) ulteriorly invading the uterine arteries walls [23–25]. As a result, these cells replace the endothelial and muscular linings of uterine spiral arteries, a process that initiates maternal blood flow to the placenta and greatly enlarges the diameter and low resistance of

maternal spiral arteries, thereby increasing blood flow to the placenta and allowing an adequate supply of oxygen and nutrients to the growing fetus [26- 28]. Insufficient EVT invasion contributes to the development of preeclampsia (PE), which often results in fetal intrauterine growth restriction (IUGR), maternal hypertension, and proteinuria [28]. This insufficient EVT invasion is associated with a significant reduction in the uteroplacental blood flow, developing placental hypoxia which in turn results in further elevated oxidative stress and apoptosis, as observed in PE placentas [29–32].

10.5 Placenta Oxidative-Nitrosative Stress

Pregnancy itself is a condition of increased susceptibility to oxidative stress arising from the increased metabolic activity in placental mitochondria and reduced scavenging power of antioxidants [33]. The production of reactive oxygen species (ROS) within the fetal–placental unit induces cellular damage by acting on protein and lipids. ROS form as a natural product of the normal metabolism of oxygen and generate potentially superoxide anion, hydrogen peroxide, and hydroxyl radical [34].

Although the cause of PE still remains unknown, it has been proposed that enhanced oxidative stress is a basic component of this condition that could provide the connection between abnormal placentation and the maternal syndrome [35, 36]. Oxidative stress occurs when there is an imbalance between the production of ROS and the ability of the biological system to readily detoxify these reactive intermediates or easily repair the resulting damage [37, 38].

The placenta also produces nitric oxide (NO) [39], giving rise to another local source of free radicals, likely contributing to endothelial dysfunction [30]. In a placental environment where superoxide anion and NO are present in abundance, the interaction of the two chemical species inevitably will yield peroxynitrite, a potent prooxidant which also increases the oxidative stress (in this condition defined as nitrosative stress) observed in PE placenta [40]. As the placenta is a non-innervated organ [14], its blood flow must be regulated by autocrine/paracrine factors produced in the organ such as NO [34]. A decrease in NO availability could adversely affect placental blood flow regulation, which could, in turn, account for the abnormal fetal development [30].

10.6 Myofibroblast Placental Function

The myofibroblast are cells located intermediately between fibroblasts and smooth muscle cells. They exhibit an important cytoplasmic microfilamentous apparatus such as bundles of actin microfilaments with associated contractile proteins such as non-muscle myosin [41–44]. Hence, these cells are considered to be specialized contractile fibroblast with an important role in establishing tension. By scanning

electron microscopy, it has been demonstrated that the stellate form of myofibroblast-like cells in placental villi and their tendency to establish a three-dimensional networks in this organ [13, 45, 46] require contractile structures to generate the necessary force for blood propulsion [47].

It has been suggested that the contraction of myofibroblast adjusts the blood flow in fetal vessels and increases the turgor, imparting mechanical stability to the villous tree in the maternal bloodstream [12]. It has also been proposed that contraction of longitudinally arranged myofibroblasts within anchoring villi may influence the length and width of the intervillous space, thus regulating maternal intervillous blood pressure [48, 49]. The stimulus for this type of contraction has not yet been established because the placenta is a non-innervated organ, but Suciu et al. [9, 14] have proposed that TC function would be related to mechanisms of signal transduction to myofibroblast involved in the regulation of the blood flow in fetal vessels, as well as in the shortening/lengthening of the chorionic villi. Furthermore, Suciu et al. [8, 9] have also demonstrated that TC were connected by gap junctions in a network extending into the stromal and large blood vessels of the placental myofibroblasts. These authors concluded that the close contact between these cells suggests some sort of communication or coupling. Additionally, it was also demonstrated that TC [9] and myofibroblasts [48] generate NO, which, in turn, may modulate the tone of perivascular contractile sheets.

10.7 Placenta and Telocyte Functions

The placenta provides an excellent model for understanding the relationship between hypoxia, organogenesis (organ development), and angiogenesis (blood vessel development). In order to elucidate the role of hypoxia in the regulation of cellular and organ functions, it is necessary to understand placental development and some placental pathologies.

It is well known that defects in the processes of embryonic implantation and fetal placentation can result in the condition of PE, which occurs in 5–10 % of pregnancies and is responsible for diseases of pregnancy like spontaneous abortion, preterm birth, and IUGR [50]. PE is a multisystem disorder which is a major cause of maternal morbidity and mortality worldwide. The cardinal features of PE are hypertension and proteinuria, clinical signs which are manifested after 20 weeks gestation in women who were not previously known to be hypertensive. Other signs and symptoms include edema and headache, and in severe cases, the condition is associated with seizures (eclampsia), liver and kidney dysfunction, as well as clotting abnormalities [29]. In PE pregnancies, the reduction of the uteroplacental perfusion pressure and the ensuing placental ischemia/hypoxia during late pregnancy may be caused by inadequate EVT invasion of the uterine spiral arteries in the first trimester of pregnancy [27]. Placental ischemia/hypoxia may trigger the release of placental factors that initiate a cascade of cellular and molecular events leading to apoptosis of TC [11] and endothelial and vascular smooth

muscle cell dysfunction [19], thereby increasing vascular resistance and arterial pressure [23, 51–53].

Placental function is to exchange nutrients to the fetus, excrete waste products into the maternal blood, and modify maternal metabolism at different stages of pregnancy via hormones. Therefore, it is plausible to say that the placenta functions in a similar way as the lungs, gastrointestinal tract, kidneys, liver, as well as an endocrine organ for the fetus [19, 21]. In this context, it is important to emphasize that in PE the apoptosis of placental TC [11] affects placental functions related to the regulation of fetal blood flow and the intraplacental blood volume.

Considering that the placenta functions as a lung for the fetus, some authors have postulated in human and mouse lung that besides the conventional role of mechanical support for the TC network, TC's main role in the lung would be related to intercellular communication, proliferation, differentiation, as well as growth of the stem cells and repair mechanisms in injured tissue [54, 55]. The authors based this assumption on the existence, in the human lung, of TC near the stem cell niches in the lung [54], and the existence of TC and their TP in close vicinity of blood capillary and/or nerve fibers [55]. Additionally, Popescu et al. [54] observed TC in the mouse respiratory tree, located in the interstitial space of terminal and respiratory bronchioles, as well as in alveolar ducts in which TPs were connected with alveolar epithelial cells and the vicinity of small blood vessels. This crucial relationship has been also demonstrated in the placental villi, an organ that exchanges gases between mother and fetus. TC and their TP were described in the interstitial space between trophoblast epithelial cells and blood capillary [8, 11]. Taking into account that in PE the TC suffer apoptosis [11, 14], this condition consequently will affect the gases exchange process.

Considering that the placenta also functions as gut due to its absorbing metabolites functions, it is worthwhile to point out that Vannucchi et al. [56] described the presence of TC in the mucosa, submucosa, and muscle coat of the gastrointestinal tract. The authors described that TC formed a three-dimensional network in the submucosa and in the interstitium between muscle layers, and an almost continuous layer at the submucosal borders of muscularis mucosae and circular muscle layer. Moreover, TC encircled muscle bundles, nerve structures, blood vessels, funds of gastric glands, and intestinal crypts. Additionally, Milia et al. [57] found in the normal gut that TC were observed in all the ileal wall layers, from the mucosa to the subserosa, and according to the different disposition in the wall layers, they form a network. On the contrary, in the gut from Crohn's disease, characterized by derangement of the normal disposition of the intestinal walls, these authors observed that TC have disappeared. Milia et al. [57] concluded that due to the 3-D network of TP and their strategic position between immune cells, smooth muscle cells, blood and lymphatic vessels, and nerve endings, the loss of TC might have important pathophysiological implications, contributing to the disorder of the intestinal wall architecture, gut dysmotility, and impaired immune surveillance. In this context, it seems reasonable to assume that placental TC apoptosis observed in PE [11] would affect the regulation of fetal blood flow, the intraplacental blood volume, as well as the shortening/lengthening of the chorionic villi.

In another line of evidence, PE is characterized by a maternal hypercoagulable state and intravascular coagulation, microthromboses in several organs, and impairment of the uteroplacental circulation [58]. The thromboresistance of the placental endothelium is maintained as long as natural anticoagulant pathways are functionally present in the endothelial plasma membrane [59, 60]. The main anticoagulant pathway in the placenta is mediated by thrombomodulin (TM), an endothelial cell-surface glycoprotein [61]. In this regard, Bosco et al.[32] found immunohistochemical expression of TM in the stromal cells of placental villi of PE, and these authors concluded that the presence of TM in stromal cells may suggest a role in preserving the function of these cells in villous contractility and modulation of the intervillous space affecting both maternal and fetal–placental circulation. This is further supported by the lack of IURG in these PE cases. These authors further postulate that TM-positive placental stromal cells correspond to TC and myofibroblasts (Fig.10.1a) and that their functions and communication between them favor the metabolic exchange and protect the organ against the hypercoagulable state. The lack of autonomic innervations in the placenta implicates that the blood flow must be regulated by humoral mechanisms and by autocrine/paracrine factors produced in the organ [33]. The main vasoactive agent, NO, is secreted by the endothelium and by stromal placental TC and myofibroblasts, a fact that further supports this idea [9, 12]. Additionally, Kroll and Waltenberger [62] found that vascular endothelial growth factor (VEGF) enhances the activity of endothelial NOS (eNOS) and inducible NOS (iNOS) in endothelial cells via KDR receptor. VEGF can induce the production of NO in the placenta, but an excess of NO and superoxide anion induces the formation of an excess of peroxynitrite [63], thus increasing the nitrosative stress. Therefore, the increased VEGF expression observed by Parra-Cordero et al. [64] and Bosco et al. [65] in the stromal TC and myofibroblasts of PE placentas (Fig. 10.1b) suggests an increase in the NO production and subsequently an increase in peroxynitrite formation (Fig. 10.1c) and finally an increase of the apoptotic programmed cell death, evidenced by a greater expression of the proapoptotic protein BAX in TC and myofibroblast (Fig. 10.1d). The apoptosis in TC causes loss of their TP [11, 66] and hence of the intercellular connections between the myofibroblasts and smooth muscle cells from the blood vessels.

Bosco et al. [65] have also suggested that the oxidative and nitrosative stress developed in PE placentas is followed by a significant increase of maternal plasma vWF levels. Additionally, Dong et al. [67] and Li et al. [68] demonstrated that ultra-large vWF multimers (UL-vWF), unlike plasma forms of vWF secreted by stimulated endothelial cells, are anchored to the endothelial surface as extraordinarily long string-like structures capable of binding platelets. These UL-vWF multimeric strings were rapidly cleaved in the presence of the normal plasma metalloprotease ADAMTS-13, limiting thrombus growth [68–70]. These multimers are also more reactive with platelet receptors in the presence of high fluid shear stress [69]. Furthermore, Lancellotti et al. [71] found that peroxynitrite oxidizes the vWF-cleaving metalloprotease ADAMTS-13, thus contributing to the prothrombotic effects. Additionally, Myatt et al. [40] and Bosco et al. [62] also reported the presence of nitrotyrosine residues in the stromal cell of PE placentas. Taking all these

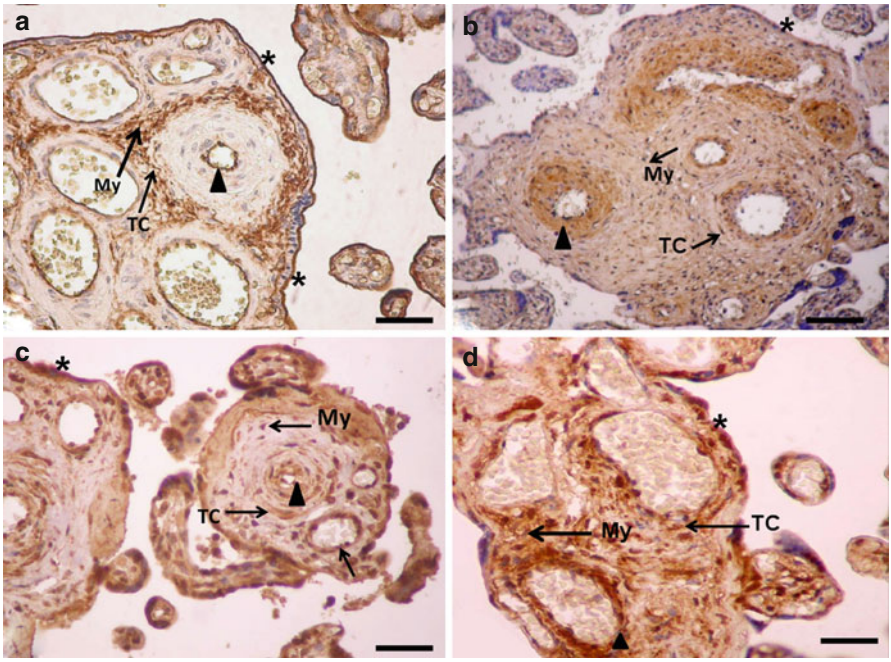

Fig. 10.1 Placentas of preeclamptic women. (**a**) Anti-thrombomodulin monoclonal antibody expression in PE placental villi. An intense immunohistochemical labeling in the apical zone of the syncytiotrophoblast (*), endothelium (*arrow head*), telocytes (*TC*), and myofibroblast (*My*) is displayed. (**b**) Antihuman VEGF165 monoclonal antibody labeling. VEGF immunostaining was moderate in telocytes (*TC*), myofibroblast (*My*), and syncytiotrophoblast (*) and intense in the muscular layer of the arteries (*arrow head*) and veins of the stem villi. (**c**) Anti-nitrotyrosine residues rabbit polyclonal antibody labeling. The labeling was intense in telocytes (*TC*), myofibroblast (*My*), syncytiotrophoblast (*), and the muscular layer of the arterioles (*arrow head*) and the veins of the stem villi. (**d**) Anti-BAX rabbit polyclonal antibody labeling. The mark for the proapoptotic protein BAX was intense in the syncytiotrophoblast (*), telocytes (*TC*), myofibroblast (*My*), and the muscular layer (*arrow head*) of the fetal blood of the stem villi. (**a**) Calibration bar 50 μm. Antibody working dilution=1:50. (**b**) Calibration bar 70 μm. Antibody working dilution=1:50. (**c**) Calibration bars 60 μm. Antibody working dilution=1:100. (**d**) Calibration bars 60 μm. Antibody working dilution=1:100. Original magnification: 400× in (**a**, **c**) and (**d**); 200× in (**b**)

evidences into account, we consider it plausible to postulate that the maternal hypercoagulable state due to the impairment of ADAMTS-13 alters the normal longitudinal contraction/relaxation of the villi, a mechanism through which TC modulate the rhythmicity of the process.

In a model of cardiac hypoxia, Kostin [66] found that increased interstitial fibrosis and fibrillar collagen lead to TC cell death via apoptosis, with shrinkage and shortening of telopodes, and Bosco et al. [11] found a considerable amount of collagen deposits located near the telopodes of TC in PE placentas. Apoptosis of placental TC from the chorionic villi leads to alteration of the TP and therefore to a possible loss of the synaptic-like connections that relate TC with themselves, with myofibroblasts and with smooth muscle cells from fetal blood vessels. All these

events point to a decrease of the contact surface of the villi with the maternal blood in the intervillous space, with a consequent reduction of maternal metabolic contribution to the fetus.

10.8 Final Remarks

Finally, we postulate that SMC of fetal blood vessels, TC, and myofibroblast act as a triad and that the coordinate function of TC contribute to the normal placental function. Apoptosis of placental TC from the chorionic villi leads to alteration of the telopodes and therefore to a possible loss of the synaptic-like connections. The loss of these synapses would lead to loss of the TC triad function probably related to signal transduction mechanisms involved in the regulation of the fetal vessels blood flow, as well as in the shortening/lengthening of the chorionic villi, providing the necessary rhythmicity to the process of maternal/fetal metabolic exchange.

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