The significance of the time and space distribution of the fibrinoid substance during the genesis and evolution of human placenta. Forensic implications

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Abstract: The authors made a micro anatomic evaluation of the fibrinoid distribution during nidation, placenta formation and phenotype changes undergone by placenta structures in ontogenesis. Based on their personal observations, they considered that the fibrinoid is a multifunctional structural element that plays an important role in the processes of genesis, regenesis and remodeling of the placenta structures during ortology and pathology, carrying a great diagnostic and prognostic value.

Key words: fibrinoid, nidation, placenta formation, intermediate cytotrophoblast

We have been interested in the study of the space and time heterogeneous distribution of the fibrinoid substance during the genesis and evolution of the human placenta, on one side, and on the other side, in the acknowledgement of its implication in the genesis, regenesis, modeling and/or remodeling of the structures inside pars fetalis and maternal hemochorial placenta.

The purpose of this paper was to evaluate the relations of the fibrinoid substance to the villous and non villous trophoblast; these relations stand for numerous processes that ensure placenta adhesion, the regulation of the chorioalantoidian and uterine placenta circulations and last but not least, the placenta structures morphogenesis.

The objective of the study was the micro anatomic analysis of the fibrinoid substance relations to the processes of proliferation, differentiation and invasion of the trophoblast and also to the placenta circulatory systems.

Materials and methods

The present study was achieved on tissue fragments harvested from 245 uterine curettages and from 1250 placenta (150 placentas from the first trimester, 250 placentas from the second and 850 placentas from the third trimester of gestation), registered in the Pathology Laboratory of the Clinic City Hospital Filantropia from Craiova, during 2001-2010.

The tissue fragments were prepared after the routine micro anatomic techniques. The anatomic iconography was accomplished by computerized acquisition and processing of the microscope images.

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Results

The assessment of the space and time distribution of the fibrinoid substance inside the human placenta system is possible by analyzing the complementary processes of nidation and placenta formation, the phenotype changes induced by the invasion of the intermediate trophoblast and last but not least by observing the vessel-fibrinoid and fibrinoid-villosity relations inside mature human placenta.

1. **Micro anatomic analysis of the relations between the fibrinoid substance and decidua layer during nidation**

When examining the serial sections through the tissue fragments harvested by uterine curettage with the 10x microscope objective, we noticed the presence of the fibrinoid substance at the level of decidua epithelial tissue as an eosin homogenous layer in the area of the invaded trophoblast (Fig. 1 A). With the 10x and 20x objectives we identified numerous decidua cells with contiguity relations to the adjacent fibrinoid layer (Fig. 1 A and B). In the proximity of the fibrinoid layer, numerous decidua cells appear without nucleus and with the cytoplasm contiguous with the adjacent fibrinoid (Fig. 1 A and C). Among the decidua cells we identified lymphocytes with a hyper chromatic, spherical nucleus (Fig. 1 D and F). The cytoplasm of decidua cells contains small spherical granules that are well visible by color complement transformation (Fig. 1 F, G, H).

2. **The micro anatomic analysis of the fibrinoid space distribution during the vascular and decidua phenotype transformations determined by the invasion of the intermediate trophoblast**

On the sections stained with Hematoxiline Eosine we identified numerous decidua and vascular phenotype transformations during the placenta formation. With the 4x objective, one can easily observe a thin layer inside the fibrinoid substance that separates the an immature placenta villosity anchoring area from a decidua territory invaded by the intermediate trophoblast that determines phenotype changes of the blood vessels and of the decidua mesenchym (Fig. 2 A). Inside the structure of the immature placenta villosities we pointed the absence of the sinusoid capillary vessels inside the central villosity mesenchym and the existence of a continuity of the villosity cytotrophoblast to the intermediate cytotrophoblast that invades the adjacent decidua (Fig. 2 B). At the 20x objective, the spiral arteries of decidua appear surrounded by giant trophoblast cells (Fig. 2 C). In some parts of the spiral arteries’ walls, there are fibrinoid deposits and intermediate trophoblast cells that achieve intra-arterial trophoblast plugs (Fig. 2 D).

3. **The micro anatomic analysis of the morph genetic synergisms of the placenta villosities inside the fibrinoid non villosity and cytotrophoblast structures**

Analyzing the serial sections through the third trimester placenta, we revealed the existence of fibrinoid bands and intermediate trophoblast cells at the periphery of the non villous structures. The 20 x objective easily shows the presence of the fibrinoid substance in a space limited to the interior by the surrounded mesenchym and to the exterior by a discontinuous trophoblast layer (Fig. 3 A). Equally we noticed a thickening of the arterial wall inside the stem villosities by fibrinoid accumulation (Fig. 3 A). The extra villosity intermediate cytotrophoblast is hyper active and participates at the genesis of immature intermediate villosities (Fig. 3 B and C) with isles of vasculogenesis (Fig. 3 C and D). Some newly formed villosities present a pedicle (Fig. 3 E) and others keep thin bands as a bound to the fibrinoid layer (Fig. 3 F).

4. **Micro anatomic analysis of the vessel-fibrinoid and fibrinoid-villosity tissue relations inside mature human placenta**

While examining with the 4x objective the serial sections through the human mature placenta we described in the area adjacent to the chorial plate, the existence of a fibrinoid substance identified as “Langhans fibrinoid stria” (Fig. 4 A); it expands around the subchorial blood vessels (Fig. 4 A). We spotted the same space distribution of the fibrinoid in the area of the basal plate as “Nitabuch uterine-placenta fibrinoid layer”. In this sector, the fibrinoid substances makes a true adventitia to the blood vessels inside placenta septum (Fig. 4 B). In the inter villosities spaces we pointed fibrinoid bridges between the adjacent placenta villosities that lack of trophoblast (Fig. 4 C-G).
Fig. 1 The genesis of the fibrinoid layer inside the decidua epithelial tissue at the “intermediate trophoblast” implantation site. One can easily notice the structural heterogeneity of the decidua cells that contribute to the fibrinoid formation. 1. Hypertrophic decidua cells; 2. Decidua; 3. Apoptotic decidua cells around the fibrinoid; 4. Decidua fibrinoid layer; 5. Micro compartments inside decidua cells cytoplasm; 6. Lymphocytes; 7. Picnotic nuclei inside decidua cells. Hematoxiline Eosin Stain. Direct light examination (A-E) and after the complement color transition. x 70 (A); x 120 (B); x 280 (C-D).
Fig. 2 The effects of decidua tissue colonization by the “intermediate trophoblast”. The decidua and vascular phenotype changes are evident during the placenta formation. 1. Immature intermediate placenta villosity; 2. Well differentiated fibrinoid layer inside decidua; 3. Spiral arteries colonized by “intermediate trophoblast”; 4. Invading intermediate trophoblast; 5. Giant trophoblast cells; 6. Intra-arterial trophoblast plug. Hematoxiline Eosine Stain. x 70 (A); x 140 (B); x 280 (C, D).
Fig. 3 The differentiation potencies of the extra villous cytotrophoblast inside the extra villous fibrinoid compartments at third trimester placenta. 1. Fibrinoid stria located inside stem villous; 2. Fibrinoid in the muscle tunica of arteries with a partially closed lumen; 3. Terminal villosities developed by the intermediate cytotrophoblast resident in the adjacent fibrinoid stria. Hematoxilin Eosine Stain. x70 (A); x140 (C-F); x280 (B).
Fig. 4 A. The subchorial fibrinoid distribution and its relations to the adjacent vessels. B. The fibrinoid substance in basal plate and its relations to the uterine and placenta blood vessels. The fibrinoid substance appears as the external layer of the blood vessels wall. 

C-G. Inter villosities fibrinoid bridges. 1. Chorial plate; 2. Subchorial fibrinoid; 3. Uterine and placenta blood vessels with fibrinoid adventitia layers; 4. Inter villosities fibrinoid bridges; 5. Fibrinoid around vessels inside stem villosities. Hematoxilin Eosine Stain. x28 (A, B); x280 (C-H).
Discussions

The placenta fibrinoid described by Langhans in 1877 [5] as one of the most important components of human placenta is still in researchers’ attention because of the many problems raised by its genesis, location and role in ortology and pathology. The placenta architectural heterogeneity in ontogenesis is determined on one side by the phenotype changes of the villous and non villous structures as a result of the trophoblast stem cells implementation and on the other side, by the fibrinoid space distribution. The acknowledgement of the time and space relations between the trophoblast and fibrinoid can open new paths for the evaluation of the placenta fibrinoid morph genesis function.

The fibrinoid substance was described as being organized in “layers” inside different placenta structures. Langhans (1877) [5] described fibrinoid deposits inside chorial plate that were later called “Langhans stria”, “Langhans fibrinoid” or “subchorial fibrinoid”.

Inside basal plate, Wolska (1888) [14] and Rohr (1889) [9] identified and described a discontinuous fibrinoid layer known as “Rohr stria”, “Rohr fibrinoid” or “superficial fibrinoid layer”. Nitabuch (1887) [7] noticed the presence of a discontinuous lamella structure at the junction between uterus and placenta; this structure was later identified as “Nitabuch fibrinoid layer”, “Nitabuch fibrinoid” or “uterine-placenta fibrinoid”.

We consider that the genesis and evolution of human placenta are dependent on the fibrinoid substance participation together with the differentiation and invasion of the intermediate trophoblast during the phases of nidation and placenta formation. Although we know that the process of permanent placenta remodeling is being achieved by the replacement of the trophoblast cells that undergo an apoptosis process, the latter’s molecular mechanism still remain unclear. It has been experimentally proven on cell cultures that the placenta villosities from the first trimester of gestation contain two trophoblast populations: the cytrotrophoblast as a precursor of syncitiotrophoblast and the extra villosity cytrotrophoblast. The ability of extra villous cytrotrophoblast to invade decidua layer (interstitial cytrotrophoblast) and to remodel the uterus blood vessels (endovascular cytrotrophoblast), is very well known. A particular attention was submitted to the non villous parts of placenta: chorionic plate, cell columns, placental septa, basal plate, marginal zone and the fibrinoid. The fibrinoid substance is an important component of the placenta non villous parts together with the extra villous trophoblast and the endometrium stroma.

The trophoblast cells from the placenta non villous parts were intensively studied. Scipiades and Burg (1930) [10] initially called them “X cells” because of their disputed origin. The trophoblast liaison was proven by auto X ray studies using 3 H thymidine (Kim and Benirsche, 1971) [3] and histologic and enzyme analysis (Stark and Kaufman, 1971) [12]. Nowadays, the reaction with the anti-keratin antibodies is used to differentiate the extra villous trophoblast cells from decidua cells (Khong et al, 1986 [4]; Muhlhauser et al, 1995) [6]. Consequently, the “X cells” were identified as elements of the extra villous trophoblast (non villous trophoblast or intermediate trophoblast).

Later on, the terminology enriched to state the special non villous locations (interstitial trophoblast, endovascular trophoblast, intra-arterial trophoblast) or to define cytohistologic entities (trophoblastic giant cells, trophocyt, spongiotrophoblast-like cells). Frank and Kaufman (2000) [2] proposed the term of “extravillous trophoblast” for the entire population of trophoblast cells present outside the placenta villosity. Still, during medical practice, the term of “intermediate trophoblast” is used (Kurman et al, 1984) [5].

The identification of trophoblast and villosities is essential for the abortion diagnosis assessment. When the villosities or fetal tissues are not present in the curettage products, one must seek for cells to state the pregnancy status or the trophoblast disease. The cytrotrophoblast elements are considered as germinal cells that give trophoblast cells: syncitium and intermediate trophoblast. The latter develops from cytrotrophoblast on the surface of the villosity or on the non villous structures and appears as “buds” and “columns” at the implantation site.

The dominant location of the intermediate trophoblast is in the nidation sector and thus one can explain why it is sometimes called “extra embryo cytrotrophoblast”. Nowadays the intermediate trophoblast is considered a heterogeneous population of trophoblast cells that include: “villous
intermediate trophoblast”, “intermediate trophoblast from the implantation site” and “chorionic intermediate trophoblast” (Wells et al, 1988 [13]; Shih et al, 1999) [11]. The intermediate trophoblast cells that infiltrate inside decidua basalis are mixed with cells from decidual stroma, glands and blood vessels (Benirschke, 2000) [1]. The location of trophoblast cells inside decidua is not specific and that makes it hard to differentiate them from the decidual cells. One must be noted that the former terminology for the trophoblast infiltrate inside the decidua and miometrum was: “syncitial endometritis”, “syncitial endomiometritis” or “placental giant cell reaction”. None of those terms is correct because we witness a physiologic and not a pathologic inflammatory phenomenon. During the nidation process, the intermediate trophoblast invades the blood vessels wall and determines remarkable phenotype changes (Philippe, 1986) [8]. Vascular involution is a frequent event inside post partum placenta villous systems and is mainly an ischemic process due to fibrinoid deposit formation. The fibrinoid excess can produce a chronic stasis. The absence of trophoblast on large areas is not accompanied by important functional changes (Philippe, 1986) [8]. The reappearance of cytotrophoblast in the third trimester of gestation is frequently signaled in pre eclampsia and in diabetes and represents an anatomic sign of hypoxia. A vascular compression, mainly involving the uterine-placenta veins, was described at the basal plate level.

Conclusions

1. Because of its location and relations, the fibrinoid substance must be considered a structural, multifunctional placenta element that plays a role in blastocyst nidation, in the genesis and evolution of the placenta villous and non villous structures
2. The space distribution and evolution of the fibrinoid substance ensure the structural stability of different placenta compartments
3. The intermediate trophoblast migration inside decidua epithelial tissue is ensured by the synchronous differentiation of the fibrinoid substance as a support of those cells penetration inside the decidua layer.
4. The fibrinoid substance has an important role in the remodeling and regenesis of the placenta structures in the third trimester of gestation, due to the residual capacity of the cytrophoblast.
5. Equally, the fibrinoid substance is implicated in the processes of vessel and angiogenesis.

References