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Special Contribution

Development and Differentiation of the Human Placental Villous Tree

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SUMMARY

This paper presents an overview on the structural aspects of villous development in the human placenta. The differentiation of early villous precursors into 5 different villous types is discussed. Three of the latter, the stem villi, the mature intermediate villi, and the terminal villi are structurally and functionally fully mature villi, with various kinds of functional specialization. The two remaining ones, the mesenchymal villi and the immature intermediate villi until term act as growth zones for the villous trees. The influence of varying oxygen tensions within the intervillous space on villous development is discussed.

INTRODUCTION

The placental villi are the only components of the human placenta which are dually supplied by the maternal as well as by the fetal circulation. In spite of their limited contribution to the total villous volume of about 45 to 55% at term (Schiebler and Kaufmann, 1981), the villi are the main site of the maternofetal as well as the fetomaternal exchange. Moreover, they are the site of production of the majority of placental hormones. All other tissue components, such as chorionic plate, basal plate, cell islands, septa, cell columns, fibrinoid deposits, and extra placental membranes are of marginal functional importance only, and therefore negligible in terms of normal and pathological function of the placenta.

In the following chapters, we will deal with the differentiation of the villous trees into villous types of different structural and functional specialization. Furthermore, the mechanisms and the control of development of the various villous types out of one single precursor type will be described. This concept of villous development is based on several previous publications of our group (Kaufmann et al., 1979; Sen et al., 1979; Kaufmann, 1982; Castellucci and Kaufmann, 1982; Kaufmann, 1985; Kaufmann et al., 1987; Kaufmann et al., 1988; Castellucci et al., 1989).

BASIC VILLOUS MORPHOLOGY

Although the term placenta is characterized by different types of villi with differing structural and functional specializations (Fig. 1), all villi exhibit the same basic structure (Fig. 1c). The villi are covered

Key words: Villous tree (絨毛樹), Stem villi (幹絨毛), Terminal villi (末端絨毛), Intermediate villi (中間絨毛), Capillary growth (毛細血管の発育)

by the trophoblast. This is an epithelium-like surface layer which separates the maternal blood flowing around the villi within the intervillous space, from the villous interior. Unlike other epithelia, the trophoblast is not composed of individual cells, but rather consists of a continuous multinucleated layer of syncytiotrophoblast without any separating cell membranes. Underlying the syncytiotrophoblast, one

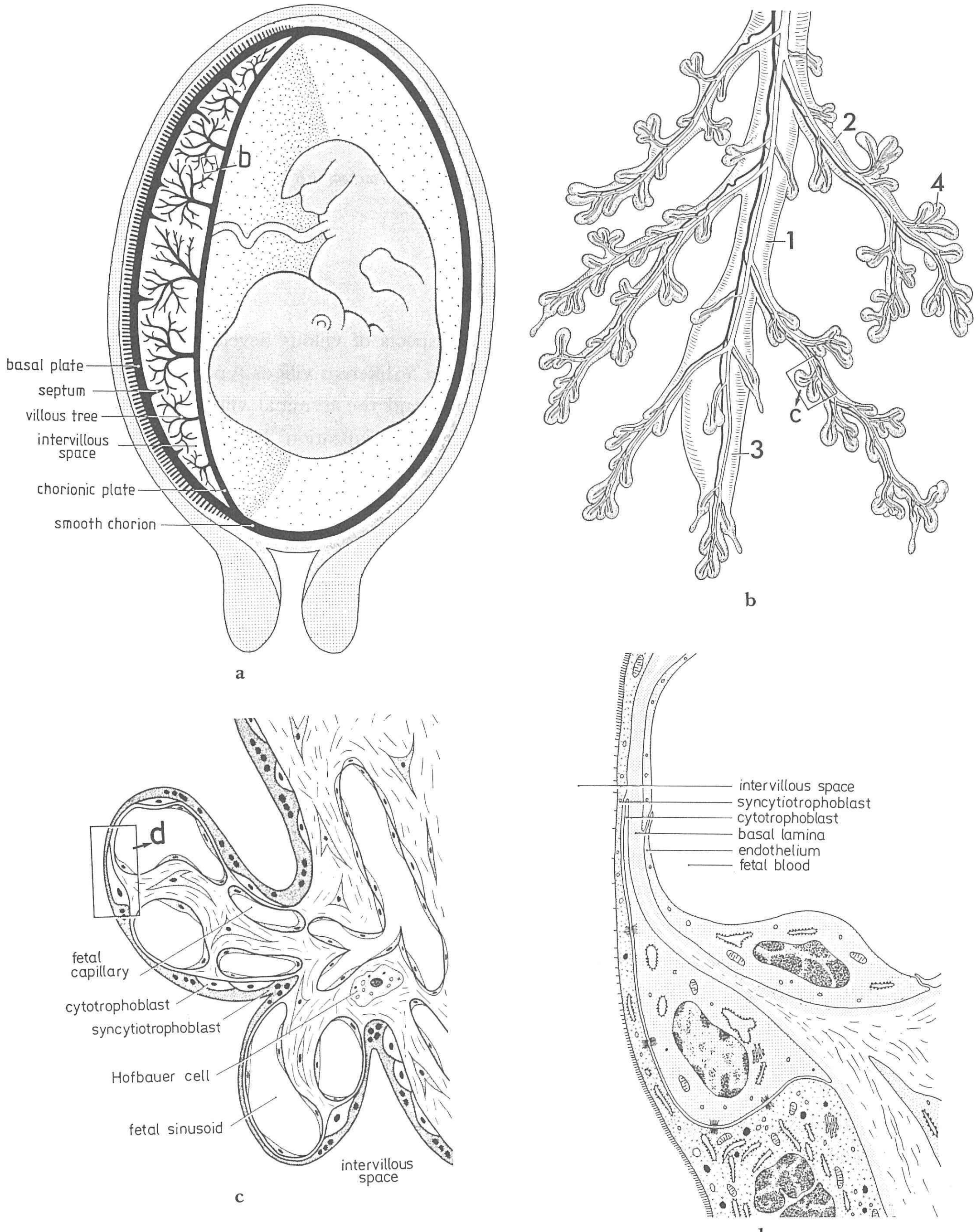

Fig. 1

can find single cytotrophoblastic cells (Langhans cells). They serve as stem cells of the syncytium which in the course of syncytial fusion has lost the potency of mitotic division. By continuous proliferation with subsequent syncytial fusion, the Langhans cells support syncytial growth and regeneration. In normal term placental villi, about 20% of the villous surfaces are bilayered, composed of superficial syncytiotrophoblast with underlying cytotrophoblast.

The trophoblastic basal lamina separates the villous trophoblast from the villous stromal core (Fig. 1d). The core is composed of various types of fixed connective tissue cells, of macrophages (Hofbauer cells), which regulate stromal development, of connective tissue fibers, and of fetal vessels (Fig. 1c). In the villous stems the latter are arteries and veins or arterioles and venules. Within the peripheral ramifications of the villous trees, the fetal vessels are represented by fetal capillaries or so-called sinusoids.

Maternal and fetal blood are separated by the following tissue layers which make up the so-called placental barrier : syncytiotrophoblast, an incomplete layer of cytotrophoblast, the trophoblastic basal lamina, connective tissue space, endothelial basal lamina, and fetal capillary endothelium (Fig. 1d). Since the maternal blood within the intervillous space is directly floating around the villous trophoblastic surfaces without an own vessel wall, the human placenta belongs to the hemochorial type of placentation. Depending on the stage of pregnancy and on the villous type, the connective tissue may be locally reduced to such an extent, that the endothelial and the trophoblastic basal lamina fuse with each other and thus reduce the maternofetal diffusion distance considerably. Such areas of intimate contact among fetal capillaries and trophoblastic cover are called vasculo-syncytial membranes or epithelial plates. In these places the maternofetal diffusion distance may be reduced to 2 micron or less. Within the terminal villous ramifications at term, the mean materno-fetal diffusion distance amounts to about 5 micron.

VILLOUS TYPES OF THE TERM PLACENTA

Depending on the position of each single villous segment within the villous tree, the villous caliber and the stromal structure vary considerably. This is the basis for the classification of the various villous types. However, it must be pointed out, that these are not isolated villi of varying kind of differentiation, but rather differently specialized segments of a continuous villous system (Fig. 2). Because of this, there are continuous transitions among the single villous types which sometimes cause considerable problems when attempting to classify villi. The main structural parameters for villous classification comprise :

a. the type fo fetal vessels (Leiser et al., 1985 ; Kaufmann et al., 1979, 1985, 1988 ; Demir et al., 1989) ;

b. the type and arrangement of fixed connective tissue cells (Kaufmann et al., 1977 ; Martinoli et al.,

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Fig. 1 Basic morphology of human placental villi. The marked areas refer to the higher magnified next figure.

a : roughly simplified longitudinal section across uterus, placenta and membranes in the human. The chorionic sac consisting of placenta (left half) and membranes (right half) is intensely black stained.

b : Very peripheral ramifications of the mature villous tree, consisting of a stem villus (1) which continues in a bulbous immature intermediate villus (3) ; the slender side branches (2) are the mature intermediate villi, the surface of which is densely covered with grape-like terminal villi (4).

c : Highly simplified light microscopical section of two terminal villi, branching off from a mature intermediate villus (right).

d : Schematized electron microscopical section of the placental barrier, demonstrating the typical layers of the latter.

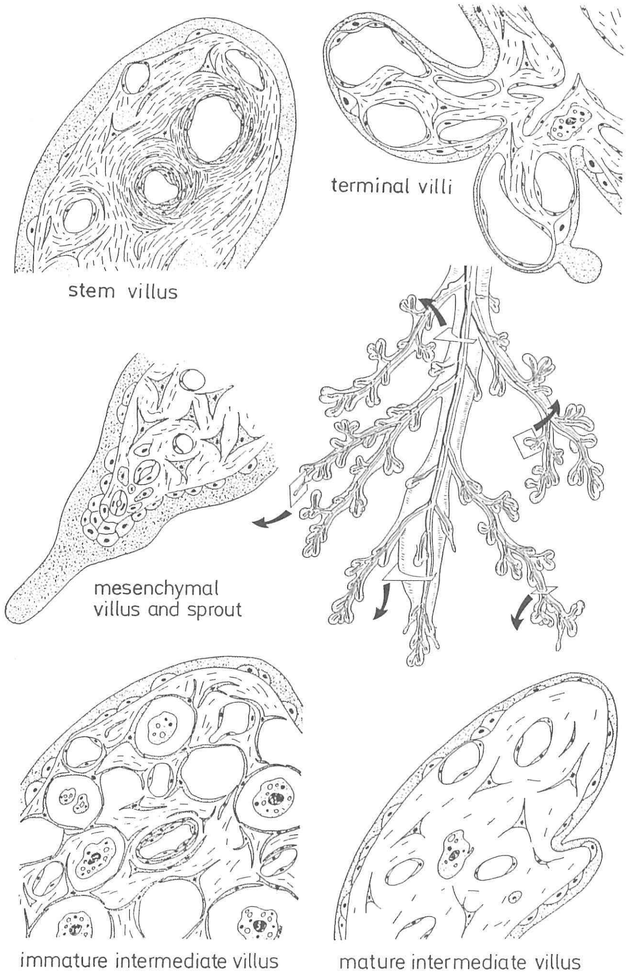

Fig. 2 Roughly simplified schematic drawing of a peripheral part of the mature placental villous tree together with typical cross sections of the various villous types. For further details see text. Modified after Castellucci et al., 1989.

1984) ;

c. the amount and the localization of the macrophages (Castellucci and Kaufmann, 1982) ;

d. the amount of connective tissue fibers (Kaufmann et al., 1977) ;

e. the extension of vasculo-syncytial membranes (Sen et al.,1979).

As will be seen later, most of these paramenters depend on each other. The central paramenter, influencing all the other ones, and thus initiating villous differentiation, seems to be fetal vascularization (Kaufmann et al., 1988).

So far the following 5 villous types have been defined. According to their position within the villous trees and to structural peculiarities, they may even be further subdivided. For further quantitative date we refer to Sen et al. (1979). We have summarized these villous types in a schematic drawing (Fig. 2) which demonstrates a representative peripheral part of a villous tree of the mature placenta.

1. *Stem villi* are characterized by a condensed fibrous stroma and by arteries and veins or arterioles and venules with a light microscopically identifiable media and/or adventitia (Figs. 2, 5). Stem villi are of mechanical importance for the villous trees. They probably participate in fetal blood flow distribution to the more peripheral exchange zone. They amount to about 16% of the total villous volume of the term placenta. The stem villi comprise

a. the main stem (*truncus chorii*) of a villous tree which connects the latter with the chorionic plate ;
b. the following four generations of branchings (*rami chorii* of the 1st to IVth order) which are short, thick branches derived from the truncus already in the vicinity of the chorionic plate ;
c. up to 10 further generations of branchings (*ramuli chorii* of the 1st to 10th order) which are more slender branches, extending into the periphery of the villous trees.
d. A special subgroup of stem villi is represented by the *anchoring villi*. These are ramuli chorii which are connected to the basal plate by a cell cloumn, the latter acting as growth zone for this ramulus as well as for the basal plate.

2. *Mature intermediate villi* are long, slender, peripheral ramifications of the last generation of stem villi. They are characterized by the absence of vessels with a light microscopically identifiable media and/or adventitia, by ample loose connective tissue, poor in fibers, and by richly developed, but largely undilated fetal capillaries (Fig. 2). They normally follow a zig-zag course with numerous slight bents. About 36% of the total villous volume at term are occupied by this villous type. The mature intermediate villi are main sites of hormone production within the villous tree. In addition, they have a considerable share in maternofetal exchange. Moreover, they produce the terminal villi (cf. below) and probably regulate the fetal blood flow of the latter.

3. *Terminal villi* are the final, grape-like ramifications of the mature intermediate villi, characterized by a high degree of fetal capillarization and by the presence of highly dilated capillary segments, the so-called sinusoids (Fig. 2). Their scarce connective tissue is poor in fibers. Larger fetal vessels like arterioles and venules are always lacking. At term about 40% of the villous volume are composed of terminal villi. They represent the main sites of fetomaternal and maternofetal exchange.

4. *Immature intermediate villi* are bulbous villi which are continuations of the stem villi. Like the mature intermediate villi, they are in an intermediate topographical position among stem villi and the most peripheral villous branches. They prevail in immature placentas, but normally persist in small groups in the centers of the villous trees until term. There they amount to 2 to 10% of the total villous volume. At the end of the first trimester, more than 90% of the villous volume are composed of this villous type. Histologically, these villi are characterized by a very peculiar reticular stroma which is composed of roundish stromal channels (Fig. 2). Within the lumina of the latter numerous macrophages can be found. Collagen fibers and fetal vessels are restricted to the small spaces between the stromal channels. The fetall vessels comprise narrow capillaries as well as arterioles and venules of smaller caliber. These villi represent the immature forerunners of stem villi and thus act as growth zones for the villous stem system.

5. *Mesenchymal villi* are the most primitive villi. Structurally, they exhibit a primitive mesenchymal stroma which is only poorly capillarized. Larger fetal vessels are completely absent. At their tips, they continue into massive trophoblastic sprouts (Fig. 2). Numerous mitoses within the stroma as well as in the cytotrophoblast, the latter occupying more than half of the villous surface, indicate that these are highly proliferative villi. They prevail in the first stages of pregnancy where they are forerunners of immature intermediate villi. In later stages of pregnancy they are inconspicuous, mostly small and slender structures which can be found along the surface of the immature intermediate villi or at the tips of mature intermediate villi. They amount to less than 1% of the total villous volume at term. Also in this stage, they act as zones of villous proliferation and branching.

DEVELOPMENT OF THE VILLOUS TREES

The mechanisms of villous maturation sofar have attracted only little attention since they seemed to

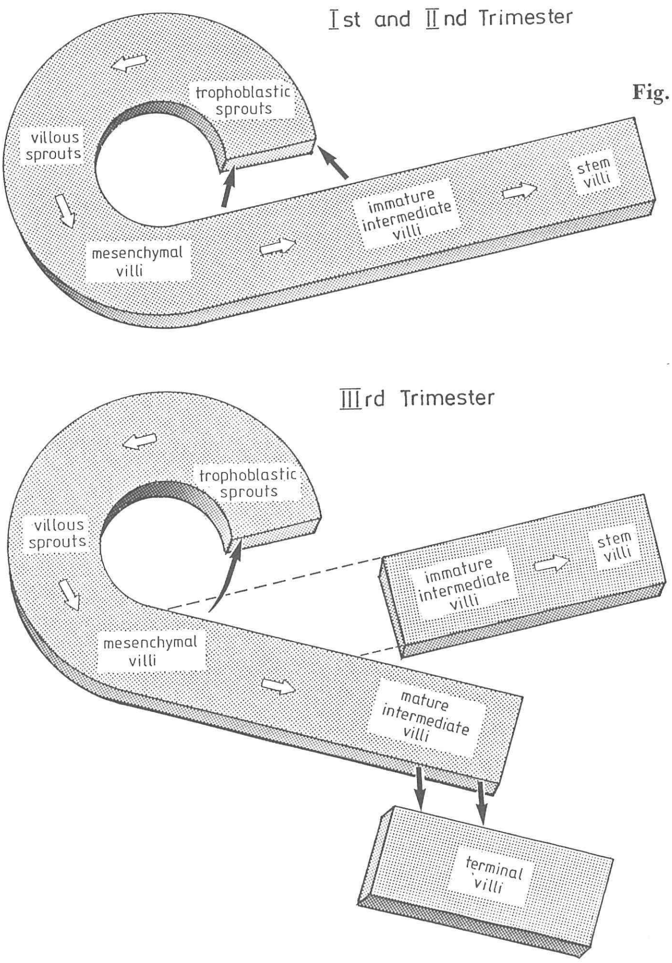

Fig. 3 Routes of villous development in early and late pregnancy. Light arrows : transformation of one villous type into another. Dark arrows : new production of villi or sprouts along the surface of other villi.
Upper half : 1st and 2nd trimester ; trophoblastic sprouts are produced along the surfaces of mesenchymal and immature intermediate villi. Via villous sprouts they are transformed into mesenchmal villi. The latter differentiate into immature intermediate villi which produce new sprouts before they are transformed into stem villi.
Lower half : throughout the 3rd trimester, the mesenchmal villi become transformed into mature interrmediate villi which later produce terminal villi along their surfaces. There is no longer transformation of mesenchymal into immature intermediate villi.
The remaining immature intermediate villi differentiate into stem villi. Thus their actual number is steeply decreasing towards term. Because of this, also the base for the formation of new sprouts is reduced, and the growth capacity of the villous trees gradually slows down. Modified after Castellucci et al., 1989.

be largely unimportant for the understanding of placental pathology. This was supported by the experience that in conventional paraffine histology it is extremely difficult to identify the various villous types and the various stages of villous differentiation. Improved histological methodology and easier availability of exactly defined human material of most stages of pregnancy enabled us, to deal with the mechanism of villous maturation and differentiation in some more detail (Kaufmann, 1982 ; Castellucci et al., 1989). Although our insights are still very superficial, and our conclusions are accordingly preliminar, we felt that we should deal with this particular field since clinical methods like chorion biopsy and Doppler studies recently have caused respective demands. And it is foreseeable that these demands will increase.

The first tertiary villi recognizeable in the early human placenta are represented by mesenchymal villi. Up to the 6th week p.m., the massive trophoblastic primary villi are transformed into secondary villi by invagination fo extraembryonic mesenchyme. Immediately after, the first capillaries are formed, giving rise to the first tertiary villi, which are the mesenchymal villi considered here.

From the 6th week p.m. onwards, new mesenchymal villi are derived by vascularization of trophoblastic sprouts (Fig. 3). These are trophoblastic outgrowths of the surfaces of mesenchymal and immature intermediate villi resulting from trophoblastic proliferation. In this context, we should point to the fact that not all histologically visible so-called "sprouts", i.e. fungiform outgrowths from the villous surface, are real signs of trophoblastic sprouting. Some of those represent stages of expulsion of aged syncytial nuclei, others are simply flat sections of villous surfaces.

Starting between the 7th and 8th week p.m., the mesenchymal villi transform into immature intermediate villi. This process is characterized a. by a considerable increase in villous diameter, b. by the formation of the stromal channels (Fig. 2), in which numerous macrophages are present (Enders & King, 1970 ; Kaufmann et al., 1979 ; Castellucci & Kaufmann, 1982 ; Castellucci et al., 1984 ; King, 1987), and c. by a decrease in thickness of the syncytiotrophoblast, and in number of the Langhans cells. The reticular stroma is the most characteristic feature of the immature intermediate villi. It seems to play an important role during transformation of these villi into stem villi. The accumulation of connective tissue fibers in the course of the early scare formation in the skin is preceeded by a similar reticular architecture of the connective tissue cells. The significance of this stromal type seems to be defined by the role of the Hofbauer cells which as macrophages are probably strongly involved in the remodelling of the connective tissue (Castellucci et al, 1984). For the moment, there are no hints as to a specific function of the immature intermediate villi other than to be an developmental precursor of stem villi (Fig. 3).

Additional development of immature intermediate villi out of mesenchymal villi gradually stops at the end of the 2nd trimester. Their transformation into stem villi, however, continues until term. Because of this, the amount of immature intermediate villi steeply decreases (Fig. 3). Sometimes, they completely disappear before term. Mostly, however, small amounts persist in the centers of the villous trees, serving as growth zones (Fig. 5).

As described above, the development of the stem villi is closely related to the formation of the immature intermediate villi. As early as in the 8th week p.m., the central vessels of the proximal segments of the immature intermediate villi near to the chorionic plate, start building up a compact adventitia and thus slowly become transformed into arteries and veins. Centrifugal expansion of the adventitia leads to a reduction of the surrounding reticular connective tissue. Stem villi are established by our definition (Castellucci et al., 1989) as soon as the superficial sheet of reticular connective tissue underneath the trophoblast is thinner than the fibrous center surrounding the stem vessel, and the stem vessels have been transformed into arteries and veins or arterioles and venules. The persistence of a small rim of reticular connective tissue underneath the trophoblast in the term placenta can be regarded as a reliable sign of placental immaturity.

The formation of stem villi depends on the availability of immature intermediate villi. Therefore, the expansion of villous stem gradually stops in the course of the last trimester as soon as the majority of immature intermediate villi has been transformed and new ones are no longer produced.

One of the most important steps for the understanding of villous development takes place at the beginning of the last trimester. At this time, the transformation of the newly formed mesenchymal villi into immature intermediate villi switches towards a transformation into mature intermediate villi (Fig. 3), (Castellucci et al., 1989). Different from the immature intermediate villi, the mature ones normally do not transform into stem villi. Rather, they are responsible for the development of the terminal villi.

The first terminal villi as defined by our group (Kaufmann et al., 1979 ; Sen et al., 1979) are formed shortly after the first mature intermediate villi. This process is closely related to the longitudinal growth of the capillaries within the mature intermediate villi (Fig. 4). As soon as the longitudinal capillary growth exceeds the longitudinal growth of the mature intermediate itself, the capillaries become coiled and form loops (Kaufmann et al., 1985). Because of the slender shape of these villi, the loops bulge the trophoblas-

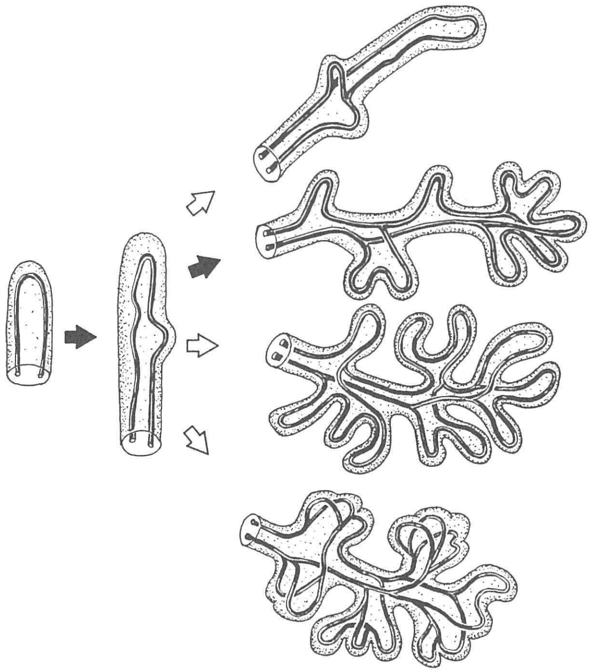

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Fig. 4 Highly simplified diagram of the terminal villus development in relation to capillary growth. As long as longitudinal capillary growth corresponds to the longitudinal growth of the mature intermediate villus (left two figures), the latter remains straight and does not form side branches. However, as soon as longitudinal capillary growth exceeds the longitudinal villous growth, capillary loops are formed bulging against the surface, hence causing the development of terminal villi. Varying degrees of imbalance between villous and capillary growth result in different types of terminal villous development, such as terminal villi deficiency (1), normal mature placenta (2), hypermaturity (preterm maturation) (3), and hypoxic hypervascularization (4). Modified after Kaufmann et al., 1988.

tic surface and finally protrude it as grapelike outgrowths into the intervillous space. This process is not accompanied by a corresponding trophoblastic proliferation, and therefore takes place under considerable stretching of the trophoblast. The final result are the numerous vasculo-syncytial membranes of the terminal villi. It follows that the terminal villi are no active outgrowths induced by proliferation, but rather passive formations caused by capillary coiling. The slight bends of the mature intermediate villi at those points where the terminal villi branch off (Figs. 2, 4(2)), illustrate the mechanical forces which have been active during capillary growth and coiling.

CAPILLARY GROWTH AS RELATED TO THE DEVELOPMENT OF TERMINAL VILLI

Thorough comparison of the capillary arrangement in normally as well as in abnormally matured terminal ramimications demonstrates that the development of terminal villi depends on capillary growth (Kaufmann et al, 1985). More than 95% of the terminal villi arise from the surfaces of mature intermediate villi by bulging of coiled capillaries. So called "hypermature villi" (Salvatore, 1968; Kaufmann, 1982; Kaufmann et al, 1985) show an increased number of terminal villi, together with longer, wider, and more coiled capillaries (Fig. 4(3)). In contrast, cases of "terminal villi deficiency" (Schweikhart & Kaufmann, 1983, 1987; Kaufmann et al, 1985) exhibit nearly naked mature intermediate villi, almost devoid of terminal villi (Fig. 4(1)). The respective terminal capillaries are much shorter, usually uncoiled, with a few sinusoidal dilatations, only. As is depicted in Figure 4, we have concluded from these observations that the development of terminal villi is influenced by the balance of the longitudinal growth of the mature intermediate villi with that of their capillary loops. The more capillary growth exceeds the longitudinal villous growth, the more the capillaries become coiled. The single coiles are bulged against the surfaces of the mature intermediate villi and thus produce the terminal villi. Thus, we interprete the terminal villi as passive outpockettings rather than as results of trophoblastic proliferation.

Because of the correlation discussed above, over-or under-stimulated capillary growth will result in various types of villous maldevelopment, such as terminal villi deficiency (Fig. 4(1)), or hypermaturity (premature maturation of the villous trees) (Fig. 4(3)). As special entity is hypercapillarization as a consequence of hypoxia in pregnancy. This phenomenon we have often observed in preeclampsia, in maternal anemia, or in pregnancies in high altitude. Different from hypercapillarization following hypermaturity (Fig. 4(3)), in chronic hypoxia hypercapillarization takes place by increased capillary branching (Scheffen et al., 1989). The resulting complex capillary networks cause short, multiply indented terminal villi (Fig. 4(4)).

INTERVILLOUS SPACE AS RELATED TO THE VILLOUS TREES

Wigglesworth (1967), studying corrosion casts of the fetal vessels, suggested that most of the villous trees are arranged as hollow-centered bud like structures. When injecting the spiral arteries, this author found the injection mass collected in the loose centers of the villous trees. This is in agreement with most descriptions of the maternal arterial inlets as being located near to the centers of the villous trees (Schuhmann & Wehler, 1971 ; Schuhmann, 1981), or at least as derecting their blood streams into these centers (Panigel & Pascaud, 1968). The 50 to 200 venous outlets per placenta are thought to be arranged around the periphery of the villous trees. Thus each fetomaternal circulatory unit is composed of one villous tree together with a corresponding centrifugally perfused part of the intervillous space (Fig. 5). This unit has been called a placentone by Schuhmann and Wehler (1971). Most placentologists agree upon that under in vivo conditions the majority of the 40 to 60 placentones per placenta are in intense contact with each other, more or less broadly overlapping. This is highly probable since structural borderlines such as sufficient placental septa are lacking. Following our own experience, the peripheral placentones are more clearly separated from each other and thus exhibit typical structural differences between their central and their peripheral zones. In the thicker more central regions of the placenta, most villous trees overlap (Fig. 5). This causes less distinct differences between maternal inflow and outflow area of the placentone. According to the studies of Schuhmann and Wehler (1971) the centers of typical placentones exhibit loosely arranged villi, most of them of the immature intermediate type, providing large intervillous space for the maternal arterial inflow.

If one follows these considerations, the immature intermediate villi together with their sprouting mesenchymal side branches (Figs. 2, 5) are concentrated in the placentone centers and thus in the zones of highest pO_2 in the intervillous space. Schuhmann found that 3H-thymidine incorporation as index for the mitotic rate is twice as high in the placentone center as compared to the periphery (Geier et al, 1975). This is seemingly in contrast to several experimental and pathohistological findings which suggested that low oxygen concentration serves as a stimulus for trophoblast proliferation and villous sprouting. The most likely explanation for this discrepancy is, that oxygen delivery to the centrally located, large villi in the central cavity and its vicinity is reduced, due to high blood flow velocity and long diffusion distances. The surrounding densely packed zones, though already located nearer to the venous pole probably have the much higher oxygen delivery since blood flow velocity is reduced in the slender intervillous clefts and diffusion distances are short. This results in high mean pO_2 values at the villous surfaces which is a prerequisite for effective maternofetal oxygen transfer, but at the same time inhibits villous proliferation and stimulates villous differentiation.

These relations may be the basis for regulatory mechanisms. Wide intervillous clefts in the periphery of the villous trees of immature placentas which lack fine and richly branched terminal villi,

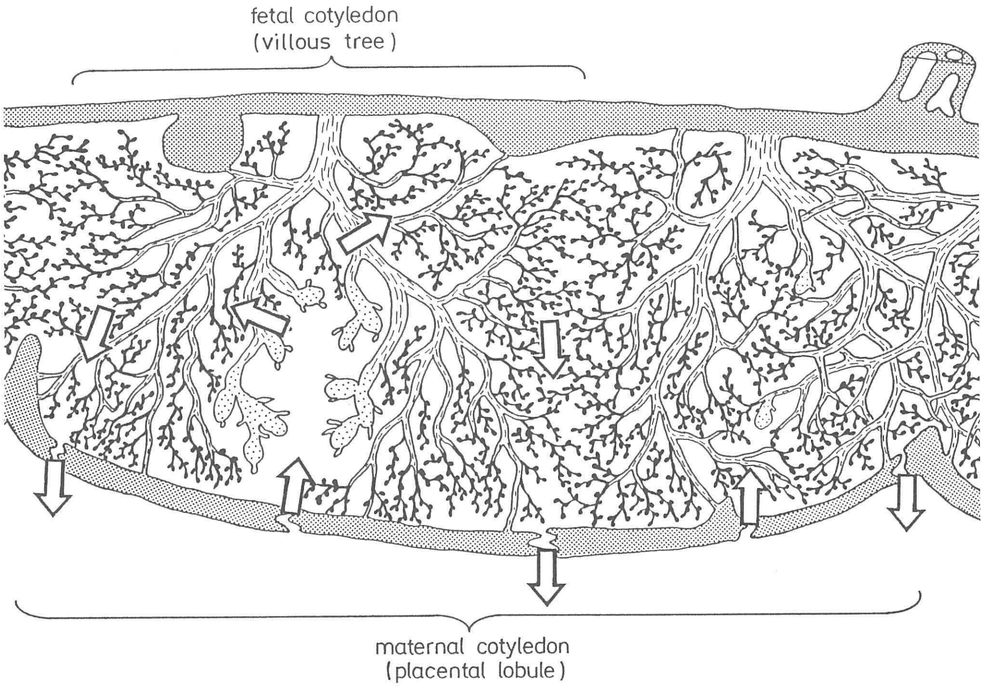

Fig. 5 This diagram demonstrates the typical spatial relations between villous trees, single villous types, and maternal blood stream. According to the placentone theory by Schuhmann, 1981, a placentone is one villous tree together with the related part of the intervillous space. In the case of typical placentones (left half of the diagram) which prevail in the periphery of the placenta, the maternal blood enters the intervillous space near the center of the villous tree and leaves the intervillous space near the clefts between neighbouring villous trees. In the term placenta, the larger stem villi (line shaded), the immature intermediate villi (point shaded) and their tiny branches, the mesenchymal villi (unshaded) are concentrated in the centers of the villous trees, surrounding a central cavity as maternal inflow area. The mature intermediate villi (black) together with their terminal branches (black, grape like) make up the periphery of the villous trees, near the venous outflow area. One or few villous trees occupy one placental lobule which is deliminated by grooves in the basal surface of the placenta. In the central parts of the placenta, the villous trees due to size and near-by location may partly overlap (right half of the diagram) so that the zonal arangement of the placentone disappears. Modified from Kaufmann, 1985.

result in long diffusion distances and high blood flow velocities, and thus in a reduced oxygen delivery. The resulting intravillous pO_2 in this area is low. This stimulates villous sprouting and in particular capillary sprouting (Bacon et al., 1984; Scheffen et al, 1989). As already discussed above, increased capillary sprouting is followed by the production of new terminal villi. The latter narrow the intervillous space, reduce blood flow velocity and diffusion distances, and thus increase oxygen delivery. Finally the elevated pO_2 inhibits further villous branching. In this hypothesis, maternal blood stream, oxygenation, and villous branching act as limbs of a simple feedback mechanism, which regulates growth of the villous trees. As a further consequence, a functional diversity of the placentone is obtained. Whereas the centers act as proliferative zones which guarantee placental growth until term, the periphery is the functionally fully active exchange and secretory area. This has been demonstrated histochemically and biochemially by the higher activity of enzymes like alkaline phosphatase (Schuhmann et al., 1976) and by the higher conversion rate of steroid hormones (Lehmann et al., 1973) in the placentone periphery.

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ヒト胎盤絨毛樹の発達と分化

本論文はヒト胎盤絨毛の発達構造についての概論をのべたものであり，1990年1月30日本学病院6階臨床講堂において行われた胎盤研究会での特別講演要旨である．Peter Kaufmann 教授は，欧州胎盤学会の代表幹事であり，これまで数々の胎盤に関する基礎的な研究報告を発表して来ている世界的にも高名な解剖学者である．

【論文要旨】

胎盤絨毛は母児循環によって供給されている構成成分であり，母児間物質交換の主要路であるだけでなく，多くの胎盤ホルモンの産生部位でもある．その機能を担う胎盤絨毛の分化と発達について，著者はこれを5つのタイプに分けて記述している．

A. 絨毛タイプ：

1. 幹絨毛：本絨毛は中膜と外膜をもつ動静脈の胎児毛細血管と線維状間質をもち，絨毛樹の重要な部分構成となる．それには絨毛膜板と連結する絨毛樹の主幹として，次に4世代分枝をもち，さらに10世代分枝迄末梢に広がる．そして幹絨毛のサブグループとしての付着絨毛を現わし，細胞柱として基底板に連結する．

2. 成熟中間絨毛：幹絨毛の最終生成の細長い末梢分枝である．弛緩した結合織をもち線維に乏しいが，胎児毛細血管は拡張せず，夥しい彎曲をもつジグザグコースをとる．満期胎盤では全絨毛の約36%がこのタイプによって占められる．ことに絨毛樹内でのホルモン産生部位である．

3. 末端絨毛：成熟中間絨毛の最終のブドウ状分枝であり，高度の胎児毛細血管とジヌソイドを有する．満期胎盤の約40%を占め，母児間の物質交換の主要部位である．

4. 未熟中間絨毛：幹絨毛の連続である球根状の絨毛である．成熟中間絨毛のように，幹絨毛と末梢の絨

毛枝の間の中間型である．未熟胎盤に多いが，正常満期胎盤絨毛樹の中心部に小グループで存在し，全絨毛の2〜10%を占める．ことに妊娠初期絨毛の90%以上が本タイプによって占められる．

5．間葉性絨毛：最も原始的な絨毛である．構造上ほんの僅かだけ毛細血管化されている原始的な間葉性間質を示し，大きな胎児血管を欠くが，先端ではトロホブラスト芽に接続する．満期胎盤絨毛の1%以下を占めるが，間質内とサイトトロホブラスト内に夥しい核分裂があり，高度に増殖する絨毛である．

B．絨毛樹の発達

初期胎盤に認められる最初の第三次絨毛は間葉性絨毛である．妊娠第6週までトロホブラスト性原始絨毛は胚外性間葉の陥入によって第二次絨毛に変形される．最初の毛細血管が作られて第三次絨毛を生じ，間葉性絨毛となり，トロホブラスト芽の血管化が進む．さらに第7〜8週で，間葉性絨毛は未熟性中間絨毛に変形する．この過程は絨毛直径の増加，間質チャンネル形式，シンシチウム細胞の厚さの減少とラングハンス細胞数の減少などによる．そして妊娠第II期の終わりには間葉性絨毛から未熟中間絨毛への発達は停止する．ことに幹絨毛の発達は未熟中間絨毛形成に密接に関与している．とくに妊娠後期では，新しく作られた間葉性絨毛の未熟中間絨毛への変形が，成熟中間絨毛への変形に代って行く．末端絨毛は最初の成熟中間絨毛後直ちに作られる．この末端絨毛の発達は，毛細血管の発育による．たとえば末端絨毛欠損症はほとんど末端絨毛を欠く裸の成熟中間絨毛を示す．

そのほか過刺激あるいは低刺激による毛細血管の発達の不良を生じ，早期成熟や過毛細血管化などが見られる．

(相馬広明．紹介と要約)