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Review

Keratins in the human trophoblast

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Summary. Besides microfilaments and microtubules, intermediate filaments are major components of the cytoskeleton. In epithelial cells intermediate filaments are formed by heterodimers of specific keratins, whose expression pattern highly depends on the type of epithelium and differentiation degree of the cell. During the process of blastocyst implantation and subsequent development of the human placenta a very specialized epithelium appears at the feto-maternal interface. Arising from the trophectoderm of the blastocyst, the epithelium-like layer surrounding the early embryoblast, different trophoblast subtypes differentiate. They either develop into polar cells fulfilling real epithelial functions, or apolar tumor-like cells invading the maternal uterine wall to adapt the maternal tissue to progressing pregnancy. Thus, the whole trophoblast population, with all its subtypes, can be considered as an epithelial compartment and hence expresses keratin filaments. However, differentiation of trophoblast into different phenotypes may be linked to remodeling of the cytoskeletal composition, depending on spatiotemporal requirements of the respective cells. Here, we focus on the keratin composition of different trophoblast subtypes, how these keratins are used in trophoblast research and what is known about placental keratins in pregnancy pathologies.

Key words: Placenta, Trophoblast, Differentiation, Keratin, Intermediate Filament

Keratins

Keratins, also known as cytokeratins, are intermediate filament forming proteins expressed in vertebrate epithelial cells (Fuchs, 1983). Besides microfilaments and microtubules, intermediate filaments represent a major component of the cytoskeleton and may account for up to 80% of total protein content in differentiated cells of stratified epithelia (Pekny and Lane, 2007). Keratins build a scaffold and thereby influence cell architectural properties such as cell polarity and shape. The expression pattern of keratins highly depends on the type of epithelium and differentiation degree of epithelial cells. With the beginning of the molecular age, including systematic sequencing of the human genome, the panel of known keratins has been extended by a large set of new candidate genes. In total the human genome encodes 54 functional keratin genes, which are divided into the categories epithelial keratins and hair keratins. Moreover, another category represents a group of 13 keratin pseudogenes (Schweizer et al., 2006).

There are 17 human type I epithelial keratins, also known as acidic keratins, which are designated - based on the former cytokeratin nomenclature - as K9-K28 (numbers 11, 21, 22 are unused for historical reasons (Schweizer et al., 2006)). Human type I epithelial keratins have a molecular weight between 40 and 56.5kDa. Human type II epithelial keratins are also referred to as basic keratins and comprise a group of 20 genes coding keratins K1-K8, K71-K80 and K81-K86 with a molecular weight ranging from 52-67kDa. Keratins usually form heterodimers of one type I and one type II keratin in a parallel orientation (Er Rafik et al., 2004). Such heterodimers may be seen as the first building units of a keratin filament, which are heteropolymers of equimolar amounts of acidic and basic keratins. This heteropolymeric structure requires a strict control of keratin expression in order to obtain stoichiometry of the keratin pairs and to produce keratin filaments that are specific for certain stages of differentiating epithelial cells. Lateral and longitudinal aggregations of heteropolymers in terms of self-bundling of tetramers and octamers finally lead to the formation of a keratin filament. Some keratins, such as K5, fulfill specific functions and cannot be replaced by other keratins, whereas others were shown to be redundant and

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can assemble in various combinations (Porter and Lane, 2003).

Simple epithelia, such as gut epithelium, pseudostratified epithelium of the trachea or glandular simple epithelia, usually produce the basic keratin K8, together with its acidic binding partner K18 and a panel of other differentiation dependent keratins such as K7, K19, K20 and K23 (Bragulla and Homberger, 2009). In these simple epithelia, keratins only account for up to 5% of total cell protein. Like in simple epithelia, cells of stratified epithelia produce acidic keratins (e.g. K1, K5) and matching basic keratin partners (e.g. K10, K14) to form heterodimers, which are, however, differentially expressed with specific stages of differentiation (Bragulla and Homberger, 2009). Basal cells of stratified epithelia usually form heterodimers of K5 and K14, whereas suprabasal cells express additional keratins, depending on the type of stratified epithelium (Bowden et al., 1984).

With the development of the human placenta a very specialized epithelium appears at the feto-maternal interface. This epithelium comprises a layer of mononucleated cells resting on the basal membrane. In areas where there is no direct contact with other tissues a second multinucleated layer develops, contributing to the establishment of the placental barrier. In areas where there is direct contact with other tissues such as the maternal endometrium, tumor-like apolar cells develop, which detach from the epithelium and invade the uterine wall to guarantee proper attachment of the placenta.

Human trophoblasts - unique epithelial cells

Only six to seven days after conception the blastocyst enters the uterine cavity and attaches to the uterine epithelium. At this stage trophectoderm cells, i.e. mononucleated trophoblasts, build the outer wall of the blastocyst, encompassing the blastocyst cavity and the inner cell mass, the embryoblast. Attachment to the uterine epithelium induces intercellular fusion of trophectoderm cells to form an oligonucleated syncytium, which can be seen as the emerging syncytiotrophoblast. According to current knowledge this early syncytiotrophoblast, but not the mononucleated trophoblasts, is able to penetrate through the uterine epithelium. The remaining, not fusing trophectoderm cells now become cytotrophoblasts, which are the source for different trophoblast subtypes. The syncytiotrophoblast is the most highly differentiated, i.e. most specialized type of trophoblast and no longer undergoes replication. Thus, expansion and growth of the syncytiotrophoblast is maintained by continuous proliferation and subsequent fusion of cytotrophoblasts with the syncytium. Soon after implantation small intrasyncytial vacuoles occur in the growing syncytiotrophoblast and quickly converge into a system of lacunae (Benirschke et al., 2006). The lacunae are separated from each other by trabeculae of syncytiotrophoblast, which is invaded by cytotrophoblasts around day twelve post conception. At that stage of pregnancy, the syncytiotrophoblast still displays invasive properties. The invading syncytiotrophoblast disintegrates maternal capillary walls and thereby a few maternal blood cells sluggishly enter the lacunar system. Only one day later increased cytotrophoblast proliferation and fusion with the syncytiotrophoblast leads to longitudinal trabecular growth as well as appearance of syncytial side branches protruding into the lacunar system. Further invasion of cytotrophoblasts into the syncytiotrophoblast branches initiate the formation of primitive villous trees and the lacunar system is now referred to as intervillous space. Another two days later mesenchymal cells derived from the extraembryonic mesenchyme invade the primitive villi. As a two-layered epithelium the syncytiotrophoblast together with underlying cytotrophoblasts cover the mesenchymal cores of placental villi and are therefore referred to as the villous trophoblast population. Between days 18 and 20 post conception fetal capillaries are formed by hemangioblastic progenitor cells in the villous mesenchyme. With the beginning of the fifth week villous capillary segments fuse together and form a regular capillary bed within the placenta, which is then connected to the embryonic vessel system via the umbilical cord, establishing a complete fetoplacental circulation (Benirschke et al., 2006).

Throughout the process of implantation maternal endometrial cells also undergo remarkable changes, as they start to proliferate and enlarge in size to become decidua cells. In so-called anchoring placental villi, which are attached to the decidua, cytotrophoblasts penetrate through the syncytiotrophoblast and form cell columns. In these trophoblast cell columns, the daughter cells of those trophoblasts resting on the basal membrane are pushed forward by the underlying subsequent generation of new cytotrophoblasts. As soon as they detach from the anchoring villi they are no longer referred to as villous trophoblasts but are now called extravillous trophoblasts. Proliferation can only be observed in very proximal portions of cell columns, while extravillous trophoblasts in more distal parts have left the cell cycle and start to differentiate into the invasive phenotype. Invasive extravillous trophoblasts detach from the cell columns and start to invade the decidual interstitium, where they are referred to as interstitial trophoblasts and penetrate as deep as the inner third of the myometrium.

On their way through the decidual interstitium a subset of extravillous trophoblasts encounters maternal spiral arteries and differentiates into endovascular trophoblasts. Endovascular trophoblasts invade the arteries from the interstitial side and reach the lumen of the vessels where they displace maternal endothelial cells and acquire endothelial-like functions. According to their location in invaded uteroplacental blood vessels the group of endovascular trophoblasts can be further subdivided into two more subgroups. Intramural trophoblasts are found within walls of uteroplacental

arteries, where they replace media smooth muscle cells and other vascular wall structures (Benirschke et al., 2006). The second subgroup within endovascular trophoblasts comprises intraarterial trophoblasts, which are found within the lumina of uteroplacental arteries, where they form multicellular plugs, partly occluding arterial lumens (Benirschke et al., 2006). The consequence of trophoblast invasion into spiral arteries is a transformation of these vessels into large-capacity tubes to ensure adequate blood flow and hence adequate nutrition and oxygenation of the fetus (Burton et al., 2009). Besides endovascular invasion alternative routes of trophoblast invasion have been suggested. Recently, interstitial trophoblasts have been described, which invade into uterine glands and replace the glandular epithelium (Moser et al., 2010), giving rise to the endoglandular trophoblast as another subtype within the extravillous trophoblast population, which enables histiotrophic nutrition of the embryo during the first trimester of pregnancy (Fig. 1).

Overall, placental development depends on proper formation of all its trophoblast subpopulations. Since they all arise from the trophectoderm it is important to keep in mind that they are an epithelial compartment, irrespective of phenotype or existing contact with a basement membrane. Differentiation into different subtypes, with all its different functions, may be linked to remodeling of the cytoskeletal composition. Here, focus is set on the keratin composition in different types of trophoblasts, how these keratins are used in trophoblast research and what is known about placental keratins in pregnancy pathologies.

Keratins in villous trophoblast

The keratin pattern of the villous trophoblast population resembles that of simple epithelia. K8 and K18, the hallmark keratins of simple epithelia are expressed in the cytotrophoblast as well as the syncytiotrophoblast. The fact that K8 and K18 are present in undifferentiated as well as differentiated trophoblast indicates that these keratin types are not related to trophoblast differentiation processes. However, experiments with trophoblast cell lines showed some differentiation-dependent regulation of both keratin types. When the villous trophoblast derived choriocarcinoma cell line BeWo is incubated with forskolin, both K18 mRNA and protein expression is up-regulated (White et al., 2009). Forskolin activates adenylyl cyclase, which increases intracellular cAMP levels and thereby induces trophoblast differentiation and fusion. Up-regulation of K18 during the onset of fusion was suggested to support rearrangement of the intermediate filament cytoskeleton in preparation for trophoblast fusion (White et al., 2009). However, conclusions from these experiments should be drawn with caution, since keratins may be differentially regulated in primary and transformed trophoblast cells.

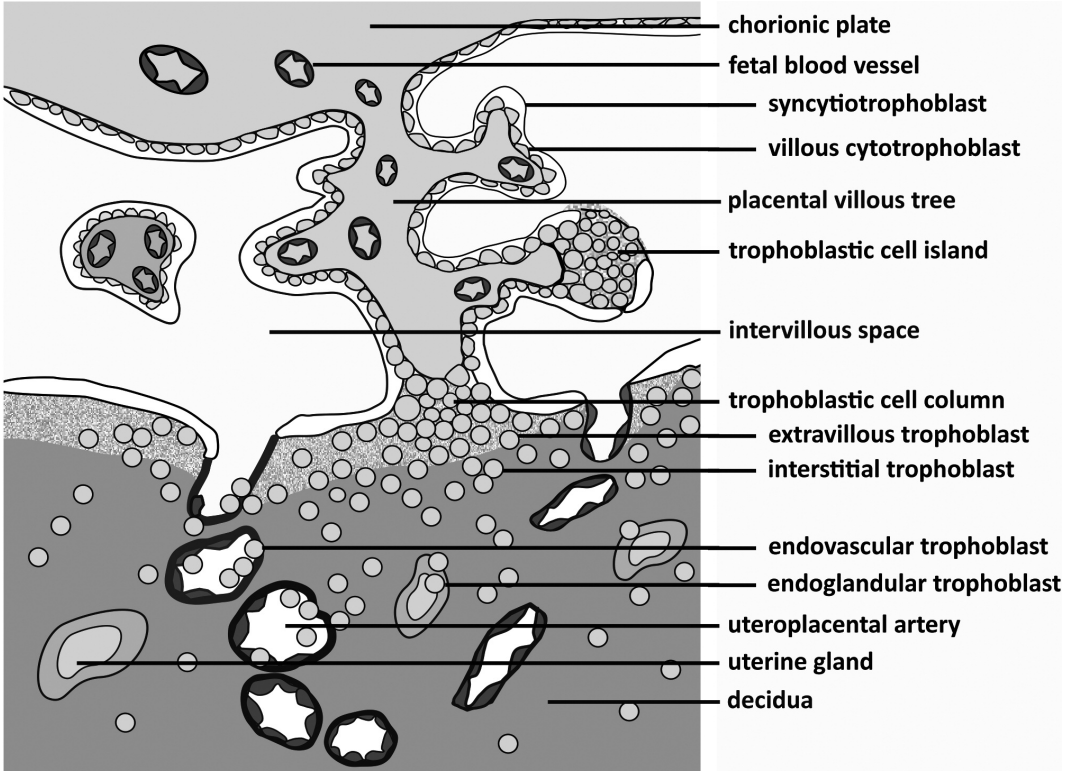

Fig. 1. Schematic drawing illustrating the distribution of the various trophoblast populations in the human first trimester placenta. Villous cytotrophoblasts and the overlying syncytiotrophoblast represent the villous trophoblast population, which covers as epithelial-like layer placental villous trees. Extravillous trophoblasts detach from trophoblastic cell columns and invade as interstitial trophoblasts the maternal dacidua. On their way they occasionally encounter uteroplacental arteries or uterine glands, where they penetrate the vascular or glandular wall and become endovascular or endoglandular trophoblasts, respectively.

While incubation with the cAMP analog 8-Bromo-cAMP increased K8 mRNA levels in the trophoblast cell line JEG-3, its expression was suppressed in primary cultures of cytotrophoblasts (Yamamoto et al., 1990). Interestingly, caspase-14 was suggested to modulate K18 expression during biochemical differentiation of BeWo cells (White et al., 2009). Silencing of caspase-14 led to increased K18 expression in BeWo irrespective of treatment with or without forskolin. The detailed mechanism underlying this observation has not been determined so far, but cleavage and activation of caspase-14 was not detected during BeWo fusion, suggesting its enzymatic activity is not required in this process. However, involvement of caspase activity in the remodeling of the trophoblast cytoskeleton during differentiation and fusion was suggested by recent studies. Caspase 8 activity was shown to be involved in remodeling of the membrane-associated cytoskeleton by cleaving the spectrin-like alpha-fodrin during intercellular trophoblast fusion (Gauster et al., 2010). Indeed, caspase mediated cleavage of keratin was shown in hepatocytes. While caspase-3 and -7 degraded K18 when present in a dephosphorylated state, no cleavage was detected in the hyperphosphorylated keratin variant (Ku and Omary, 2001).

Besides the primary keratins K8 and K18, the villous trophoblast population produces a panel of secondary keratins (Table 1). One of these is K7, which is commonly used as a marker for trophoblast isolation (Blaschitz et al., 2000; Maldonado-Estrada et al., 2004). While K7 expression in villous cytotrophoblasts was shown to be strong and stable throughout pregnancy, its expression increased in the syncytiotrophoblast with progression of gestation. Interestingly, different pretreatment of first trimester placenta sections had shown different staining results (Fig. 2). Staining of antigen-retrieved sections usually shows K7 expression in both villous cytotrophoblasts and the overlying syncytiotrophoblast. If the antigen retrieval step was omitted, K7 was exclusively found in the villous cytotrophoblast of formalin fixed paraffin embedded first trimester placenta sections (Bose et al., 2006; Widdows et al., 2009). This observation is substantiated by immunofluorescence data, showing K7 staining only in the cytotrophoblast population, but not in the syncytiotrophoblast (Gauster et al., 2009). However, this discrepancy may be explained by the spatiotemporal expression of K7 in the syncytiotrophoblast. In first trimester placental villi, K7 expression in the syncytiotrophoblast was shown to be low, and hence may be detected only with higher antibody concentrations. Moreover, K7 was detected in the syncytiotrophoblast of first trimester placenta mainly along its basal membrane, whereas apical staining appeared very slightly (Muhlhauser et al., 1995). Nevertheless, the fact that K7 staining in the syncytiotrophoblast can only be detected after antigen-retrieval tempts speculation about a different keratin filament structure in the syncytial layer as compared to mononuclear cytotrophoblasts.

Other secondary keratins detected in human villous trophoblast population are K13 and K19. The expression of K13 in the villous trophoblast showed a similar expression pattern to K7 (Muhlhauser et al., 1995). K19 was detected by immunofluorescence in villous trophoblast (Muhlhauser et al., 1995), where its expression was suggested to be up-regulated during trophoblast differentiation. This was shown for primary term cytotrophoblasts in vitro, which up-regulated K19 expression during non-stimulated or epidermal growth factor (EGF)-stimulated differentiation (Morrish et al., 1996).

Table 1. Overview of keratins expressed in different trophoblast types.

Trophoblast type	Keratin	Reference
Villous trophoblast		
Syncytiotrophoblast	7†, 8, 13, 18, 19	Muhlhauser et al., 1995
Cytotrophoblast	1§, 5, 7, 8, 13, 17*, 18, 19	Muhlhauser et al., 1995; Ahenkorah et al., 2009
Extravillous trophoblast		
Cell column		
Proximal extravillous trophoblast	7, 8, 13, 18, 19	Muhlhauser et al., 1995
Distal extravillous trophoblast	7, 8, 18, 19	Muhlhauser et al., 1995
Interstitial trophoblast	5, 7‡, 8, 18, 19	Proll et al., 1997; Muhlhauser et al., 1995; Ahenkorah et al., 2009
Endovascular trophoblast		
Intramural trophoblast	8, 17, 18, 19	Proll et al., 1997
Intraarterial trophoblast	8, 18, 19	Proll et al., 1997
Endoglandular trophoblast	7£	Moser et al., 2010

†: in FFPE placenta detected with antigen-retrieval; *: only in cells associated with extracellular matrix; §: detected with Western blot technique in isolated cytotrophoblasts (Sawicki et al., 2003); ‡: decreasing expression with increasing invasion distance (Muhlhauser et al., 1995); £: others not tested.

Keratins in the extravillous trophoblast

Extravillous trophoblasts, derived from the pool of trophoblasts originating from the trophectoderm of the blastocyst, are derived from an epithelial layer of cells. Their epithelial-like phenotype is characterized by the expression of a wide range of keratin types, including K7, K8, K13, K17, K18 and K19. During differentiation into different subtypes of extravillous trophoblasts the primary keratins K8 and K18 are more or less constitutively expressed, while the secondary keratins K7, K13 and K17 were shown to undergo considerable changes in expression (Table 1). These changes may be linked to detachment from the villous basal membrane and escape from the active cell cycle, which determines these extravillous trophoblasts to achieve an interstitial, apolar phenotype. Changes in cell polarity may in turn require a different set of keratin filaments, and may explain the observation that proximal regions of cell columns express K13, while more distal parts do not (Muhlhauser et al., 1995).

With ongoing differentiation on their passage through cell column layers, where they are pushed forward by proliferation pressure of following cell generations, extravillous trophoblasts achieve an invasive phenotype. The invasive phenotype enables

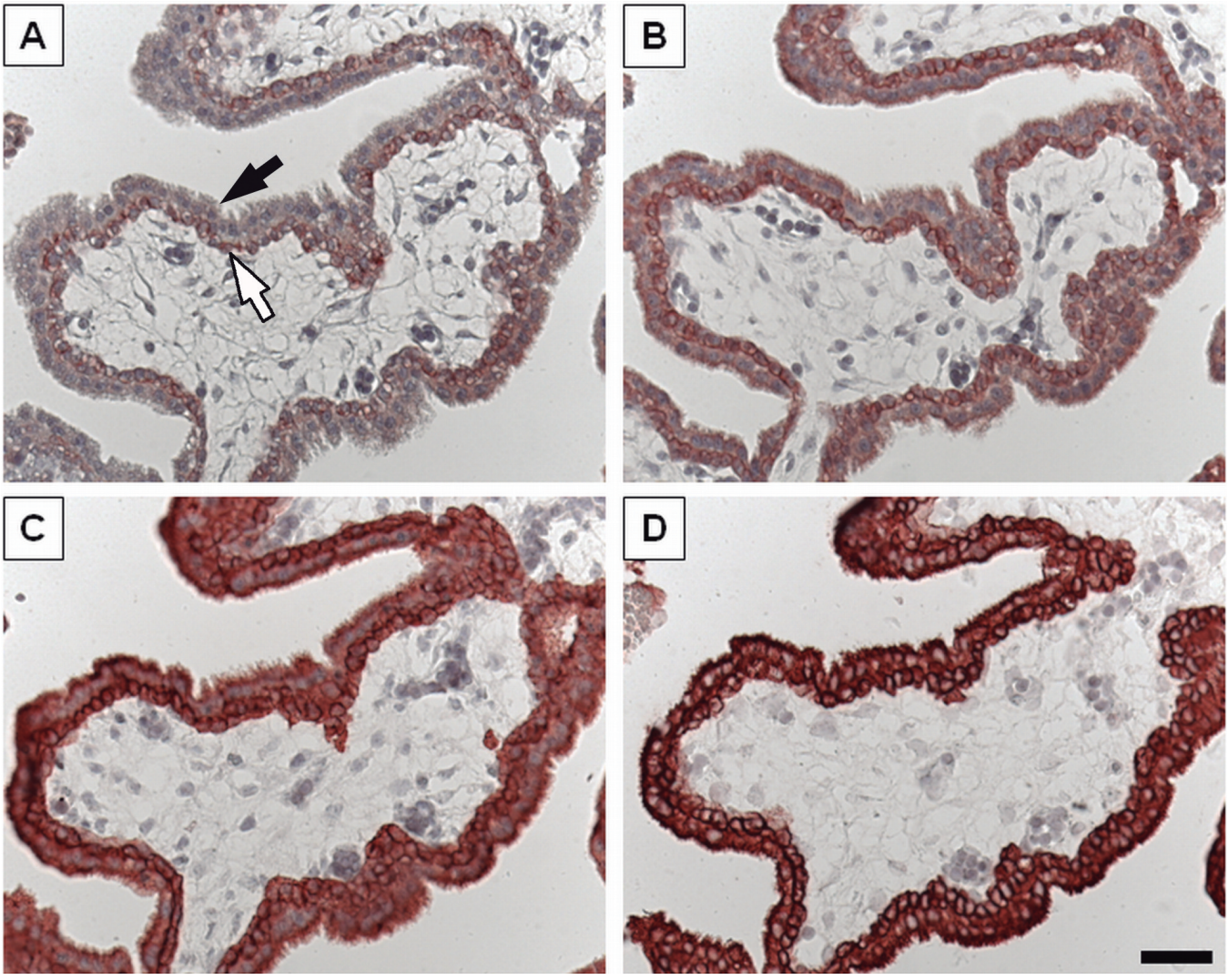

Fig. 2. Effect of different antigen retrieval on cytokeratin 7 staining of human first trimester placenta. Serial sections of formalin fixed paraffin embedded human first trimester placenta were either untreated **(A)** or subjected to different approaches of antigen retrieval such as microwave cooking (20 minutes at 720W) in citrate buffer, pH=6 **(B)**, target retrieval buffer, pH=9 (DAKO) **(C)** or trypsin digestion for 15 minutes at room temperature **(D)**. Slides were all stained with the same concentration of mouse monoclonal anti-cytokeratin 7 antibody (OV-TL 12/30, 33.3ng/ml), giving different staining intensities and staining patterns of villous cytotrophoblast (open arrow) and syncytiotrophoblast (filled arrow). Bar: 50 μm.

trophoblasts to migrate into maternal tissue, i.e. the uterine wall, where these cells again show changes in their intermediate filament composition. Extravillous trophoblasts that have just invaded the basal plate, show a high K7 expression, but with ongoing invasion and increasing distance from anchoring villi their K7 expression decreases until it is completely missing in these cells (Muhlhauser et al., 1995).

On their journey through maternal tissues interstitial trophoblasts may encounter maternal spiral arteries, with the final goal to adjust these vessels to the needs of the fetus. Such extravillous trophoblasts even replace endothelial cells. Now these cells switch from the interstitial into the endovascular phenotype, which again seems to be linked to a shift in the composition of intermediate filaments. In particular this applies to expression of K17, which was shown to be expressed, among extravillous trophoblasts, only in the subpopulation of intramural trophoblasts (Fig. 3) (Proll et al., 1997). As mentioned above extravillous trophoblasts, including endovascular trophoblasts, have lost their contact with the villous basal membrane and are embedded in the extracellular matrix, as has been demonstrated by eosin and PAF-Halmi staining (Proll et al., 1997). While the association of K17 expression and loss of contact with the basal membrane by the same cell type has been shown for certain tumors (Guelstein et al., 1988), other studies suggested that the extracellular matrix may indeed play a role in regulation of K17 expression. This was suggested by the observation that only cytotrophoblasts associated or in contact with fibrin deposits were positive for K17 (Muhlhauser et al., 1995). Interestingly, K17 was considered as an intermediate filament specific for myoepithelia (Guelstein et al., 1993). Thus, it appears conceivable that after replacement of smooth muscle and endothelial cells, the endovascular trophoblasts take over specific functions, such as lining of blood vessels and withstanding vascular shear stress.

Keratins as markers in trophoblast research

In recent years much effort has been undertaken to improve isolation and culture of primary trophoblasts. Experiments with primary trophoblasts have many advantages compared to immortalized trophoblast cell lines, but certainly may be affected by low cell purity. Since mesenchymal cells isolated from human first trimester placenta were shown to express K8 and K18, characterization of primary trophoblast purity based on K8/K18 antibodies had its clear limitations. Consequently, K7 instead of K8/18 has been suggested for characterization of primary trophoblasts (Haigh et al., 1999; Blaschitz et al., 2000). For *in situ* analyses, however, staining for K7 alone may not be the best choice - in particular when different subpopulations of the extravillous trophoblast should be distinguished. In this regard endovascular trophoblasts may be mixed up with endoglandular trophoblasts and thus double staining with specific markers for extravillous trophoblasts such as anti-HLA-G in combination with anti-K7 has been suggested (Moser et al., 2011). Unambiguous histological identification of invaded trophoblasts is essential for analyses of the degree and depth of trophoblast invasion into the uterine wall. This way shallow trophoblast invasion accompanied by a reduced percentage of remodeled maternal uterine spiral arteries has been associated with pregnancy pathologies, such as early-onset preeclampsia/intrauterine growth restriction (Kadyrov et al., 2006).

Beside trophoblast invasion a tightly controlled cellular turn-over, including proliferation, differentiation and apoptosis of trophoblasts was shown to be fundamental for placenta physiology. Regarding

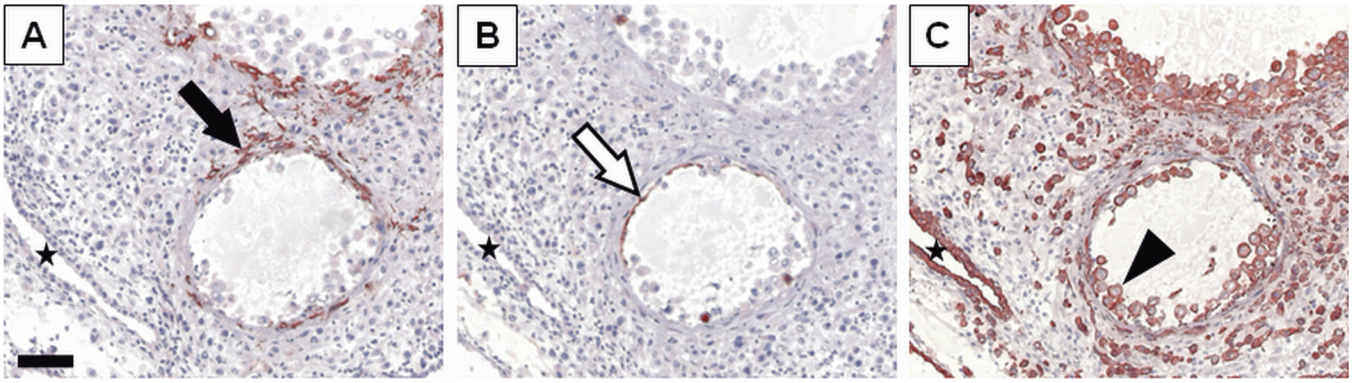

Fig. 3. Intramural trophoblasts express keratin 17. Immunohistochemistry of human first trimester decidua basalis cryosections shows K17 staining in intramural trophoblasts (filled arrow), which invaded uterine spiral arteries **(A).** At sites where trophoblasts invaded uterine spiral arteries, endothelial staining with QB-End/40 (open arrow) was detected only partially, suggesting ongoing replacement of endothelial cells **(B)**. Note that the decidual stroma, as well as uterine glands (asterisks) did not show any K17 staining, indicating that K17 is solely expressed in intramural, but not in interstitial, endoglandular or intraarterial trophoblasts. Intraarterial trophoblasts (arrowhead) in the lumina of uterine spiral arteries were identified by staining with anti-cytokeratin 8, 18, 19 antibody **(C).** Immunohistochemistry was performed as previously described (Proll et al., 1997). Bar: 100 μm.

identification of apoptotic trophoblasts, histological detection of cleaved K18 turned out to be a useful tool. During apoptotis K18 is cleaved in simple epithelial cells by active caspases, which lay bare a K18 epitope (CK18 neo-epitope) only detected in apoptotic cells. By the use of a monoclonal antibody (M30) raised against this K18 neo-epitope, apoptotic trophoblasts can be detected by immunohistochemistry (Kadyrov et al., 2001).

Placental keratins and pregnancy pathologies

In general, mutations in most of the keratins have been associated with specific tissue fragility disorders. For human placenta development the functional role of these structural proteins is certainly underestimated. Based on what can be deduced from various mouse studies, the absence of keratin in the human trophoblast would likely have the consequence of cell fragility and placental hemorrhaging (Watson, 2007). This assumption is based on studies with keratin knockout mouse models, suggesting simple keratins are not required until mid-gestation. In fact, $K8^{-/-}$, $K8^{-/-}/K19^{-/-}$ and $K18^{-/-}/K19^{-/-}$ knockout conceptuses died at E10.5 and all showed placental hemorrhaging (Hesse et al., 2000; Tamai et al., 2000; Jaquemar et al., 2003). In human, keratin intermediate filaments seem to be mandatory for proper development, since no K8 and K18 deficiencies are reported for the human population. However, dysregulation of keratin expression has been reported for many pregnancy disorders.

Expression analyses of placental mid-trimester biopsies showed a significant over-expression of K8 in Down syndrome placentas when compared to age-matched control samples (Klugman et al., 2008). Moreover, these authors showed a marked inverse relationship between K8 expression and the expression of TNF-related apoptosis-inducing ligand (TRAIL) in 8 out of 11 Down syndrome placentas. The authors suggested this inverse relationship may be the result of a negative feedback, as TRAIL induced apoptosis could increase K8 expression and elevated K8, in turn may control apoptosis by down-regulating TRAIL (Klugman et al., 2008). Increased apoptosis as a consequence of this negative feedback was assumed as the reason why some Down syndrome fetuses do not survive until term.

Dysregulation of keratins K7, K8, K18 and K19 expression has been associated with preeclampsia in several studies, although discrepancies about up- or down-regulation of respective keratins suggest a more complex effect of this pregnancy complication on placental intermediate filaments. Immunofluorescence confocal laser scanning microscopy studies showed a decrease in these four keratins in villous as well as extravillous cytotrophoblasts in preeclampsia (Ockleford et al., 2004; Ahenkorah et al., 2009). Down-regulation of K7 in preeclamptic villous tissue was confirmed by another immunohistochemistry and Western blot study showing considerably lower expression of membrane associated K7 (Riquelme et al., 2011). These observations are, however, in contrast to immunohistochemistry studies showing increased K18 and K19 expression in preeclamptic placentas (Tempfer et al., 2000; Hefler et al., 2001). K19, in particular, was suggested as a marker for the severity of preeclampsia, since its relative staining rate of the syncytiotrophoblast was higher in placental tissues from women with preeclampsia when compared to gestational age matched healthy controls. Moreover, median serum levels of K19 were significantly higher in women with preeclampsia and inversely correlated with fetal birth weight (Tempfer et al., 2000). Overall, these contradictory results may be explained by severity of cases, different antibody clones and staining procedures, as well as different sets of diseased women.

K20 was recently considered as a biomarker of gestational trophoblastic disease (GTD), which comprises a wide spectrum of tumors arising from abnormal trophoblastic tissue development (Stackievicz et al., 2002). These tumors range from complete benign or partial hydatiform moles to malignant tumors, such as invasive mole, choriocarcinoma, and rare placental-site trophoblastic tumors (Seckl et al., 2010). RT-PCR analyses revealed K20 expression only in complete hydatiform moles, choriocarcinoma and in 50% of cases with partial hydatiform moles, but not in healthy placental tissue obtained from pregnancy terminations (Stackievicz et al., 2002).

Concluding remarks

Keratin filaments in human trophoblasts are composed of heterodimers of K8/K18, usually found in simple epithelia. Besides these primary keratins, secondary keratins K7 and K19 are also expressed throughout the whole trophoblast population. During placenta development trophoblasts differentiate into different subtypes and thereby may modify their keratin filament composition and structure in order to adapt to spatiotemporal requirements. In pregnancy pathologies aberrant adaption of the trophoblast cytoskeleton to spatiotemporal requirements may not only lead to dysfunction of the trophoblast subtype but also of the placenta as a whole.

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