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Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts

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Trophoblast research over the past decades has underlined the striking similarities between the proliferative, migratory and invasive properties of placental cells and those of cancer cells. This review recapitulates the numerous key molecules, proto-oncogenes, growth factors, receptors, enzymes, hormones, peptides and tumour-associated antigens (TAAs) expressed by both trophoblastic and cancer cells in an attempt to evaluate the genes and proteins forming molecular circuits and regulating the similar behaviours of these cells. Among the autocrine and paracrine loops that might be involved in the strong proliferative capacity of trophoblastic and cancer cells, epidermal growth factor (EGF)/EGF receptor (EGFR), hepatocyte growth factor (HGF)/HGF receptor (HGFR) (Met) and vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) loops may play a predominant role. Similar mechanisms of migration and invasion displayed by trophoblastic and malignant cells comprise alterations in the adhesion molecule phenotype, including the increased expression of α1β1 and αvβ3 integrin receptors, whereas another critical molecular event is the down-regulation of the cell adhesion molecule E-cadherin. Among proteases that may play an active role in the invasive capacities of these cells, accumulating evidence suggests that matrix metalloproteinase-9 (MMP-9) expression/activation is a prerequisite. Finally, an overview of molecular circuitries shared by trophoblast and cancer cells reveals that the activation of the phosphatidylinositol 3′-kinase (PI3K)/AKT axis has recently emerged as a central feature of signalling pathways used by these cells to achieve their proliferative, migratory and invasive processes.

Key words: cell signalling/pregnancy/trophoblasts

Introduction

The human placenta undergoes dramatic structural reorganization during pregnancy so as to be functionally synchronized with the development of embryonic fetal and maternal compartments (Ohlsson *et al*., 1993). Although the placenta is a normal tissue, its constituent cells, the trophoblastic cells, share several common features with malignant cells. Their high cell proliferation, their lack of cell-contact inhibition, their migratory and invasive properties as well as their capacity to escape effectors of the immune system, in particular during the first trimester of pregnancy, have led to the definition of the trophoblast as a 'pseudo-malignant' type of tissue or as a 'physiological metastasis' (Strickland and Richards, 1992; Genbacev *et al*., 1997; Redman, 1997; Even-Ram *et al*., 1998; Mullen, 1998). This review will focus on subpopulations of normal trophoblastic cells that closely mimic malignant cells. After the presentation of behavioural resemblances between normal trophoblastic and malignant non-trophoblastic cells, the many key molecules commonly expressed by these cells will be described in an attempt to gauge the genes and proteins that participate in molecular circuits implicated in their similar behaviours. Moreover, this review will show how the complex body of knowledge generated by trophoblast and cancer research during the last few decades is in line with the hypothesis that trophoblastic and cancer cells use comparable mechanisms implemented by identical molecular circuitries to achieve their proliferative, migratory and invasive processes. Finally, the comparison of placenta and tumours will be crucial to our knowledge of major signalling cascades and key molecules implicated in invasion and migration processes. The identification of these pathways and molecules could provide novel targets for the diagnosis and treatment of both cancer diseases and pathological pregnancies, enabling the translation of basic reseach discoveries into clinical applications.

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Comparable behaviours of normal trophoblastic and malignant non-trophoblastic cells: proliferation and migration/invasion

In humans, after fertilization in the oviduct, a series of symmetrical cell divisions create a mass of totipotent cells, the morula, still enclosed within the zona pellucida. The first differentiation event occurs after the compaction of the morula with the formation of the blastocyst. Cells that lie outside of the morula become trophectoderm, the first epithelium in mammals, and trophoblasts are derived from trophectoderm cells present in the blastocyst. They form the fetal compartment (placenta) of the fetal–maternal interface during pregnancy and are extra-embryonic tissues. When the blastocyst invades the decidua of the uterine wall during implantation (6th–7th day after ovulation), trophoblast cells are on the front line and become invasive as they differentiate (Boyd, 1980; Redman *et al*., 1993; Cross *et al*., 1994; Loke and King, 1995). Trophoblasts include various populations of cells with differing morphologies. At an early stage, the founding population comprises cytotrophoblast stem cells attached to the trophoblast basement membrane and actively proliferating. These trophoblast cells follow two differentiation pathways, the villous and extravillous pathways, and differentiate into villous and extravillous populations. In the villous pathway, villous cytotrophoblasts (vCTBs) remain in the fetal compartment, where they fuse to form multinucleate, weakly proliferating syncytiotrophoblasts (STs) that cover the floating chorionic villi (Figure 1). These villi, which are in direct contact with maternal blood in the intervillous space, perform nutrient and gas exchange for the fetus. In the other pathway, which is the focus of the present review, a subset of proliferative cytotrophoblast cells differentiates into extravillous (intermediate) cytotrophoblasts (evCTBs). These cells leave the trophoblast basement membrane and form columns of non-polarized cells, the anchoring chorionic villi that attach to and then penetrate the uterine wall. At the base of anchoring villi, evCTBs form clusters of proliferating cells (proliferating evCTBs) (Lacroix *et al*., 2005). As they further differentiate, evCTB cells lose the ability to divide within cell columns and become mobile and highly invasive (invading evCTBs). Moreover, the cytotrophoblast cell columns spread laterally and fuse with the neighbouring columns to form a cytotrophoblast shell that encircles the embryonic sac. The invading evCTB cells arise from this cytotrophoblast shell. Amongst the invading (intermediate) evCTB cells, interstitial evCTB cells invade the decidualized endometrium and the proximal third of the myometrium (interstitial invasion), whereas some evCTB (endovascular evCTB) cells invade the uterine spiral arteries (endovascular invasion). During interstitial invasion, interstitial evCTB cells, either individually or in small clusters, blend with resident decidual, myometrial and immune cells. Following invasion into the decidua, the interstitial trophoblastic cells become isolated fusiform pleiomorphic cells. By 8 weeks of pregnancy, interstitial evCTB cells have extensively colonized the full thickness of the uterine mucosa to reach the decidual–myometral border. As the cells move deeper into the decidua, interstitial evCTB cells become multinucleated and more rounded (placental bed giant cells). During the second trimester, there is further invasion into the inner myometrium, and most of the trophoblast cells here possess the morphology of placental bed giant cells.

Thus, the behaviour of highly proliferative vCTB stem cells and proliferative evCTBs (intermediate proliferating evCTBs at the base of cell columns) closely resembles that of transformed cells displaying a tumorigenic phenotype after neoplastic transformation. This transformation is accomplished by localized tumours in the absence of metastasis (Gupta *et al*., 2005). Both cytotrophoblastic cells and cancer cells are highly proliferative and display a lack of cell-contact inhibition, two major traits shared by all types of human tumours. However, in contrast to that of tumour cells, the proliferation of evCTB cells is tightly regulated, and these cells quit cell growth during invasive differentiation (Pollheimer and Knofler, 2005). Following the differentiation of proliferative evCTBs into migratory and invasive evCTBs (intermediate invading evCTBs of cell columns, interstitial evCTBs and endovascular evCTBs), the behaviour of invasive evCTBs closely resembles

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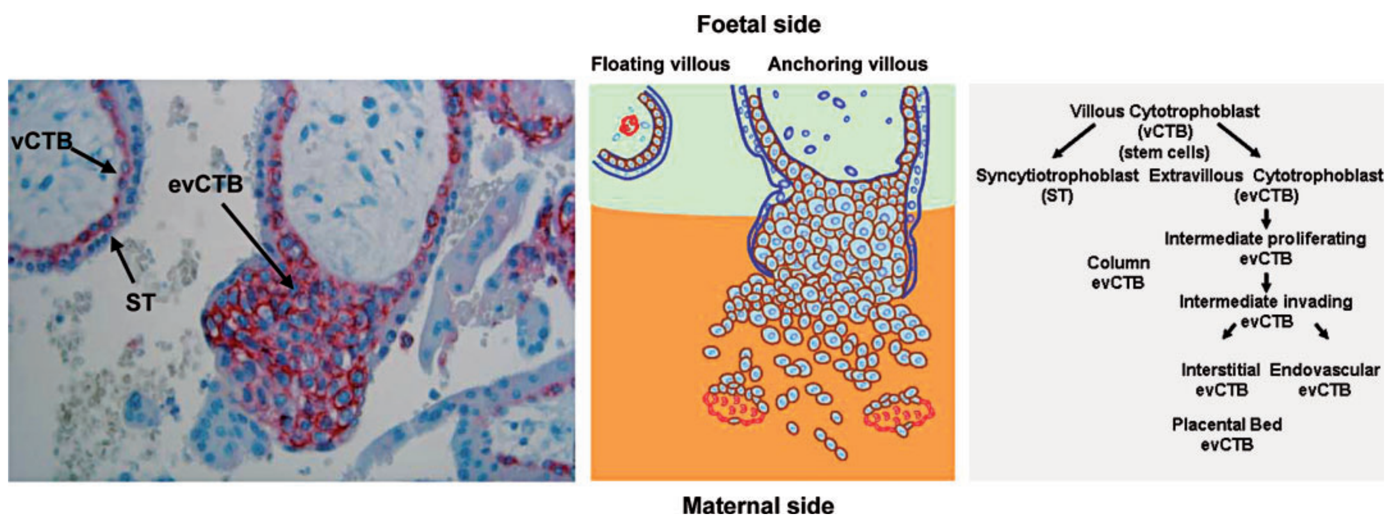

Figure 1. Left: immunohistochemical staining of early placenta with antibody to cytokeratin 07. This antibody stains (brown colour) the villous cytotrophoblasts (vCTBs) and the extravillous cytotrophoblasts (evCTBs) but does not stain the syncytiotrophoblasts (STs) (blue colour). Middle: Schematic representation of floating and anchoring villi. Right: Diagram of different trophoblast subpopulations.

that of transformed cells displaying a metastatic phenotype after malignant transformation (Poste and Fidler, 1980). In effect, these evCTBs possess one major aptitude shared by all metastatic tumours, that of migration/invasion. In migratory and invasive evCTBs, as well as in malignant cells, invasion is not due to passive growth pressure but rather due to an active process that involves attachment to the basement membrane followed by detachment and proteolysis of the basement membrane before its penetration (Liotta, 1984; Bischof and Campana, 2000; Staff, 2001). However, the migratory and invasive capacities of invading evCTB cells are spatially and time regulated. Ultimately, cytotrophoblastic cells and malignant cells share similar behaviour resulting from similar capacities. These capacities enable either the accomplishment of successful embryo implantation and pregnancy progression when kept under control or the achievement of neoplastic and malignant transformation when such capacities are no longer kept under control.

Resemblance of the expression of key molecules implicated in proliferation, migration and invasive processes

The analogous behaviours of normal cytotrophoblast and cancer cells originate in part from their individual genetic programmes, and notably from their transcriptional and translational activities that result in the production of proteins. Thus, the road towards a better comprehension of the common characteristics shared by these cells must include the knowledge of genes and proteins similarly expressed by the two types of cells and which might play an important role in their analogous proliferative, migratory and invasive capacities. Amongst these genes and proteins are proto-oncogenes, growth factors, cell-surface receptors, enzymes, enzyme receptors and enzyme inhibitors, as well as various hormones and peptides. In addition, this comprehension must also include the elucidation of genes and proteins that could enable their immune escape.

Proto-oncogenes

Proto-oncogenes are normal cellular genes homologous to the viral oncogenes that induce cancer. Proto-oncogenes, once activated, become oncogenes that are also capable of inducing neoplasia. Activation occurs through various mechanisms such as mutation, gene amplification or chromosome rearrangement. Proto-oncogene products can be classified into cytokines, tyrosine kinases, receptors, G-proteins, cell-cycle regulators, DNA repair enzymes and transcription factors (Hesketh, 1995; Ruddon, 1995; Bischof and Campana, 2000). They are thus responsible for essential processes, including cell proliferation, migration and invasion. Proto-oncogenes play an important role in the aetiology of cancers, because their transcription is one of the first steps leading to malignant cell transformation (Bishop, 1987). Thus, it is noteworthy that several proto-oncogenes are similarly expressed by both normal trophoblasts and cancer cells. In the cancer catalogue, many oncogenes act by mimicking normal growth signalling in one way or another (Hahn and Weinberg, 2002). Similarly, several proto-oncogenes encoding growth factor receptors are expressed by trophoblast cells. The c-*erbB1* (*HER1*, *ERBB1* or *EGFR*) proto-oncogene is expressed exclusively by the cytotrophoblast in 4- to 5-week placenta and predominantly in the ST after 6 weeks of gestation (Maruo and Mochizuki, 1987; Sugawara *et al*., 1994; Maruo *et al*., 1995). Owing to its mRNA expression pattern, it is thus not surprising that the cDNA sequence of human epidermal growth factor receptor (EGFR), the prototypical receptor tyrosine kinase (RTK), was isolated and characterized in 1984 both from normal placenta cells and from tumour cells (A431 epidermoid carcinoma cells) (Ullrich *et al*., 1984; Gschwind *et al*., 2004). This proto-oncogene encoded a 170-kDa transmembrane glycoprotein, the EGFR, which belongs to the c-*erbB* family of RTKs and which is involved in the pathogenesis of numerous tumours of different histological type, including breast cancers (Hynes and Lane, 2005). At least four other proto-oncogenes, namely c-*erbB2* (*HER2/neu*, *ERBB2*), c-*fms* (*CSF1R*), c-*met* (*MET*) and c-*kit* (*KIT*), encode RTKs and are expressed by both normal trophoblasts and cancer cells (Table I). C-*erbB2* is expressed by the evCTB (Fulop *et al*., 1998) and codes for an RTK which, like the EGFR, is expressed by tumours of different histological types and is a target of cancer (immuno)therapy (Gschwind *et al*., 2004). C-*fms* codes for the colony-stimulating factor receptor (CSF1R) and is expressed by the ST (Fulop *et al*., 1998), whereas c-*met* is expressed by the cytotrophoblast (Kauma *et al*., 1997) and codes for the hepatocyte growth factor/scatter factor (HGF/SF) receptor Met, a receptor that controls growth, invasion and metastasis in cancer cells (Birchmeier *et al*., 2003). C-*kit* (*KIT*), which is expressed by villous trophoblast cells (Doneda *et al*., 1997), codes for the stem cell factor (SCF) receptor that plays an important role in cell proliferation and cell migration (Kauma *et al*., 1996).

Several other proto-oncogenes that do not code for RTKs are also expressed by normal trophoblast cells and tumour cells. C-*Abl* (*ABL1*) codes for a protein that displays serine/threonine kinase activity and that has been implicated in a range of cellular processes, including cell migration (Hantschel and Superti-Furga, 2004). C-*fos* (*FOS*), c-*jun* (*JUN*), c-*myc* (*MYC*) and c-*ets1* (*ETS1*) code for transcription factors and are all expressed by evCTBs (Goustin *et al*., 1985; Quenby *et al*., 1998; Bamberger *et al*., 2004; Takai *et al*., 2005), with the exception of c-*jun* that is also expressed by the villous trophoblasts (Bamberger *et al*., 2004). It was recently demonstrated that the Fos protein is important in anchor cell invasion (Montell, 2005; Sherwood *et al*., 2005) and that Fos is likely to contribute to cell invasion during both normal development of trophoblasts and pathological processes leading to metastases: Fos and Jun are expressed at the appropriate time and place in trophoblast cells so as to stimulate trophoblast invasion during the development of the placenta (Bischof, 2001). Fos, which forms heterodimers with Jun, also appears to contribute to tumour metastasis in at least some types of cancer: the expression of c-*fos* correlates with poor prognosis in squamous cell lung carcinomas (Volm *et al*., 1993), and *c-fos* is expressed at higher levels in malignant prostate cancer than in benign prostatic hyperplasia (Aoyagi *et al*., 1998). C-*myc* (*MYC*) transcripts display strong expression in evCTB cells of early placenta (Pfeifer-Ohlsson *et al*., 1984): analyses of RNA from different periods of placental development show a 20- to 30-fold excess of c-*myc* transcription at 5 weeks as compared with terminal placenta. This ratio of transcription is within the same order of magnitude as that observed between the tumoral colon cell line COLO 320 HSR and normal colon cells (Alitalo *et al*., 1983; Pfeifer-Ohlsson *et al*., 1984; Sarkar *et al*., 1986). This proto-oncogene is part of the post-receptor intracellular signalling pathway for the stimulation of cell proliferation by

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Table I. Proto-oncogenes expressed by normal trophoblastic and malignant non-trophoblastic cells

Proto-oncogenes	Expression	
	Normal trophoblasts	Malignant tumours
c-ras (*RAS*)	Villous cytotrophoblasts (vCTBs) (Sarkar *et al*., 1986)	Colorectal (Downward, 2003)
c-kit (*KIT*)	vCTBs (Doneda *et al*., 1997)	Breast (Crisi *et al*., 2005)
		Testis (Nakai *et al*., 2005)
c-jun (*JUN*)	Cytotrophoblast (CT), extravillous cytotrophoblasts (evCTBs) (Bamberger *et al*., 2004)	Lung (Maeno *et al*., 2006)
		Kidney (Oya *et al*., 2005)
c-met (*MET*)	CT (Kauma *et al*., 1997)	Colon (Resnick *et al*., 2004)
		Gastric (Birchmeier *et al*., 2003; Han *et al*., 2005)
c-fos (*FOS*)	vCTB (Doneda *et al*., 1997)[a]	Cervical (van Riggelen *et al*., 2005)
	evCTB (Bamberger *et al*., 2004)	Breast (Calaf and Hei, 2004)
c-myc (*MYC*)	CT, evCTB (Pfeifer-Ohlsson *et al*., 1984; Goustin *et al*., 1985; Roncalli *et al*., 1994)	Breast (Sirotkovic-Skerlev *et al*., 2005)
		Endometrium (Geisler *et al*., 2004)
c-erb-B1 (*ERBB1, HER1*)	CT (before 6 weeks)	Breast (Gschwind *et al*., 2004; Hynes and Lane, 2005)
	Syncytiotrophoblast (ST) (after 6 weeks) (Maruo and Mochizuki, 1987; Hofmann *et al*., 1992; Sugawara *et al*., 1994[a]; Maruo *et al*., 1995)	Ovary (Henic *et al*., 2006)
c-erb-B2 (*ERBB2, HER2*)	evCTB (Fulop *et al*., 1998)	Breast (Hynes and Lane, 2005)
		Gastric (Pinto-de-Sousa *et al*., 2002)
		Cervical (Nakano *et al*., 1997)
		Ovary (Frutuoso *et al*., 2001)
c-sis (*SIS, PDGFB*)	evCTB (Goustin *et al*., 1985)	Leukaemia (Romero *et al*., 1986)
		Osteosarcoma (Graves *et al*., 1984)
c-fms (*CSF1R*)	evCTB (Jokhi *et al*., 1993)	Liver (Yang *et al*., 2004)
	ST (Fulop *et al*., 1998)	
c-Abl (*ABL1*)	Trophoblasts (T) (Park *et al*., 1992)	Leukaemia (Hantschel and Superti-Furga, 2004)
		Ovarian (Niyazi *et al*., 2003)

[a]Expression observed at the mRNA level.

a growth factor, and increased wild-type *MYC* expression occurs frequently in human cancers (Dang *et al*., 2005). Immunoperoxidase studies have shown that c-*myc* transcripts are also translated in cytotrophoblasts (Maruo and Mochizuki, 1987). C-*ets1* (*ETS1*) is a downstream target of the HGF/SF pathway. Reciprocally, ETS1 acts as a transcriptional factor for the *MET* gene (Paumelle *et al*., 2002) and is thus implicated in cell proliferation and cell migration (Birchmeier *et al*., 2003). This proto-oncogene is strongly expressed by evCTB cells during the first trimester of pregnancy (Takai *et al*., 2005).

Apart from proto-oncogenes encoding transcription factors, two proto-oncogenes also expressed by both normal trophoblasts and malignant tumours, c-*sis* (*SIS*, *PDGFB*) and c-*ras* (*RAS*), code for proteins with different functions. The c-*sis* proto-oncogene encodes one of the two chains (the B-chain) constituting platelet-derived growth factor (PDGF). The c-*sis* proto-oncogene is transcribed in early placenta at levels comparable with transcription in human tumour (sarcoma) cell lines actively producing PDGF (Goustin *et al*., 1985), and the maximal levels of c-*sis* transcripts are found in particularly active and invasive evCTB cells (Goustin *et al*., 1985). The c-*ras* family of proto-oncogenes (*K-RAS*, *N-RAS* and *H-RAS*) codes for RAS proteins (small monomeric membrane-localized GTPases) that play an essential role in controlling the activity of several crucial signalling pathways that regulate cellular proliferation (Downward, 2003; Malumbres and Barbacid, 2003). *C-ras* transcripts were found in early villous trophoblast at 4 weeks after conception, and expression was not apparent at 8 weeks after conception (Sarkar *et al*., 1986).

Finally, all these proto-oncogenes interact in a complex, only partially elucidated way to control cellular proliferation, migration and invasiveness, and it is remarkable that each type of trophoblast expresses a subtly different combination of proto-oncogenes (Quenby *et al*., 1998). Moreover, it is noteworthy that several of those proto-oncogenes, including c-*erbB1*, c-*myc*, c-*ets1*, c-*sis* and c-*ras*, are preferentially expressed by trophoblast cells during the first weeks of pregnancy, a time at which the proliferative, migratory and invasive properties of these cells are at their peak.

Growth factors and their receptors

Growth factors and their receptors play a central role in cell proliferation. Indeed, normal cells require mitogenic growth signals (GSs) before they can move from a quiescent state into an active proliferative state. These signals are transmitted to the cell by transmembrane receptors that bind distinct classes of signalling molecules: diffusible growth factors, extracellular matrix (ECM) components and cell-to-cell adhesion/interaction molecules (Hanahan and Weinberg, 2000). It is now established that ectopic synthesis or excessive production of these classes of molecules may lead to the expression of a transformed phenotype. Interestingly, many of these growth factors and their receptors are similarly expressed by normal trophoblasts and malignant non-trophoblastic tumours (Tables II and III).

Among the growth factors expressed by both normal trophoblasts and malignant non-trophoblastic tumours are EGFs (Ladines-Llave *et al*., 1991), CSF1 (Hamilton *et al*., 1998), transforming growth

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Table II. Growth factors expressed by normal trophoblastic and malignant non-trophoblastic cells

Growth factors	Expression	
	Normal trophoblasts	Malignant tumours
Epidermal growth factor (EGF)	Cytotrophoblast (CT) (late), syncytiotrophoblast (ST) (early) (Ladines-Llave *et al*., 1991)	Endometrial carcinoma (Bellone *et al*., 2005)
Platelet-derived growth factor (PDGF)-like	CT[a] (Goustin *et al*., 1985)	Gastric (Wada *et al*., 1998)
Insulin-like growth factor-1 (IGF-1)	CT (early and late), ST (late) (Maruo *et al*., 1995)	Liver[a] (Luo *et al*., 2005) Gastric[a] (Zhao *et al*., 2005)
IGF-2	CT[a] (Ohlsson *et al*., 1989)	Liver[a] (Dong *et al*., 2005) Breast (Giani *et al*., 2002)
Colony-stimulating factor-1 (CSF1)	Extravillous cytotrophoblasts (evCTBs) (Hamilton *et al*., 1998)	Breast (Sapi, 2004) Endometrial carcinoma (Smith *et al*., 1995)
Vascular endothelial growth factor (VEGF)	evCTB (Clark *et al*., 1996)	Thyroid (Vieira *et al*., 2005)
Transforming growth factor (TGF)-β	ST (Dungy *et al*., 1991)	Lung (Saji *et al*., 2003)
Placental growth factor (PIGF)	Trophoblasts (T) (Torry *et al*., 1999)	Breast (O'Brien *et al*., 2003)

[a]Expression observed at the mRNA level.

Table III. Growth factor receptors expressed by normal trophoblastic and malignant non-trophoblastic cells

Growth factor receptors	Expression	
	Normal trophoblasts	Malignant tumours
Insulin receptors (IRs)	Cytotrophoblast (CT), syncytiotrophoblast (ST) (Jones *et al*., 1993)	Prostate (Huang *et al*., 2003)
Insulin-like growth factor (IGF)-IR	CT (early and late), ST (late) (Murata *et al*., 1994)	Adrenocortical (Ilvesmaki *et al*., 1993)
IGF-2R	Villous cytotrophoblast (vCTB)[a] (Ohlsson *et al*., 1989)	Adrenocortical (Ilvesmaki *et al*., 1993)
Corticotrophin-releasing factor (CRF)-R2	CT[a] (Florio *et al*., 2000)	Central and peripheral nervous system (Reubi *et al*., 2003)
Epidermal growth factor receptor (EGFR)	CT, ST (Maruo and Mochizuki, 1987; Hofmann *et al*., 1992; Sugawara *et al*., 1994[a]; Maruo *et al*., 1995)	Breast (Gschwind *et al*., 2004; Hynes and Lane, 2005) Ovarian (Henic *et al*., 2006)
Hepatocyte growth factor receptor (HGFR)	CT (Kauma *et al*., 1997)	Colon (Resnick *et al*., 2004) Gastric (Birchmeier *et al*., 2003; Han *et al*., 2005)
Erythropoietin-R	vCTB, extravillous cytotrophoblasts (evCTBs), ST (Fairchild Benyo and Conrad, 1999)	Lung (Dagnon *et al*., 2005) Breast (Acs *et al*., 2002)
Vascular endothelial growth factor receptor (VEGFR)-1 (Flt-1) VEGFR-2 (KDR)	evCTB (Athanassiades *et al*., 1998; Tseng *et al*., 2006)	Breast (Meunier-Carpentier *et al*., 2005)
Granulocyte–macrophage colony-stimulating factor receptor (GM-CSFR)	vCTB, evCTB (Jokhi *et al*., 1994)	Prostate (Rivas *et al*., 1998)
G-CSFR	evCTB[a] (McCracken *et al*., 1999)	Colon (Yang *et al*., 2005)
ERBB2	evCTB (Fulop *et al*., 1998)	Breast (Hynes and Lane, 2005) Gastric (Pinto-de-Sousa *et al*., 2002) Cervical (Nakano *et al*., 1997) Ovary (Frutuoso *et al*., 2001)
CSF1R	evCTB (Jokhi *et al*., 1993) ST (Fulop *et al*., 1998)	Prostate (Ide *et al*., 2002) Breast (Sapi, 2004) Liver (Yang *et al*., 2004) Endometrial carcinoma (Smith *et al*., 1995)
Platelet-derived growth factor (PDGF)-AAR	Trophoblasts (T) (Gurski *et al*., 1999)	Breast (Carvalho *et al*., 2005)

[a]Expression observed at the mRNA level.

factor-α (TGF-α) (Horowitz *et al*., 1993), TGF-β (Dungy *et al*., 1991), insulin-like growth factor (IGF) (Maruo *et al*., 1995), in particular IGF-2 (Ohlsson *et al*., 1989), placental growth factor (PIGF) (Maglione *et al*., 1991, 1993; Torry *et al*., 1999), vascular endothelial growth factor (VEGF) (Clark *et al*., 1996), erythropoietin (Conrad *et al*., 1996) and PDGF-like protein (Goustin *et al*., 1985). A trophoblast-derived growth factor has also been described as being similarly expressed by normal trophoblasts and malignant non-trophoblastic tumours (Sen-Majumdar *et al*., 1986b): this peptide is actively expressed in cytotrophoblastic and ST cells in the human carcinoma cell line A431 and in the bladder and breast tumour cells (Bishayee *et al*., 1984; Sen-Majumdar *et al*.,

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1986a; Roy-Choudhury *et al.*, 1988). This 34-kDa protein is one of the most abundant molecules present on trophoblast membranes, especially during the first trimester of pregnancy. Its amino acid sequence resembles that of the calpactins, a family of proteins capable of binding calcium, phospholipids and actin. Finally, it is noteworthy that most of those growth factors, with the exception of TGF-β, are expressed by cytotrophoblast cells.

Among growth factor receptors expressed by both normal trophoblasts and malignant non-trophoblastic tumours, there are those encoded by proto-oncogenes which, once activated, become oncogenes capable of inducing neoplasia. These receptors, as described above, include EGFR EGFR/ERBB1, HER2/neu RTK ERBB2, CSFR and HGF/SF receptor Met. Moreover, the trophoblast cells are rich in receptors for many other growth factors including the insulin receptor (Jones *et al.*, 1993), the IGF-I receptor (Murata *et al.*, 1994), the IGF-II receptor (Ohlsson *et al.*, 1989), VEGF receptors (VEGFR-1 or Flt-1 and VEGFR-2 or KDR) (Athanassiades and Lala, 1998; Athanassiades *et al.*, 1998; Chakraborty *et al.*, 2002; Tseng *et al.*, 2006), the erythropoietin receptor (Fairchild Benyo and Conrad, 1999), the granulocyte–macrophage (GM)-CSFR (Jokhi *et al.*, 1994), the granulocyte (G)-CSFR (McCracken *et al.*, 1999) and the PDGF receptor (Gurski *et al.*, 1999). Again, it is striking that a large majority of these receptors are expressed by cytotrophoblast cells.

Enzymes

Invasion and migration are complex processes, and their genetic and biochemical determinants remain incompletely understood. At the mechanistic level, they are closely allied processes, which justifies their association with one another as representing a common function of both normal and cancer cells. The two processes utilize similar operational strategies involving changes in physical coupling of cells to their microenvironment and activation of extracellular proteases. Many proteases, protease receptors and protease inhibitors are similarly expressed by both normal trophoblasts and malignant cells (Table IV). These proteases include several members of the family of matrix metalloproteinases (MMPs) (Bischof *et al.*, 2000). MMPs, also called matrixins, are a family of at least 17 human zinc-dependent endopeptidases collectively capable of degrading essentially all components of the ECM. Normal trophoblasts and cancer cells express (i) MMP-2 (also called gelatinase A) and MMP-9 (also called gelatinase B) (Bjorn *et al.*, 2000; Isaka *et al.*, 2003), which digest collagen type IV (the major constituent of basement membranes) and denatured collagen (gelatine); (ii) MMP-11 (also called stromelysin-3), which digests collagen; and (iii) a membrane-bound MMP, membrane-type MMP-1 (MT-MMP-1), which is thought to activate progelatinase A. Most MMPs are secreted as inactive proenzymes that become activated in the extracellular compartments. In addition to MT-MMPs, several enzymes are capable of activating these proenzymes, the most prominent being plasmin. The latter enzyme is activated from plasminogen by the urokinase plasminogen activator (uPA), which is also secreted by normal trophoblastic and malignant non-trophoblastic cells and is involved in the invasive behaviour of these cells. Both trophoblasts and cancer cells also express the uPA receptor (Zini *et al.*, 1992), which can bind active uPA and localize proteolysis to the leading edge of migrating cells (Estreicher *et al.*, 1990; Roldan *et al.*, 1990; Strickland and Richards, 1992). The activity of the plasminogen activator is inhibited by the plasminogen activator inhibitor (PAI-1), which is also expressed by both trophoblasts and malignant tumours. Moreover, the activity of MMPs in the extracellular space is inhibited by the tissue inhibitors of metalloproteinases (TIMPs) that bind specifically to the highly conserved zinc-binding site of active MMPs at molar equivalence. The TIMP gene family consists of four structurally related members, TIMP-1, TIMP-2, TIMP-3 and TIMP-4, and both normal trophoblastic and malignant non-trophoblastic cells express TIMP-1. Other enzymes such as heparan sulphate-degrading endoglycosidase, similarly referred to as heparanase, are expressed by cytotrophoblasts (Klein and Von Figura, 1976; Haimov-Kochman *et al.*, 2002), and the expression of heparanase correlates with the metastatic behaviour of cancer cells (Parish *et al.*, 1987; Nakajima *et al.*, 1988; Friedmann *et al.*, 2000). In addition, two protease receptors are also expressed by normal trophoblasts and cancer cells: the protease-activated receptor (PAR) (O'Brien *et al.*, 2003) and the receptor for thrombin, a serine protease (Even-Ram *et al.*, 1998). Taken together, these data show that trophoblasts and malignant cells possess many similar components implicated in molecular circuitries aimed at degrading the ECM.

Various (glyco)protein hormones, peptides and receptors

Various hormones, peptides and receptors similarly expressed by normal trophoblasts and malignant cells are quite impressive (Table V), especially when bearing in mind that many of those molecules may have a direct or indirect impact on the proliferative, migratory and invasive properties of these cells. Amongst these hormones, peptides and receptors are the following: a growth hormone variant (hGH-V) (Scippo *et al.*, 1993), human placental lactogen (HPL) (Sasagawa *et al.*, 1987), prolactin (PRL) (Kasai *et al.*, 1982), urocortin (Clifton *et al.*, 2000), Met-enkephalin (Sastry *et al.*, 1980), β-endorphin (Laatikainen *et al.*, 1987), dynorphins (DYN) (Ahmed *et al.*, 1992), somatostatin (Watkins and Yen, 1980), thyrotrophin-releasing hormone (TRH) (Bajoria and Babawale, 1998), GnRH (Chou *et al.*, 2004), inhibin (Shih and Kurman, 1999), activin (Caniggia *et al.*, 1997), follistatin (Petraglia *et al.*, 1994), neuropeptide Y (NPY) (Petraglia *et al.*, 1989), renin (Tomita *et al.*, 1987; Egan *et al.*, 1988), oxytocin (Chibbar *et al.*, 1993), relaxin (Bryant-Greenwood *et al.*, 1987), leptin (O'Brien *et al.*, 1999; Castellucci *et al.*, 2000), tumour necrosis factor-alpha (TNF-α) (Haynes *et al.*, 1993), ACTH (Saijonmaa *et al.*, 1988), corticotrophin-releasing factor (CRF) (Saijonmaa *et al.*, 1988), their receptors CRF-R1 and CRF-R2 (Florio *et al.*, 2000) and a receptor for leukaemia inhibitory factor (LIF) (Sharkey *et al.*, 1999). Recent studies have shown that molecules such as pro-early placenta insulin-like peptide (pro-EPIL), a novel peptide involved in the motility and invasiveness of cancer cells (Bellet *et al.*, 1997a; Brandt *et al.*, 2002), and metastin, a peptide encoded by metastasis suppressor gene *KiSS-1* (Ohtaki *et al.*, 2001; Bilban *et al.*, 2004), are also produced by both normal trophoblastic and cancer cells.

Tumour-associated antigens

An overview of the traits common to both normal trophoblasts and cancer cells cannot overlook tumour-associated antigens (TAAs) expressed by both types of cells (Table VI), even though the implication of these antigens in the comparable behaviour of such

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Table IV. Enzymes, enzyme receptors and enzyme inhibitors expressed by normal trophoblastic and malignant non-trophoblastic cells

Enzymes, enzyme receptors and enzyme inhibitors	Expression	
	Normal trophoblasts	Malignant tumours
Membrane-type matrix metalloproteinase-9 (MT-MMP-9) (gelatinase B)	Cytotrophoblast (CT) (Isaka *et al*., 2003; Cohen *et al*., 2006b)	Ovarian[a] (Hu *et al*., 2004)
Heparanase	CT (Haimov-Kochman *et al*., 2002)	Breast (Cohen *et al*., 2006a) Pancreas (Schoppmeyer *et al*., 2005)
Thrombin receptor	CT (Even-Ram *et al*., 1998)	Breast (Even-Ram *et al*., 1998)
Urokinase plasminogen activator (uPA)	Extravillous cytotrophoblasts (evCTBs) (Floridon *et al*., 1999)	Bladder (Champelovier *et al*., 2002) Breast (Kim *et al*., 1997) Gastric (Iwamoto *et al*., 2005)
uPA receptor	evCTB (Floridon *et al*., 1999)	Gastric[a] (Iwamoto *et al*., 2005) Breast (Kim *et al*., 1997)
Tissue inhibitor of metalloproteinase-1 (TIMP-1)	evCTB (Huppertz *et al*., 1998)	Breast[a] (Nakopoulou *et al*., 2002) Ovarian[a] (Hu *et al*., 2004) Colon[a] (Pesta *et al*., 2005)
MT-MMP-1	evCTB (Nawrocki *et al*., 1996)	Colon[a] (Okada *et al*., 1995)
Protease-activated receptor (PAR)	evCTB (O'Brien *et al*., 2003)	Breast (Boire *et al*., 2005)
MT-MMP-11	evCTB (Maquoi *et al*., 1997; Cohen *et al*., 2006b)	Gastric (Deng *et al*., 2005)
MT-MMP-2	evCTB[a] (Bjorn *et al*., 2000) evCTB (Isaka *et al*., 2003; Cohen *et al*., 2006b)	Ovarian[a] (Hu *et al*., 2004) Colon[a] (Pesta *et al*., 2005)
Plasminogen activator inhibitor (PAI-1)	Trophoblasts (T) (Zini *et al*., 1992)	Colorectal[a] (Sakakibara *et al*., 2005) Gastric[a] (Iwamoto *et al*., 2005)

[a]Expression observed at the mRNA level.

cells is unclear. The prototypic TAA expressed by both trophoblasts and cancer cells is the beta subunit of hCGβ. hCG is a glycoprotein hormone composed of two non-covalently linked molecules, the alpha subunit (hCGα) and the beta subunit (hCGβ). Alpha and beta subunits of hCG are produced by ST cells and secreted into the maternal circulation preferentially in the form of the α/β dimer that constitutes hCG (Ozturk *et al*., 1988). hCG is found in the blood of pregnant women at 6–8 days after fertilization (Tyrey, 1982), but hCGβ mRNA is already detectable at the 8-cell stage (Bonduelle *et al*., 1988). The free hCGβ subunit is also produced by numerous non-trophoblastic malignant tumours of different histological types, including bladder, pancreatic and cervical carcinomas (Marcillac *et al*., 1992). Indeed, the similarity between normal trophoblastic cells and malignant non-trophoblastic cells is particularly striking at the level of hCGβ gene expression: the beta subunit of hCG, which is comprised of 145 amino acid residues, is encoded by four non-allelic *CG* beta (*CGβ*) genes. Type I *CGβ* allelic genes beta-7 and beta-6 possess a GCC codon corresponding to an alanine at position 117 of hCGβ, whereas type II *CGβ* genes beta-8, beta-5 and beta-3 and its allele beta-9 possess a GAC codon corresponding to an aspartic acid at the same position (Figure 2). In normal trophoblast, hCGβ is encoded by type II *CGβ* genes, whereas normal non-trophoblastic tissues of a different histological origin (breast, prostate, skeletal muscle, bladder, adrenal glands, thyroid, colon and uterine) express only type I *CGβ* genes. In contrast, non-trophoblastic tumours of differing histological origins, including breast, bladder, prostate and thyroid cancers, express type II *CGβ* genes. Experiments performed on tumour tissues and their normal counterparts have confirmed that the malignant transformation of non-trophoblastic cells is associated with the expression of type II *CGβ* genes expressed by normal trophoblastic cells (Bellet *et al*., 1997b). These observations are a salient illustration of the exquisite similarity between normal trophoblast and malignant non-trophoblastic tumours in terms of the expression of certain genes.

Apart from the prototypic TAA hCGβ, several other TAAs are also expressed by trophoblasts, including prostate-specific antigen (PSA), an antigen overexpressed by prostate cancers (Malatesta *et al*., 2000), osteopontin (OPN) (Briese *et al*., 2005a) and CEACAM1, a member of the carcinembryonic antigen (CEA) family (Bamberger *et al*., 2001). Moreover, the pregnancy-specific β-glycoprotein (PS-βG) family is characteristic of trophoblasts (Lei *et al*., 1992) and contains molecules displaying close homologies to CEA (Oikawa *et al*., 1989; Leslie *et al*., 1990). In addition, recently identified genes from the melanoma antigen (MAGE), G antigen (GAGE) and P antigen (PAGE) families that encoded tumour-specific shared antigens expressed by either melanomas or a prostate cancer cell line are also expressed in the placenta (Chen *et al*., 1998; De Backer *et al*., 1999; Kwon *et al*., 2005).

Taken together, these data indicate that numerous genes and proteins are similarly expressed by normal trophoblastic cells and malignant non-trophoblastic cells. In line with that observation, a recent study using DNA microarrays showed that cancer cells overexpress genes that are preferentially expressed in only one type of normal tissue, such as placenta. On the basis of the latter observations, it was suggested that the ability to overexpress genes normally preferentially expressed in tissues other than those of the cancer's origin is a general property of cancer cells and that this capacity is of major importance in determining the behaviour of the cancer, including its metastatic potential (Lotem *et al*., 2005).

Similar mechanisms of proliferation

Several comparable mechanisms may explain the high proliferative capacity of both trophoblastic and cancer cells. Amongst them, and as shown by recapitulation of the many key molecules

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Table V. Various (glycoprotein) hormones, peptides and receptors expressed by normal trophoblastic and malignant non-trophoblastic cells

(Glyco) protein hormones, peptides, receptors	Expression	
	Normal trophoblasts	Malignant tumours
Somatostatin	Cytotrophoblast (CT) (Watkins and Yen, 1980)	Pancreas (Tamiolakis *et al*., 2005)
Metastin	CT (Bilban *et al*., 2004)	Breast (Martin *et al*., 2005)
Activin A	CT (Caniggia *et al*., 1997)	Endometrium[a] (Otani *et al*., 2001) Liver (Wagner *et al*., 2004)
Neuropeptide Y (NPY)	CT (Petraglia *et al*., 1989)	Pancreas (Waeber *et al*., 1995) Pituitary (Grouzmann *et al*., 1998)
Relaxin	CT (Bryant-Greenwood *et al*., 1987)	Breast (Tashima *et al*., 1994)
Corticotrophin-releasing factor (CRF)	CT (Saijonmaa *et al*., 1988)	Endometrium[a] (Florio *et al*., 2003) Bronchial carcinoid (Suda, 1994)
Pro-early placenta insulin-like peptide (Pro-EPIL)	Villous cytotrophoblast (vCTB) (Bellet *et al*., 1997a)	Breast (Brandt *et al*., 2002)
CRF-R2	CT[a] (Florio *et al*., 2000)	Central and peripheral nervous system (Reubi *et al*., 2003)
Leukaemia inhibitory factor (LIF-R)	vCTB–extravillous cytotrophoblasts (evCTBs) (Sharkey *et al*., 1999)	Prostate (Garcia-Tunon *et al*., 2005) Ovary (Savarese *et al*., 2002)
GnRH	evCTB (Chou *et al*., 2004)	Ovarian (Grundker and Emons, 2003) Breast (Grundker *et al*., 2002) Endometrium (Grundker *et al*., 2002)
Leptin	evCTB (Castellucci *et al*., 2000)	Breast (O'Brien *et al*., 1999; Somasundar *et al*., 2004)
Human placental lactogen (HPL) or human chorionic somatomammotropin (HCS)	evCTB (Sasagawa *et al*., 1987)	Breast (Bonneterre *et al*., 1990)
Methionine enkephalin	Villous placenta (Sastry *et al*., 1980)	Thyroid, pituitary, carcinoid (Bostwick *et al*., 1987)
Inhibin	Syncytiotrophoblasts (STs) (Shih and Kurman, 1999)	Ovary (Yamashita *et al*., 1997) Breast (Shih and Kurman, 1999)
Follistatin	ST (Petraglia *et al*., 1994)	Endometrium (Ciarmela *et al*., 2004)
Prolactin (PRL)	ST (Kasai *et al*., 1982)	Colon (Otte *et al*., 2003)
Thyrotrophin-releasing hormone (TRH)	ST (Bajoria and Babawale, 1998)	Melanoma (Ellerhorst *et al*., 2004)
Beta endorphin	ST (Laatikainen *et al*., 1987)	Breast (Nesland *et al*., 1988)
Growth hormone (GH)	ST (Scippo *et al*., 1993)	Breast (Ahmed *et al*., 1992; Mol *et al*., 1995; Laban *et al*., 2003)
Urocortin	ST (Clifton *et al*., 2000)	Prostate (Arcuri *et al*., 2002)
TNF-α	ST (Haynes *et al*., 1993)	Ovary (Kulbe *et al*., 2005)
CRF-R1	ST[a] (Florio *et al*., 2000)	Central and peripheral nervous system (Reubi *et al*., 2003)

[a]Expression observed at the mRNA level.

Table VI. Tumour-associated antigens (TAAs) expressed by normal trophoblastic and malignant non-trophoblastic cells

TAAs	Expression	
	Normal trophoblasts	Malignant tumours
CEACAM1	Extravillous cytotrophoblasts (evCTBs) (Bamberger *et al*., 2001)	Colorectal (Nittka *et al*., 2004)
Osteopontin (OPN)	evCTB (Briese *et al*., 2005b)	Ovary (Kim *et al*., 2002) Breast (Das *et al*., 2004)
hCG-β	Syncytiotrophoblast (ST) (Yoshida, 2005)	Gonadal and non-gonadal (Marcillac *et al*., 1992)
Prostate-specific antigen (PSA)	ST (Malatesta *et al*., 2000)	Prostate (Hood *et al*., 2005)

expressed by the two types of cells, many are growth factors or growth factor receptors, suggesting that autocrine and paracrine growth might be important mechanisms in their proliferation.

Autocrine and paracrine growth

Although most soluble mitogenic growth factors are made up of one cell type to stimulate the proliferation of another (the process of heterotypic signalling), many cells acquire the ability to synthesize growth factors to which they are responsive, creating a positive feedback signalling loop often termed autocrine stimulation. Autocrine signalling (production of, and response to, a ligand by the same cell) is a similar mechanism of signal transduction in normal physiological processes. During tumorigenesis, misregulated autocrine signalling can render cancer cells less dependent on survival and growth factors from surrounding tissues. Several autocrine loops are common features of both trophoblastic and cancer cells, and notably the EGF/EGFR loop (Hofmann *et al*., 1992; Maruo *et al*.,

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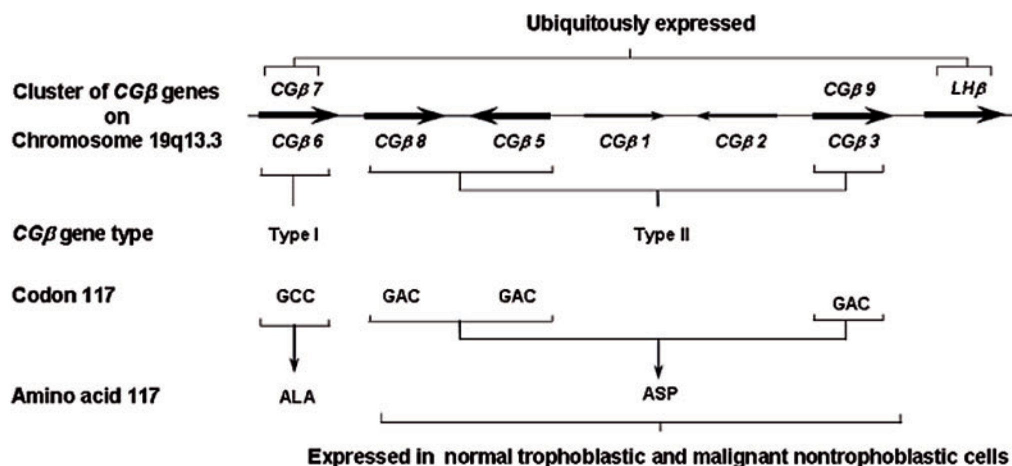

Figure 2. Organization of the CGβ/LHβ gene cluster and expression of human *CGβ* genes that code for the hCGβ subunit, a prototypic tumour-associated antigen. Normal trophoblastic and malignant non-trophoblastic cells express type II *CGβ* genes encoding the hCGβ subunit with an aspartic acid residue (ASP) at position 117. Normal non-trophoblastic cells express type I *CGβ* genes encoding the hCGβ subunit with an alanine residue (ALA) at position 117. *LHβ*: gene encoding the beta subunit of human lutropin.

1995; Petraglia *et al*., 1996), the IGF-2/IGF-2R loop (Ohlsson *et al*., 1989), the CSF1/CSF1R loop (Hamilton *et al*., 1998), the PDGF/PDGFR loop (Goustin *et al*., 1985) and the VEGF/VEGFR (Flt-1 and KDR) loop (Ahmed *et al*., 1995; Athanassiades and Lala, 1998; Athanassiades *et al*., 1998). The engagement of RTKs with growth factors such as EGF or IGF-2 promotes the activation of mitogen-activated protein kinase (MAPK) signalling (Lewis *et al*., 1998). Amongst the numerous MAPKs that are classified into four different families, protein kinases belonging to the extracellular-regulated kinase (ERK) family are the MAPKs predominantly activated by growth factors. A highly complex network of protein kinases regulates the activity of MAPKs through sequential phosphorylations at critical Ser, Thr and Tyr residues. Proteins of the MAPK kinase kinase (MAPKKK) family such as Raf or MEKK phosphorylate MAPK kinases (MAPKKs) including MEKs. The MAPKKs then activate the four major families of MAPKs including the ERK family. ERKs have been shown to play an important role in growth-factor-dependent regulation of trophoblast growth and migration (Pollheimer and Knofler, 2005). In the placenta, the expression of ERK1 and ERK2 was detected in vCTBs, but their active phosphorylated forms were only present until the 12th week of gestation, suggesting a predominant role during early pregnancy (Kita *et al*., 2003).

Apart from MAPK signalling, a second pathway downstream from RTKs involves phosphatidylinositol 3′-kinase (PI3K) and AKT and is an important regulator of cell proliferation and survival (Vivanco and Sawyers, 2002). Phosphorylated RTKs interact with p85 subunits of PI3K and recruit the enzyme to the membrane, whereas GTPases activate PI3K through binding of its p110 subunit. At the membrane, PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) and thereby converts PIP2 to phosphatidylinositol(3,4,5)triphosphate (PIP3), which activates the serine/threonine protein kinases AKT and PDK1. AKT/kinase B (PKB), a serine/threonine protein kinase that possesses three isoforms, phosphorylates a plethora of other target proteins that control proliferation, survival and cell size (Toker and Yoeli-Lerner, 2006), whereas PDK1 phosphorylates different protein kinase C (PKC) subunits. PKC and Ca/calmodulin-dependent kinase II (CaMKII) are also controlled through the PIP3-mediated increase in cytosolic Ca^{2+} levels. PIP3 levels are tightly regulated by lipid phosphatases such as phosphatase and tensin (PTEN) homologue converting PIP3 to PIP2 (Vivanco and Sawyers, 2002). The activation of the PI3K/AKT pathway and loss-of-function mutations of PTEN, which acts as a tumour suppressor, have been noted in a wide range of cancers (Cully *et al*., 2006). One of the critical targets of AKT is mTOR that plays a crucial role in PI3K-mediated oncogenesis (Vivanco and Sawyers, 2002). The kinase mTOR controls cell-cycle progression and cell size/mass through phosphorylation of proteins controlling protein translation (Fingar and Blenis, 2004). The activation of PI3K also plays a role in migration/invasion, for example, during IGF-I-induced migration of vascular smooth muscle cells (Duan *et al*., 2000). PI3K also plays a crucial role in growth-factor-mediated trophoblast migration. The activation of PI3K with specific peptides resulted in increased motility of SGHPL-5 evCTB cells, whereas the inhibition of PI3K reduced basal and HGF-induced migration (Cartwright *et al*., 2002). The integrated action of PI3K and ERK in EGF-stimulated phosphorylation and migration of HTR-8/SVneo evCTB cells was also demonstrated (Qiu *et al*., 2004a,b).

Growth factors can also activate focal adhesion kinase (FAK), a widely expressed non-receptor protein tyrosine kinase that has a growth/migration-promoting role. The activation of FAK is achieved by phosphorylation at different amino acid residues, in particular by phosphorylation at Tyr-397, and FAK activity was shown to be associated with tumour progression of cancer cells towards a malignant phenotype (Gabarra-Niecko *et al*., 2003). It is thus noteworthy that the phosphorylated form of the kinase was predominantly detected in interstitial cytotrophoblasts and was more abundant during the first weeks of pregnancy, colocalizing with the extravillous trophoblast markers MMP-2 and α5 integrin. In addition, the down-regulation of FAK reduced the outgrowth/migration of villous explant cultures and diminished the invasion of isolated cytotrophoblasts through Matrigel-coated chambers (Ilic *et al*., 2001; MacPhee *et al*., 2001). FAK also has an impact on activities of Rho proteins, a family (RhoA, Racl, Cdc 42) of particular GTPases regulating diverse biological processes such as

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cell cycle, cell–cell/focal adhesions, polarization and cell migration (Hall, 1998; Goode *et al*., 2000). The downstream effectors of Rho include p21-activated kinase (PAK), which cross-talks to the MAPK pathway by modulating Raf and Rho-associated, coiled-coil containing protein kinase (ROCK). The functionality of the RhoA–ROCK signalling cascade has also been suggested during trophoblast migration. Experiments based on presumptive extravillous trophoblast obtained after plating of minced first-trimester placental fragments showed that the treatment of these cells with selective Rho and ROCK inhibitors reduced spreading and migration through fibronectin-coated filters (Shiokawa *et al*., 2002).

The effects of autocrine signalling can also be amplified by paracrine signalling between neighbouring homotypic and heterotypic cells. Within normal tissue such as the placenta, cells are also instructed to grow by their neighbours (paracrine signals) or via systemic (endocrine) signals. Cell-to-cell growth signalling is likely to operate in the vast majority of human tumours as well; virtually, all are composed of several distinct cell types that appear to communicate via heterotypic signalling (Hanahan and Weinberg, 2000). Amongst paracrine loops common to both trophoblasts and cancer cells is the HGF/HGFR (Met) loop: cytotrophoblasts express Met (HGFR) (Saito *et al*., 1995), whereas mesenchymal cells within the stromal cores of chorionic villi produce HGF (Kauma *et al*., 1997). The binding of HGF to Met leads to the phosphorylation of two C-terminal tyrosine residues and the generation of a multidocking site. These phosphotyrosines mediate high-affinity interactions with Src homology 2 (SH2) domains of many proteins, including the p85 subunit of PI3K that can then transduce signals to downstream targets (Birchmeier *et al*., 2003). HGF/SF signals induce proliferative and anti-apoptotic responses in various cell types. In cancer cells, HGF/SF signals control growth, invasion and metastasis. Similarly, HGF/SF and Met provide essential signals for survival and proliferation of trophoblasts (Birchmeier *et al*., 2003). HGF also increases trophoblast mobility and invasion: experiments performed with the extravillous trophoblast cell line SGHPL-4 demonstrate that the PI3K signalling pathway is involved in basal trophoblast mobility and that both MAPK and PI3K signalling pathways are important in HGF-stimulated mobility (Cartwright *et al*., 2002). Another paracrine loop common to both normal trophoblasts and neoplasia is the VEGF/VEGFR loop. VEGFs are crucial regulators of vascular development during embryogenesis (vasculogenesis) as well as of blood-vessel formation (angiogenesis) of both normal tissues and malignant tumours in the adult. In a broader perspective, the VEGFRs induce cellular processes that are common to many growth-factor receptors, including cell migration, survival and proliferation (Olsson *et al*., 2006). Several reports indicate that cytotrophoblasts in cell columns and in the placental bed express the VEGF receptor-1 (VEGFR-1 or Flt-1), one of the three VEGF RTKs, and that VEGFA (usually called VEGF) itself, one of the five members of the VEGF family, is expressed by cytotrophoblasts as well as by fetal macrophages in chorionic villi and by maternal macrophages in the uterine wall (Ahmed *et al*., 1995; Clark *et al*., 1996; Shiraishi *et al*., 1996). Moreover, VEGFR-1 also binds placenta growth factor (PlGF), another member of the VEGF family expressed by normal trophoblasts and by cancer cells. In extravillous trophoblast, it has been reported that VEGFA and PlGF stimulate proliferation but not migration or invasiveness of these cells (Athanassiades and Lala, 1998; Athanassiades *et al*., 1998). Thus, evCTB, via VEGFR-1, could respond in either a paracrine or an autocrine fashion to VEGFA and PlGF (Zhou *et al*., 1997b). The VEGFR-1 tyrosine kinase exhibits all the conserved motifs that are required for kinase activity. Several VEGFR-1 tyrosine phosphorylation sites and their potential interacting partners, including the p85 subunit of PI3K, have been described (Olsson *et al*., 2006). Indeed, the level of phosphorylation of VEGFR-1 in response to VEGFA is low (Waltenberger *et al*., 1994; Seetharam *et al*., 1995). However, a particular feature of the VEGFA ligand is the dramatic upregulation of its expression levels under hypoxic conditions. Hypoxia, a condition that may affect both evCTB and cancer cells, allows the stabilization of hypoxia-inducible factors (HIFs) that bind to specific promoter elements that are present in the promoter region of VEGFA (Pugh and Ratcliffe, 2003). Similarly, the expression of VEGFR-1 is directly regulated by HIFs (Gerber *et al*., 1997).

Taken together, these data show that several autocrine and paracrine loops can be used by normal proliferative trophoblasts and by cancer cells to expand in number.

Evasion of apoptosis

The ability of cell populations to expand in number is determined not only by the rate of cell proliferation but also by the rate of cell attrition. Programmed cell death (apoptosis) represents a major source of this attrition. Numerous observations indicate that the apoptotic program is present in latent form in virtually all cell types throughout the body. The apoptotic machinery can be broadly divided into two classes of components, sensors and effectors. The sensors are responsible for monitoring the extracellular and intracellular environment for conditions of normality or abnormality that influence whether a cell should live or die. These signals regulate the second class of components, which function as effectors of apoptotic death (Hanahan and Weinberg, 2000). The sensors include cell-surface receptors that bind survival or death factors. Examples of these ligand/receptor pairs similarly expressed by trophoblasts and cancer cells are the survival signals conveyed by IGF-1/IGF-2 through the receptor IGF-1R (Lotem and Sachs, 1996; Butt *et al*., 1999). Signalling through the IGF receptor has been shown to have a potent survival function and protects cells from various apoptotic stimuli (Butt *et al*., 1999). The IGF pathway is unique in that, upon ligand binding and receptor autophosphorylation, insulin receptor substrate-1 (IRS-1) associates with IGF-1R. Tyrosine phosphorylation of IRS-1 in turn leads to the binding and activation of PI3K. The phosphorylation of inositol membrane lipids at the 3′ position by PI3K is a critical step in the IGF-IR signalling pathway. Many kinases have been identified that associate with these 3′-phosphorylated membrane lipids and subsequently participate in the kinase signalling cascade. AKT, one of the kinases in this activation cascade, has a distinct function in promoting cell survival by phosphorylating and blocking the proapoptotic activity of proteins such as BCL2-antagonist of cell death (BAD). Apart from the PI3K-AKT-mTOR system, another downstream network of IGF-1R includes the RAF-MAPK system. The activation of these pathways stimulates proliferation, as underlined previously, and inhibits apoptosis. In cancer cells, several model systems have provided evidence that IGF-1 receptor activation increases not only proliferation but also

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metastasis (Khandwala *et al*., 2000; Pollak *et al*., 2004). In trophoblast cells, it remains to be determined whether the activation of this receptor is primarily involved in proliferation, or rather, in the invasive capacities of these cells (Chakraborty *et al*., 2002).

Similar mechanisms of migration and invasion

A striking similarity between cytotrophoblasts and neoplastic cells lies in their proliferative capacities. Additional cellular changes enable these cells to acquire migratory and invasive capacities so as to undergo transformation into either invasive evCTB, 'physiological metastasis', or malignant cells capable of metastasizing. To accomplish this transformation, the two types of cells utilize similar operational strategies, involving changes in the physical coupling of cells to their microenvironment and activation of extracellular proteases. As might be expected, in addition to producing proteinases that degrade the ECM, all highly invasive cells, including evCTB cells, share an altered adhesion molecule phenotype (Plantefaber and Hynes, 1989; Albelda *et al*., 1990; Giancotti and Ruoslahti, 1990; Behrens *et al*., 1993; Oka *et al*., 1993).

Altered adhesion molecule phenotype

Several classes of proteins involved in the tethering of cells to their surroundings in a tissue are altered in cells possessing invasive or metastatic functions (Hanahan and Weinberg, 2000). The affected proteins include integrins, which link cells to ECM substrates. Integrins are heterodimeric receptors resulting from combinatorial expression of various α- and β-receptor subunits. These combinations lead to over 22 different integrin subtypes that have distinct substrate preferences. Other affected proteins belong to two different classes of cell–cell adhesion molecules (CAMs): the first class comprises cadherins, which mediate Ca^{2+}-dependent cell–cell adhesion, and the second class comprises various adhesion receptors belonging to the immunoglobulin family. Notably, all of these cell adhesion receptors convey regulatory signals to the cell (Aplin *et al*., 1998).

In effect, trophoblasts change their adhesive properties during invasion. This occurs *in vivo* when the cytotrophoblast cells leave their basement membrane to differentiate into evCTB cells. The invasion of cytotrophoblasts leads to a decrease in the expression of adhesion receptors characteristic of cytotrophoblast stem cells and an increase in the expression of adhesion receptors that are characteristic of vascular cells. Besides enabling cytotrophoblasts that line the maternal vessels to masquerade as vascular cells, these receptors also improve the ability of extravillous trophoblastic cells to invade the uterine wall (Campbell *et al*., 1995; Damsky and Fisher, 1998). Human cytotrophoblast stem cells within the villi express α6β4 integrin, a receptor for epithelial laminin. As they leave the basement membrane, they down-regulate the α6β4 integrin and begin to express the α5β1 integrin, a fibronectin receptor, and move into the fibronectin-rich matrix of the invasive cell columns (Redman, 1997). Within the uterine wall, they produce α1β1 integrin, a receptor for laminin and type IV collagen that contributes to the acquisition of an invasive phenotype by evCTBs (Damsky *et al*., 1992, 1994). Cytotrophoblasts also express other integrins in response to the acquisition of invasiveness. In particular, cytotrophoblasts express αv integrins that seem to be important in the formation of some types of metastatic tumours (Redman, 1997). Integrin αvβ5 is characteristic of vCTBs, whereas αvβ6 is only expressed on the cells at the base of the invasive cell columns. evCTBs in the uterine interstitium and maternal vasculature, like endothelial cells during angiogenesis, express integrin αvβ3. Because the treatment of isolated cytotrophoblasts with antibody to integrin αvβ3 significantly hampers their invasion, it was suggested that increased expression of this integrin by evCTB *in vivo* stimulates their motility and invasiveness (Zhou *et al*., 1997b). In a similar way, changes in integrin expression are also evident in invasive and metastatic cells. During their migration, invading and metastasizing cancer cells experience changing tissue microenvironments that can present novel matrix components. Accordingly, successful colonization of these new sites (both local and distant) requires adaptation, which is achieved through shifts in the spectrum of integrins displayed by the migrating cells. Indeed, carcinoma cells facilitate invasion by shifting their expression of integrins from those that favour ECM present in normal epithelium to other integrins, including αvβ3 that preferentially bind the degraded stromal components produced by extracellular proteases. αvβ3 is the integrin expressed by evCTBs in the uterine wall, and studies have implicated integrin αvβ3 in the transition of cancer cells to an invasive phenotype *in vivo* (Albelda *et al*., 1990; Felding-Habermann *et al*., 1992; Irish *et al*., 2006), emphasizing the fact that normal cytotrophoblasts and cancer cells perform similar integrin switching to acquire invasive capacities. Indeed, integrin ligation induces a complex network of signalling pathways to control cell migration (Guo and Giancotti, 2004). Integrin binding to ligands activates FAK, which binds and activates multiple signalling proteins. FAK autophosphorylation causes it to bind to adaptor growth-factor-receptor-bound protein 2 (GRB2) and to activate another small G protein, RAS. FAK activation also promotes SRC-dependent phosphorylation of the adaptator protein SHC, leading to GRB2 recruitment and RAS activation. Activated RAS recruits RAF to the cytoplasmic membrane, where it can be activated by protein kinases such as SRC, thereby leading to mitogen-activated protein kinase kinase (MEK) and ERK activation. Once activated by FAK or SHC, RAS can activate PI3K and RAF. Activated SRC can also phosphorylate CRK-associated substrate (CAS), leading to RAC activation. Activated RAC, in conjunction with activated CDC42 and with activated ERK, can then regulate numerous biochemical pathways that are necessary for the migratory phenotype (Hood and Cheresh, 2002).

In addition to integrin receptor switching, a switch in the expression of cadherins (another class of molecules implicated in cell adhesion) also plays a significant role in the invasive properties of both normal trophoblasts and malignant cells. In the placenta, the adhesion molecule E-cadherin mediates a strong intracellular interaction between cytotrophoblasts, as it does in all other normal epithelia (Birchmeier, 1995; Zhou *et al*., 1997a). When cytotrophoblasts differentiate in cell columns and move into the placental bed, E-cadherin expression is progressively lost. Similarly, E-cadherin function is apparently lost in a majority of epithelial cancers (Irish *et al*., 2006). Because E-cadherin serves as a widely acting suppressor of invasion and metastasis by epithelial cancers, its functional elimination represents a key step in the acquisition of this capacity. Thus, cadherin modulation, like integrin modulation, contributes to the acquisition of an invasive phenotype by differentiating cytotrophoblasts (Damsky *et al*.,

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1994). Cadherins are generally regulated at both the mRNA and the protein level by means of changes in subcellular distribution, translational or transcriptional events and degradation. Various signal transduction pathways impact the regulation of E-cadherin levels and subcellular distribution. Very recently, AKT, a downstream effector of PI3K, was shown to regulate levels of E-cadherin mRNA and protein: at the molecular level, AKT represses transcription of the E-cadherin gene. Moreover, cells producing a constitutively active form of AKT produce a transcription factor, Snail, which is known to repress the expression of the E-cadherin gene (Grille *et al*., 2003; Larue and Bellacosa, 2005).

A switch in the expression of different immunoglobulin superfamily adhesion receptors also accompanies the acquisition of invasive capacities by both normal trophoblastic and neoplastic cells. Cytotrophoblasts differentiating along the invasive pathway up-regulate the expression of immunoglobulin superfamily adhesion receptors characteristic of endothelial cells. Vascular adhesion molecule-1 (VCAM-1), which interacts with integrins $\alpha 4\beta 1$ and $\alpha 4\beta 7$, is not detected on vCTBs, but it is detected on evCTBs within the uterine wall. Its expression on endovascular cytotrophoblasts is particularly strong. vCTBs do not express another member of the immunoglobulin superfamily adhesion receptors, platelet endothelial adhesion molecule-1 (PECAM-1); however, this adhesion molecule, which can interact with itself or with $\alpha v\beta 3$ (Piali *et al*., 1995), is expressed on cytotrophoblasts within cell columns. Cells involved in both interstitial and endovascular invasion display particularly potent expression (Zhou *et al*., 1997a). The highly invasive behaviour of these evCTBs may account for the virtually unique ability to enter blood vessels, displace resident endothelial cells and colonize and remodel the arterial wall.

Changes in the expression of CAMs in the immunoglobulin superfamily also appear to play a critical role in the processes of invasion and metastasis (Johnson, 1991). The clearest case involves N-CAM, which undergoes a switch in expression from a highly adhesive isoform to poorly adhesive (or even repulsive) forms in Wilms' tumour, neuroblastoma and small cell lung cancer (Johnson, 1991; Kaiser *et al*., 1996) and a reduction in the overall expression level in invasive pancreatic and colorectal cancers (Fogar *et al*., 1997).

Proteinase production

Decidual invasion by cytotrophoblasts results from classical steps in cellular invasion, including attachment to the basement membrane followed by detachment and proteolysis of the basement membrane before its penetration. Thus, invasion is not due to passive growth pressure but rather due to active secretion of enzymes capable of degrading the ECM in which the cells are embedded, and cytotrophoblast cells are no exception (Fisher *et al*., 1985; Bischof and Campana, 2000; Mock *et al*., 2000). Interestingly, similar enzymatic mechanisms are shared by trophoblastic and malignant cells in the invasive process, and the degradation of basement membranes during metastasis is in part regulated by proteolysis, often by the same proteases implicated in implantation (Testa and Quigley, 1990; Leone *et al*., 1991; Strickland and Richards, 1992). However, these enzymatic mechanisms are employed in a highly concerted manner only in the trophoblast: in contrast to that of tumours, the invasive behaviour of cytotrophoblasts is acquired only transiently.

Early during implantation, trophoblastic cells from the outer layer of the blastocyst invade the endometrium by secretion of matrix-degrading proteases (Iruela-Arispe, 1997). ECM-degrading proteinases, such as MMP-9 and uPA, regulate placental development (Librach *et al*., 1991; Zhang *et al*., 1996). Later, after implantation, evCTBs leaving the proliferative cell cluster acquire an invasive phenotype that is characterized not only by a switch in their adhesion molecule expression (Damsky *et al*., 1992; Zhou *et al*., 1997b; Shih Ie *et al*., 2002) but also by the production of a set of proteases: metalloproteinases (Vettraino *et al*., 1996; Hurskainen *et al*., 1998; Mock *et al*., 2000), serine proteases (Liu *et al*., 2003) and cathepsin (Divya *et al*., 2002), which degrade the ECM (Lacroix *et al*., 2005). Indeed, invasive evCTB cells display elevated expression of matrix-degrading proteinases, as do cancer cells (Mignatti *et al*., 1986; Stetler-Stevenson *et al*., 1993; Huppertz *et al*., 1998). For example, they increase their production and activation of MMP-9 (gelatinase B, MMP-9), which contributes to the invasiveness of cytotrophoblasts *in vitro* (Librach *et al*., 1991; Bass *et al*., 1997; Schatz *et al*., 1999). Cytotrophoblast production and activation of MMP-9 peak during the first trimester, coinciding with maximal invasive behaviour *in vivo* (Librach *et al*., 1991; Bass *et al*., 1994; Cross *et al*., 1994; Shimonovitz *et al*., 1994). Moreover, MMP-2 (gelatinase A, MMP-2) is also expressed in evCTBs, but accumulating evidence suggests that MMP-9 may play a more important role than MMP-2 in trophoblast invasion during pregnancy and that MMP-9 expression/activation is a prerequisite to evCTB invasion (Cohen *et al*., 2006b). Thus, mechanisms regulating the expression of MMP-9 are important for evCTB invasion. MMP-9 secretion in invasive cytotrophoblasts is stimulated by various factors including TNF-α (Meisser *et al*., 1999) and EGF (Qiu *et al*., 2004a,b), whereas TGF-β inhibits trophoblastic MMP-9 secretion (Meisser *et al*., 1999). TIMPs are also important regulators of MMP activity (Denhardt *et al*., 1993). Although several members of the TIMP family have been identified, proteolysis by MMP-9 is mostly regulated by the action of endogenous TIMP-1 (Itoh and Nagase, 1995). Thus, it is noteworthy that EGF induces the secretion of not only MMP-9 but also TIMP-1, identifying this growth factor produced by trophoblastic cells as one of the key regulators of trophoblast invasion. Recently, it was convincingly demonstrated *in vitro* that EGF induces MMP-9 and TIMP-1 secretion through simultaneous activation of both the PI3K and MAPK signalling pathways in evCTBs, resulting in the activation of several transcription factors (Qiu *et al*., 2004a,b; Pollheimer and Knofler, 2005), as is the case in cancer cells (Vivanco and Sawyers, 2002; Cully *et al*., 2006). For instance, EGF activates the PI3K and MAPK/ERK pathways, which modulate the activation of NFκB and AP-1, respectively, in human head and neck squamous cell carcinoma lines (Bancroft *et al*., 2002), whereas transcription factors Ets-1 and Ets-2 are activated in response to EGF in human breast tumour cells (Watabe *et al*., 1998).

Amongst serine proteases, the serine protease uPA promotes matrix degradation by extravillous trophoblasts, and it was shown that uPA stimulates human extravillous trophoblast migration by using phospholipase C, PI3K and MAPK (Liu *et al*., 2003). Other enzymes such as heparanase are secreted by trophoblasts and

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cancer cells and have been implicated in the invasive behaviour of these cells (Vlodavsky *et al*., 1999; Dempsey *et al*., 2000). The overexpression of heparanase cDNA in weakly metastatic tumour cells confers high metastatic potential in experimental animals (Vlodavsky *et al*., 1999), suggesting a critical role for heparanase during cell invasion associated with tumour metastasis and angiogenesis (Nakajima *et al*., 1988; Vlodavsky *et al*., 1999; Elkin *et al*., 2001; Parish *et al*., 2001).

Finally, the activation of extracellular proteases and the altered binding specificity of cadherins, CAMs and integrins are clearly central to the acquisition of invasiveness by trophoblasts and to the acquisition of metastatic ability by malignant cells. However, the regulatory circuits and molecular mechanisms that govern these shifts remain elusive and, at present, seem to differ from one tissue environment to another.

Immune escape

To invade neighbouring tissues, normal trophoblastic and malignant non-trophoblastic cells must escape effectors of the immune

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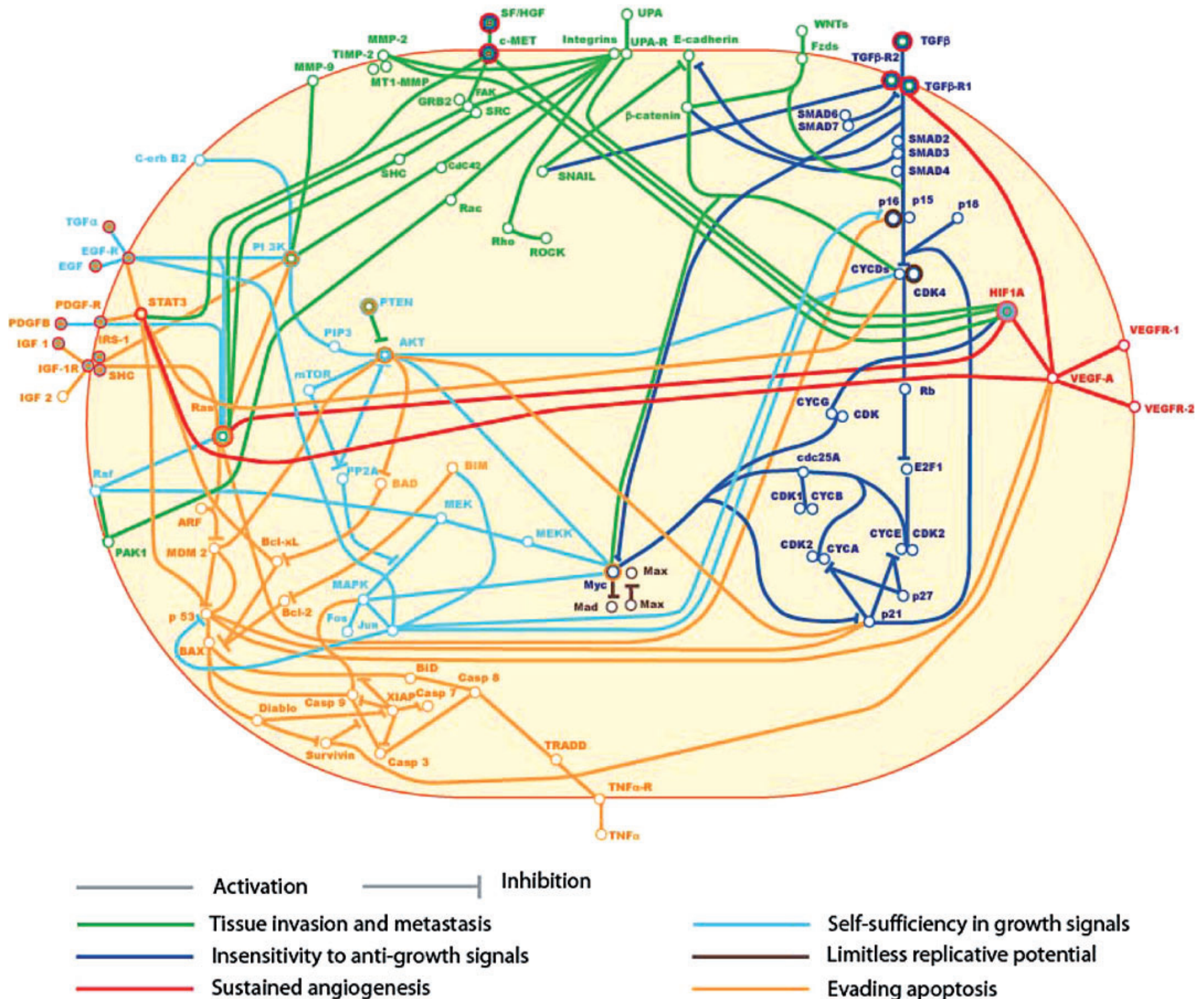

Figure 3. Schematic map of major signalling pathways (molecular circuitries) that may be shared by both trophoblastic and malignant cells so as to acquire six traits important for malignant growth: tissue invasion and metastasis (green), insensitivity to growth-inhibitory (antigrowth) signals (dark blue), sustained angiogenesis (red), self-sufficiency in growth signals (light blue), limitless replicative potential (brown) and evasion of programmed cell death (apoptosis) (orange) (Hanahan and Weinberg, 2000; Hahn and Weinberg, 2002). This figure simplifies complex interacting regulatory networks. Casp, caspases; CDK, cyclin-dependent kinase; CYC, cyclin; EGF, epidermal growth factor; erbB2, HER2/neu receptor tyrosine kinase; FAK, focal adhesion kinase; GRB2, growth-factor-receptor-bound protein 2; HIF, hypoxia-inducible factor; IGF-1 and IGF-2, insulin-like growth factors 1 and 2; IRS1, insulin-receptor substrate 1; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; MEKK, MAPK kinase kinase; MET, hepatocyte growth factor/scatter factor (HGF/SF) receptor; MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinase; PDGF, platelet-derived growth factor PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol(3,4,5)triphosphate; PTEN, phosphatase and tensin homologue; SHC, SRC-homology-2-domain transforming protein; SRC, Src family kinase; STATs, signal transducers and activators of transcription; TGF-α, transforming growth factor-α; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumour necrosis factor-α; TOR, target of rapamycin; uPA, urokinase plasminogen activator.

system. Remarkably, maternal immune surveillance of foreign cell-surface antigens fails to reject the embryonic conceptus despite the expression of paternal antigens on trophoblasts. The placenta separates fetal and maternal blood and lymphatic systems, and it is the fetal trophoblast that plays the most important role in the evasion of recognition by the maternal immune system (Weetman, 1999). Trophoblast cells fail to express major histocompatibility complex (MHC) class I or class II molecules. Similarly, MHC class I down-regulation is an important mechanism in tumour escape from T-cell-mediated immune responses: approximately 40–90% of human tumours have been reported to be MHC class I deficient (Bubenik, 2003). Moreover, evCTB cells strongly express the non-classic MHC gene encoding HLA-G, which may down-regulate natural killer (NK) cell function. Using other mechanisms, tumours induce, in NK cells, the same inactivating reactions that the fetal trophoblast engenders *in utero* (Sinkovics and Horvath, 2005). In addition, the trophoblast expresses the Fas ligand (FasL/CD95L), thereby conferring an immune privilege (a property of some sites in the body whereby immune responses are limited or prevented): maternal immune cells expressing Fas will undergo apoptosis at the placental/decidual interface. Tumour cells frequently exhibit de-novo expression of Fas ligand. Coupled with resistance to Fas-mediated apoptosis, FasL expression enables many cancers to deliver a pre-emptive strike against or to 'counterattack' the immune system (Houston and O'Connell, 2004). However, a role for FasL in immune privilege has been challenged (Green and Ferguson, 2001).

Corresponding molecular circuitries of proliferation, migration and invasion

Cells respond to extracellular stimuli through a series of signalling cascades. From receptor activation to a biological effect, each signal follows a pathway recruiting effectors and adapters, varieties of proteins that interact with each other and generating a cascade of sequential steps (Knofler *et al*., 2005). Some pathways are linear, whereas others are branched, and some are linked to others to induce specific or redundant events. However, most of the time, signalling molecules are common to several pathways, forming a complex intracellular network (Knofler *et al*., 2005). Under intensive study for two decades, the wiring diagram of the signalling circuitry of the mammalian cell, while incomplete, is coming into focus, and it is now possible to lay out a circuitry that will likely mimic electronic integrated circuits (Hanahan and Weinberg, 2000). Moreover, it was suggested that most and perhaps all types of human tumours share six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in GS, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis. An overview of signalling circuitries used by trophoblast cells, although simplistic, places emphasis on the many circuitries shared with those employed by cancer cells (Figure 3). As virtually all mammalian cells carry similar molecular machinery regulating their proliferation, differentiation and death (Hanahan and Weinberg, 2000) and as most regulatory and effector components are present in a redundant form, it is not totally surprising that normal trophoblasts and malignant cells, which may have to accomplish comparable tasks to proliferate and migrate so as to ultimately invade neighbouring tissue, use, in part, similar regulatory and effector components, similar circuitries and similar mechanisms, even though the finale of these processes is strikingly different. Moreover, it should be recalled that the main difference between normal trophoblast development and malignant transformation is that cellular and molecular events follow highly regulated spatial and temporal plans during trophoblast development, whereas during malignant transformation, the order of events may be stochastic and time independent or particular events may be bypassed.

Conclusion

The ability of trophoblast cells to proliferate and then to migrate and invade the uterine wall, as well as the many common characteristics shared by normal trophoblast cells and malignant cells, makes them ideal for monitoring molecular changes taking place during the acquisition of a migrating/invasive phenotype. Moreover, normal trophoblast can be transformed into hydatidiform mole, a highly proliferative benign trophoblastic disease (Berkowitz and Goldstein, 1996), and into choriocarcinoma, one of the most metastatic tumours known (Strickland and Richards, 1992). Chorionic tumours are characterized by progressive loss of control of the proliferation, migration and invasion normally achieved by trophoblast cells. Taken together, trophoblast cells from normal placenta, hydatidiform mole and choriocarcinoma constitute a unique and fascinating model for studying mechanisms involved in these processes. Careful analysis and comparison of different trophoblast model systems will help gain valuable insight not only into the exciting area of trophoblast research but also into the vast field of cancer research.

Indeed, we are likely to derive much more from the trophoblast than simply the elucidation of the molecular mechanisms controlling migration and invasion processes. The parallel between these cells, which form the basis of life, and malignant cells, which bear the possibility of death, offers us an occasion for reflection, not without irony, on the value of human existence and its inherent fragility.

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