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Signal Transducer and Activator of Transcription 3 (STAT3) and Trophoblast Invasion

J. S. Fitzgerald¹, T. G. Poehlmann¹, P. Suman^{1,2}, S. K. Gupta², E. Schleussner¹, U. R. Markert¹

Human trophoblast cells have the fascinating property of physiological invasiveness into allogenic tissue. The underlying mechanisms, such as extra- and intracellular signalling, are very similar to those abused by a variety of tumours. The main contrasting feature to cancerous cells is the very fundamental ability of trophoblasts to auto-regulate invasion with respect to time and space. Trophoblast cells start invasion into the decidua very shortly after implantation, which approaches a maximum during the first trimester of gestation period. During this period of time, several cytokines from cells of different maternal origin, including NK cells, dendritic cells, stroma cells and endothelial cells, are present which, analogous to the situation in tumours, have the potential to trigger and enhance invasion, migration and proliferation of trophoblast cells. These mainly include interleukin-6 (IL-6), IL-11, Leukaemia Inhibitory Factor (LIF), Hepatocyte Growth Factor (HGF) and Insulin-like Growth Factors (IGF). Cytokines, upon binding to their specific receptors present on the trophoblast cells, trigger several intracellular signalling cascades. One of these signalling pathways is the Janus Kinase (Jak)/Signal Transducers and Activators of Transcription (STAT) pathway. As recent studies have shown, the tyrosine phosphorylated form of STAT3 is a major inducer of invasiveness which mainly takes place upon binding of LIF to its receptor. For auto-regulation of signals, STAT3 induces the transcription of Suppressor of Cytokine Signalling 3 (SOCS3). The balance between STAT3 and SOCS3 may be argued as one of the main tuners of trophoblast invasion for successful implantation. Disturbances in this balance may lead to serious complications like cancer and implantation failure. *J Reproduktionsmed Endokrinol* 2007; 4 (6): 322–30.

Key words: trophoblast cells, trophoblast invasion, STAT3, SOCS3, LIF

Embryo Implantation

Embryo implantation and maintenance of pregnancy are a complex coordinated event accomplished by spatial and temporal regulation of proliferation and differentiation of trophoblastic cells [1]. In spite of present technological advancements, the rate of successful pregnancies is still a major limiting factor in patients undergoing embryo transfer in IVF clinics [2]. This has compelled clinicians and basic scientists to reiterate the issue of embryo implantation.

During the implantation window, the blastocyst hatches and begins its journey toward development into a fully matured conceptus by first attaching and then invading the receptive endometrium [3]. Apposition is the primary step an embryo makes upon initial contact with the uterine mucosa (Fig. 1). The trophoblast, the outer single layer of cells in the implanting blastocyst, comes into direct contact with the endometrial cells and establishes the cell-to-cell contact with the apical plasma membrane. This kind of interaction is unique as epithelial cells normally avoid making such kind of cellular contacts [4, 5].

Markers for Early Implantation

Previous observations show that the uterus is in a state of maximal receptivity seven days post ovulation (around day 20 of an idealized 28-day cycle) for a very short period of time (about 2 days) [6]. The implantation window has also been associated with a biochemically defined milieu of uterine secretion, which forms the microenvironment of the blastocyst, particularly by significant and stage-specific protein patterns [7–9]. A number of biological markers are recognized as characteristics of the

implantation window that „date“ the endometrium and have, as such, attracted attention in recent years (Fig. 1).

The expression of adhesion molecules like integrins, selectins, and other members of immunoglobulin superfamily for the acquisition of a receptive state has been backed up by numerous studies, since the endometrial integrin profile is cyclically altered according to the menstrual phase [10]. The integrins, especially $\alpha\beta3$, display altered expression in the endometrium of infertile women, possibly resulting in a detrimental effect for blastocyst implantation [11–13]. Morphological alterations seem also to accompany the implantation window as seen in the emergence of so-called pinopodes [14], which are specialized cellular protrusions perceived through electron microscopy as smooth bulging cells on the surface of the endometrium. These progesterone-dependent organelles are assumed to assist in blastocyst adhesion by promoting uterine fluid withdrawal and preventing the cilia from sweeping off the blastocyst [6]. The attachment of blastocysts to pinopodes has been described in some studies, yet other studies show conflicting results [15, 16]. Another interesting fact is that pinopodes and leukaemia inhibitory factor (LIF), a further suggested biomarker for the implantation window that is alluded to in detail below, seem to be co-expressed in the human endometrium [17].

The three above-mentioned markers (integrins, pinopodes and LIF) have often been cited to frame the implantation window and proposed for clinical use especially in programs for assisted reproduction, however Acosta et al [18] have mentioned the asynchronous expression of these markers during different phases of implantation which questions the applicability of these markers for clinical use. In fact, a recent study indicates that pinopodes can be detected for extended periods of time and are not related to the fertility of women under investigation [19].

Differentiation of Early Trophoblast Cell Population

Clinicians might argue the reliability of these markers, but it is agreed upon that primary adhesion of the blasto-

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cyst to the endometrium is required for trophoblast invasion, and thus for successful implantation.

Adhesion seems to trigger the differentiation of the trophoderm into two discrete trophoblast subsets that immediately precede the invasion process [20]. Initial invasion into the endometrial lining is accomplished by the outer trophoblast phenotype, the syncytiotrophoblast, which creates a cavity into which the blastocyst may embed [21]. Once implantation is accomplished, syncytiotrophoblasts lose invasiveness, and instead the chorionic villi and intervillous space, but also become endocrinologically more active. The task of invasion is now „adopted“ by the cytotrophoblasts, which are considered to be trophoblast stem cells that replenish the pool of invasive trophoblast cells. Trophoblasts that exist outside of this intervillous space are termed extravillous trophoblasts and acquire the invasive phenotype in order to either anchor the chorionic villi into the Nitabuch layer or to profoundly infiltrate the decidua. They ultimately reach to the maternal spiral arteries and replace the existing endothelial layer.

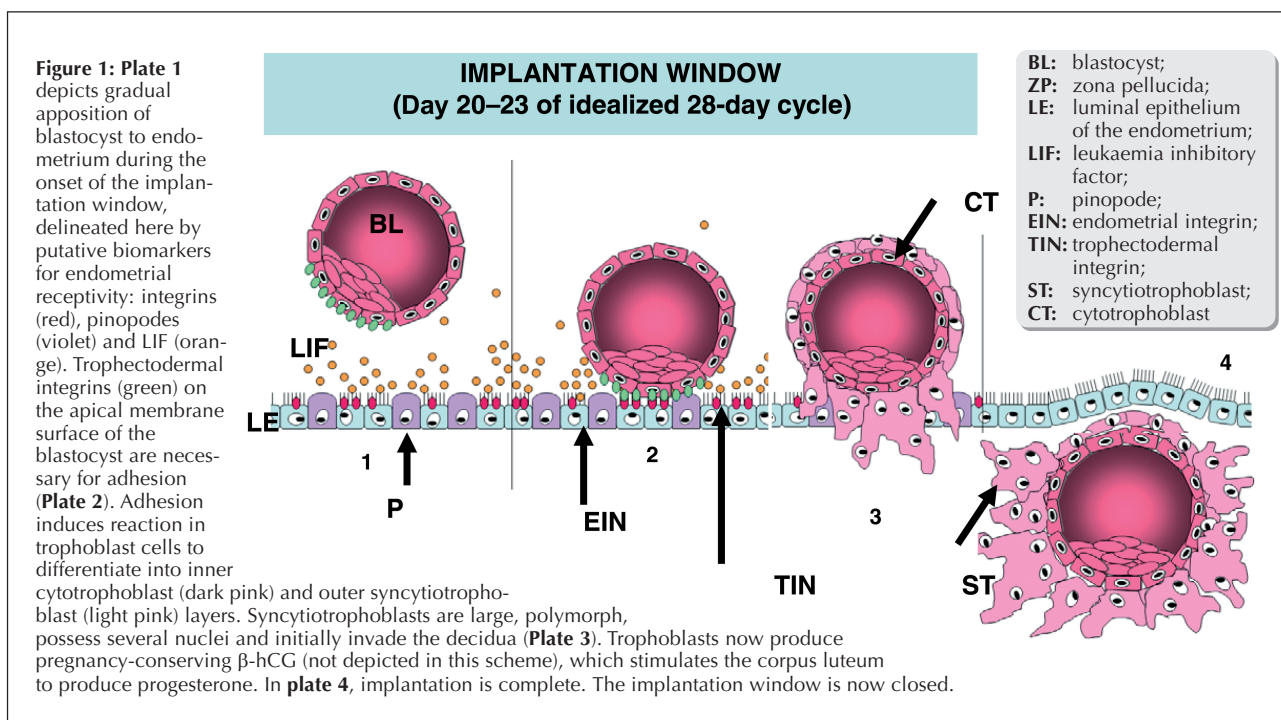
Direction of invasion seems to be determined through the expression of integrins in the decidual matrix surrounding the trophoblast cell and the ability of trophoblasts to produce matrix metalloproteinases.

Trophoblast cells of the implanting blastocyst also participate in a cyclic endocrinologic process by producing human chorionic gonadotropin (hCG), which in turn converts the corpus luteum of the menstrual cycle to the progesterone-producing corpus luteum of pregnancy that promotes decidualization and supports the development of the embryo. Progesterone is involved in immunosuppression at the foetomaternal interface and thereby protects the foetus from unwanted immune responses and rejections.

Intra-Uterine Invasion/Invasive Differentiation of Trophoblast and Decidua

As mentioned above, trophoblast cells have the potential to invade – a trait also evident in malignancies, but trophoblast cell physiology is such that they proliferate and differentiate invasively in a completely controlled physiological setting [22–25]. In fact, impairment in this type of invasion may result in pregnancy-related pathologies like pre-eclampsia. Furthermore, trophoblast cells are able to mask or protect themselves from the insults of the maternal immune system. Metastatic cancerous cells also abuse and mimic these characteristics of trophoblast cells to evade the host-immune responses against them. These two characteristics make trophoblast cells a unique model to investigate the process of invasive differentiation. The physiological and pathological settings lie in close proximity so the aberrant changes in the cellular behaviour can be analyzed in a better way. Especially intracellular events, such as signal transduction, are an attractive field to explore as it seems that trophoblast cells themselves can control their invasive growth in space and time (usually limited to the first trimester and the decidua) to a certain extent. This may be seen in trophoblast cells originating from extrauterine or xenogeneic gravities since these cells are as invasive as the trophoblasts of normal pregnancies. So, the extent of invasion by these cells could signify the spatial limitation for cellular invasion [26, 27].

Another point of interest is to look at the effects of local cytokines produced either by trophoblasts themselves or by other surrounding cells in the uterine microenvironment [28, 29]. These cytokines are often able to control trophoblast behaviour in some way, by either modulating proliferation and migration or inducing trophoblasts to differentiate into an (non-) invasive phenotype. All of these cytokines use various intracellular signal-mediating



pathways. Some of these mechanisms have been explored by several groups, but we are yet far from understanding the whole picture. The predominant signalling pathway and the possible cross talk with other signalling pathways for several cytokines are still elusive.

Cytokines Promoting Invasion

The focus of investigation has often been directed on the occurrence of cytokines during the complex event of placentation. It is known that migration and invasion of extravillous trophoblast cells are functionally controlled by a plethora of cytokines and growth factors, but the relevance of individual cytokine-induced signalling processes is still ill-defined. One of the most important candidate pathways seems to be the Janus Kinase – Signal Transducer and Activator of Transcription (Jak-STAT) cytokine signal-transducing pathway. Several cytokines that are important to reproductive medicine are known to signal through this pathway in other cells. Below is a synopsis of some of the most prominent of these cytokines and growth factors, and their influence on the reproductive field (Table 1).

Interleukin-6

IL-6 is one of the cytokines which utilize the Jak-STAT pathway for signal transduction and whose presence in the serum of cancer patients can be correlated with a higher metastatic potential of cancerous cells. IL-6 is known to enhance the invasiveness of head and neck cancer cells [30] and also of ovarian cancer cells [31]. In

human choriocarcinoma, IL-6 failed to stimulate cell growth in cultures, but knocking down the expression of IL-6 mRNA resulted in retarded cell growth [38]. Moreover, IL-6 found in the amniotic fluids of early pregnancy seems to be produced by trophoblast cells [39]. This concentration could be positively correlated to the gestational age. Cytotrophoblast cells, which show the invasive phenotype, express high levels of IL-6 [40], thereby increasing the activity of MMP-2 and MMP-9 [41]. The human endometrium is a major source of IL-6 [42, 43] while the IL-6 receptor is expressed both on maternal (endometrial epithelial cells) and foetal tissues (trophoblast and blastocyst) during implantation and placentation [42, 44, 45]. IL-6-induced expression of integrins has been correlated with embryo attachment and its production could be hemmed by hCG and progesterone [40]. Reduced expression of IL-6 was found during the secretory phase on the endometrium of women with recurrent miscarriage [46].

Interleukin-11

IL-11 is another cytokine of the “IL-6 cytokine superfamily” which also conveys its signal through the same Jak-STAT pathway. Female mice with a null mutation of the IL-11 receptor α -chain are infertile because of defective decidualization, which may be attributable to uncontrolled trophoblast invasion [47]. The same receptor subunit has been detected on developing decidual cells. IL-11 is maximally expressed at the time of decidualization in the human gravid uterus [48]. IL-11 and its receptor IL-11R α are dysregulated in the endometrium of infertile women with endometriosis during the implant-

Table 1: Summary of mentioned cytokines, location and function in normal and pathological pregnancies as well as in cancer cells

Cytokine	Location in human pregnancy	Effect of expression alteration in human reproduction	Effect on cancer cells
IL-6	<ul style="list-style-type: none"> Probably produced by trophoblast in early pregnancy Maximum expression in endometrium at implantation Receptor on endometrial epithelial cells, trophoblast and blastocyst (during implantation / decidualization) 	<ul style="list-style-type: none"> Reduced expression in peri-implantation endometrium of excessive ovarian responders after IVF treatment (implantation failure) Reduced expression of IL-6 in secretory phase endometrium of women with recurrent miscarriage 	<ul style="list-style-type: none"> Serum concentration associated with metastatic potential of cancer cells [30, 31]
IL-11	<ul style="list-style-type: none"> Maximum expression during decidualization Receptor found on developing decidual cells Receptor found on interstitial trophoblast cells 	<ul style="list-style-type: none"> Dysregulated expression in endometrium during implantation window in endometriosis patients Production and function compromised in endometrial stromal cells from infertility patients 	<ul style="list-style-type: none"> Promotes proliferation and invasive potential of several cancer cells, e. g. breast [32], gastric [33] and colorectal [34] carcinomas
HGF	<ul style="list-style-type: none"> Expressed by placental stromal cells Receptor on trophoblast 	<ul style="list-style-type: none"> Placentas from pre-eclamptic women associated with low HGF production Altered HGF expression in placental tissue of malformed fetuses 	<ul style="list-style-type: none"> Mediates motility of some tumours by activating STAT3 [35]
LIF	<ul style="list-style-type: none"> Produced by placenta and endometrium Maximally expressed during implantation window Receptors on trophoblast and endometrial epithelial cells 	<ul style="list-style-type: none"> Dysregulated expression in endometrium during implantation window in endometriosis patients Too high and too low levels in uterine flushings have negative predictive value for implantation success 	<ul style="list-style-type: none"> Promotes proliferation and invasion of choriocarcinoma cells and other cancer [36, 37]
GM-CSF	<ul style="list-style-type: none"> Synthesis in epithelial cells regulated by oestrogen 	<ul style="list-style-type: none"> Significantly reduced blood concentrations in pregnant patients suffering from unexplained recurrent abortion 	<ul style="list-style-type: none"> Conflicting evidence

ation window [49]. Furthermore, the production of IL-11 and decidualization are compromised in endometrial stromal cells derived from patients with infertility [50]. As a matter of fact, a recent study suggests that IL-11-induced signalling initiates and maintains the decidualization process through STAT3 and SOCS3 activation [51].

Hepatocyte Growth Factor

The morphogenic Hepatocyte Growth Factor (HGF) has been described in mediating motility in tumours by activating STAT3. It seems that HGF is expressed by placental stromal cells, while the receptor is largely localized on the trophoblast [52]. Furthermore, HGF is known to arbitrate the invasive potential of trophoblast cells since trophoblast invasion is dose-dependently increased by HGF [53]. HGF knockdown in the mouse model has revealed the abnormal placental development due to a complete lack of labyrinthine trophoblast development [54, 55]. All these facts indicate that HGF is of fundamental importance in the mesenchymal induction of trophoblast growth and differentiation during the development of placenta [56]. HGF has also been implicated in the progression of pre-eclampsia in human pregnancies as placentas from pre-eclamptic women show a reduced HGF production [53]. Finally, an altered expression of HGF and STAT3 has been observed in the placental tissues of malformed foetuses [57].

Leukemia Inhibitory Factor (LIF)

LIF has been proposed to be indispensable for placentation in several species of animals [58, 59]. LIF-deficient mice, though not sterile, are infertile and fertility may be restored through infusion of LIF into the uterus [60]. The blastocysts of LIF receptor knockout mice implant, but die within 24 hours of birth due to impaired placenta function [61]. LIF is supposed to facilitate the implantation process as it is present in high concentration at the foetomaternal interface and is produced by both the human placenta and endometrium [62–64]. LIF receptors are present on the trophoblast which indicates the possible involvement of LIF in the regulation of trophoblast function [45]. There is up-regulation of HLA-G, a non-classic class I MHC molecule believed to be involved in the „masking“ of the cell from the immune system, in human choriocarcinoma cell lines in response to LIF [65]. In addition, LIF could promote the proliferation and invasion of choriocarcinoma cells and trophoblast cells [66]. Knock down of STAT3 results in loss of LIF-induced invasion in both choriocarcinoma and trophoblast cells [67]. It has been proposed that decidual NK cells secreting LIF might regulate invading trophoblast cells when they encounter them in the decidua [68]. LIF suppresses its own effects by means of a negative feedback mechanism on the Jak-STAT pathway [69]. In this context, both too low and too high levels of LIF in uterine flushings have been suggested to have negative predictive value in implantation success [70, 71].

Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF)

GM-CSF, though not of the IL-6 family of cytokines, uses the same Jak-STAT pathway for its signal transduction. GM-CSF promotes proliferation, differentiation and secretory activities of human and mouse cytotrophoblast cells in vitro [72, 73] and thus probably functionally supports the development of the placenta. Oestrogen plays a regulatory role on the biosynthesis of GM-CSF by uterine epithelial cells in mice, sheep and humans [74–76]. Even

small amounts of exogenous GM-CSF administered to mice can lead to dramatic alterations in the pregnancy outcome [77, 78]. In GM-CSF-deficient mice, foetal growth and viability are jeopardized due to compromised placental function. These effects are increasingly deleterious when the conceptus is also deficient for the same, suggesting that GM-CSF from both maternal and foetal origin is required for optimal foetal growth and survival [79]. In one of the studies, GM-CSF concentration was found to be significantly reduced in the peripheral blood of pregnant women suffering from unexplained recurrent abortion [80].

Regulation of Invasion on the Intracellular Level

The Janus Kinase / Signal Transducer and Activator of Transcription (Jak-STAT) Pathway

Intracellular mediators play an equally important role as their counterparts, extracellular mediators, in signal transduction which can be very well demonstrated by the importance of the Jak-STAT signalling pathway in trophoblast cells and their malignant derivatives, human choriocarcinoma cells.

In brief, upon binding of the ligand (cytokines) to their specific receptors, they heterodimerize with transmembrane protein gp130, which leads to the juxtaposition of receptor-associated tyrosine kinases called Janus kinases or Jaks (named after the two-headed Roman mythological god, Janus, because of their „two-headed“ structure). These Jaks cross-phosphorylate and activate each other on the cytoplasmic domains of the transmembrane receptor. Intracellular signal transducers and activators of transcription (STATs) are now recruited to these activated cytoplasmic domains and get phosphorylated. Phosphorylated or activated STATs dissociate from the receptor and form homo- and heterodimers that translocate from cytoplasm into the nucleus. In the nucleus, they regulate the target gene expression by binding to the promoter region.

Signal Transducer and Activator of Transcription 3

All of the above-mentioned cytokines share STAT3 as a common mediator for their intracellular signal transduction, at least as seen in several cells such as in lymphocytes, and also seem to have a positive influence on the invasion, proliferation and/or differentiation of trophoblast cells, thus facilitating pregnancy-related events like implantation. Disruption of gp130, the STAT3-activating subunit shared by all members of the IL-6 receptor family, leads to an identical phenotype as knocking out of LIF [81]. It has also been found that endometrial secretion of soluble gp130 (sgp130) is increased multifold during the implantation window and this secretion appears to be reduced in infertile patients [82]. The balance between soluble gp130 and its membrane-bound form may play an important role in regulating cytokine action necessary for blastocyst implantation and for further interaction between the decidualized endometrium and the invading trophoblast [83]. Interestingly, sgp130 blocks the biological activity of LIF and IL-6 [84–86].

Several reports strongly suggest the possible role of STAT3 in mammalian reproduction. Evidently, STAT3 has proven indispensable to murine pregnancy as it is activated during the early post-implantation period in mice and is essential for embryogenesis. Wild-type mouse embryos express STAT3 on the extra-embryonic visceral endoderm

7.5 days post-coitum. Concurrent to this, STAT3 $-/-$ mice degenerate and die, but can be rescued through substitution with an alternative splice form of STAT3, STAT3 β , in which the C-terminal transactivation domain is replaced with a seven amino acid extension [87–89]. Furthermore, the inhibition of STAT3 activation in the endometrium of the mouse was shown to prevent implantation [90].

STAT3 in Trophoblast Cell Function

Recent findings suggest the possibility that STAT3 is a central player in pathways triggered by diverse factors that modulate placentation [28]. Jeg-3 human choriocarcinoma cells may be utilized as an easily controllable model for invasive first-trimester trophoblast cells. This model indicates a fundamental link between STAT3 activity driven by LIF and an altered pattern of protease expression in Jeg-3 choriocarcinoma cells. An exciting observation is that the two proteases whose mRNA levels were influenced by LIF-dependent STAT3 activation have been described to contribute to invasive cell behaviour or implantation: TIMP-1 expression was found to be down-regulated in response to LIF while caspase-4 (formerly termed interleukin-1 β -converting enzyme homologue 2 [ICH-2]) was up-regulated [66].

TIMP-1 is linked to inhibition of metastasis [91]. In choriocarcinoma cells, its expression was found to be reduced due to genetic changes and this down-regulation was correlated with the hyper-invasive or malignant phenotype [92]. It is conceivable to assume that TIMP-1 expression is directly influenced by STAT3, since STAT3-driven

TIMP-1 regulation was also described in other cell types such as synovial lining cells and hepatocytes [93, 94] and the TIMP-1 promoter was shown to contain STAT3 recognition elements [94].

Caspase-4 generates the bioactive form of interleukin-1 β [95]. Its expression is low in all human tissues except ovaries and it is also secreted by pre-implantation mouse embryos. The importance of IL-1 processing by caspase-4 in implantation can be underscored by the fact that the IL-1 receptor is maximally expressed in the endometrium during the secretory phase and that the IL-1 receptor antagonist evokes a lower rate of implantation [96].

Immunoreactive IL-1 β is present in the villous cytotrophoblast, syncytiotrophoblast and intermediate trophoblast [97] and apparently suppresses, at least in endometrial stromal cells, the expression of TIMP-1 mRNA [98]. Furthermore, TIMP-1 inhibits all MMPs in an activated form, but preferentially binds to latent and active MMP-9 [99], which has been found to be critical for cytotrophoblast invasion [100]. Whether this could be indicative of an autocrine regulation requires further investigation.

Moreover, LIF promotes the in vitro and in vivo giant cell differentiation of trophoblast cells forming the invasive population of trophoblasts at the time of implantation. This differentiation is apparently contained through negative regulation via SOCS3 (Suppressor of Cytokine Signalling 3) proteins which suppress the Jak-STAT signal transducing pathway and is induced by a broad spectrum of cytokines, including LIF [101–103].

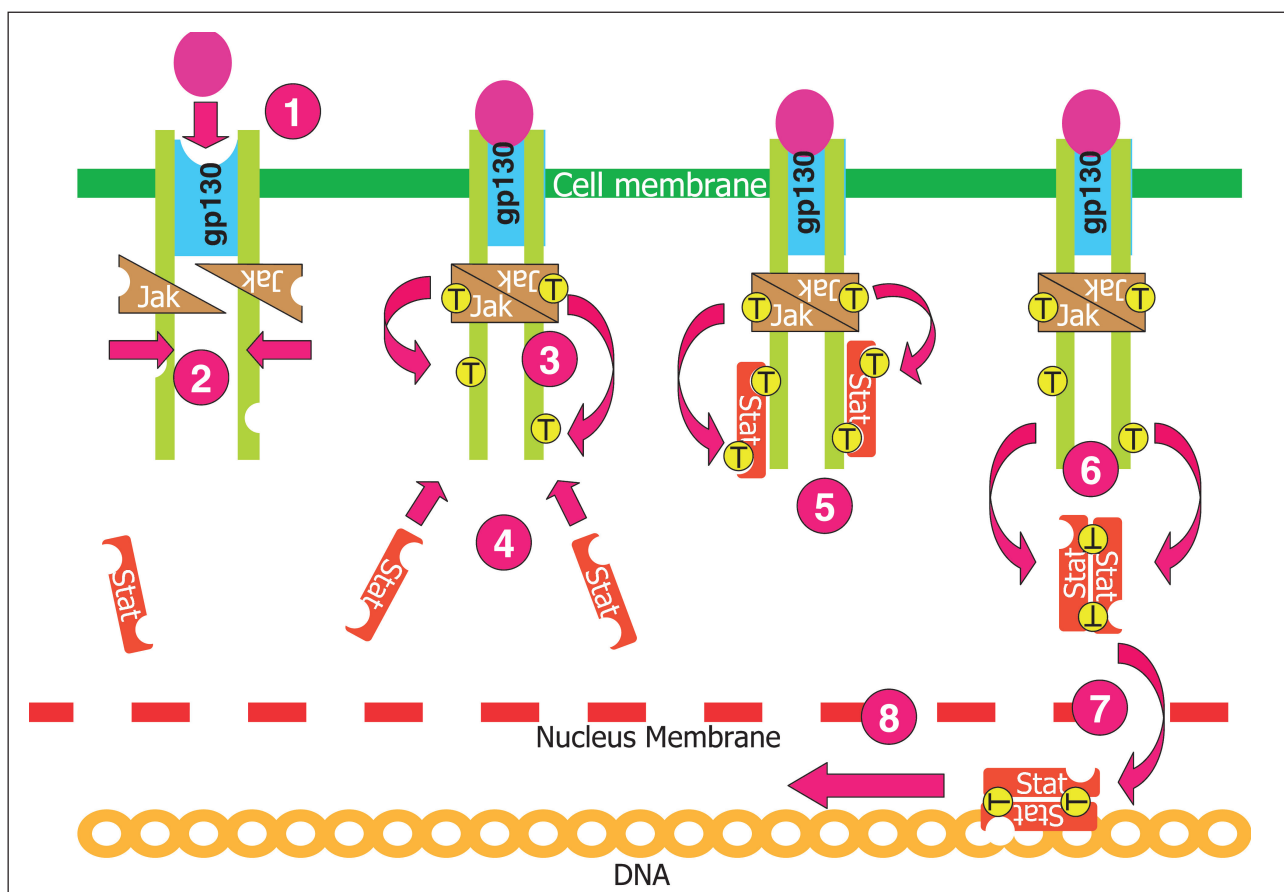


Figure 2: Jak-STAT signal transducing pathway – 1: cytokine binding to receptor; 2: receptor aggregation; 3: Jaks phosphorylate and activate each other and inner receptor ligand; 4: STATs bind to inner receptor ligand; 5: STATs are activated by Jaks; 6: activated STATs dissociate to form homo- and heterodimers; 7: STATs translocate into nucleus; 8: STATs accelerate transcription of target proteins.

STAT3 in Cancer Progression

As mentioned before, the mechanistic similarity between invasiveness of trophoblast and cancer cells allows to adapt knowledge from one field to the other. Many of the tumour invasion processes involve the activation of signalling mediators triggered by STAT3. Aberrant activity of phosphorylated, dimerized STAT3 has been linked to neoplastic cell behaviour, e. g. hyperplasia, longevity or invasion, and thus for the malignancy of cells [104]. Indeed, constitutively activated STAT3 has been found in several tumours [105].

STAT3 appears to play an essential role in the organization of motility in various types of tumour and pluripotent cells [106–108]. Moreover, STAT3 has also been implicated in the transcriptional regulation of proteases, which is crucial for invasive cellular growth [109–111].

Various reports indicate the influence of STAT3 on cellular growth behaviour (reviewed in [112]). Cell transformation by aberrant STAT3 activity in tumours probably involves up-regulation of genes promoting cell cycle progression (cyclin D1, c-myc) and/or those preventing apoptosis (bcl-xL; mcl-1; survivin) [104, 113, 114].

Molecular Mechanisms for the Regulation of STAT3 Activity

The two splice variants of STAT3, i. e. α and β , whose potential functional differences are currently the subject of intense research, were over-expressed in COS (monkey fibroblast) cells. Only STAT3 β was constitutively able to cooperate with c-Jun, another oncogenic transcription factor [115]. STAT3 β has been described as a predominant negative regulator of STAT3 α , and also STAT3 α -deficient mice can be rescued by STAT3 [116, 117]. Interestingly, a high activation level of STAT3 β was observed in the human choriocarcinoma cell line JAR in contrast to first-trimester trophoblasts [118]. The role of STAT3 β in choriocarcinoma should be investigated as it may provide the clues to identify specific STAT3 β target genes. It will be of particular importance to characterize the mechanisms that could suppress STAT3 activity in trophoblasts. This regulation may occur via the above-mentioned inhibitors of STAT signalling such as SOCS or PIAS (Protein Inhibitor of Activated STATs) [119], by receptor down-regulation or simply by the loss of cytokine secretion. The dysregulation of STAT3 expression and activation during placental development might provoke pathological consequences of defective placentation, shallow invasion in pre-eclampsia or neoplasms like human choriocarcinoma [120]. A better understanding of STAT function during placentation may lead to novel molecular and pharmacological strategies to interfere with signalling processes [112].

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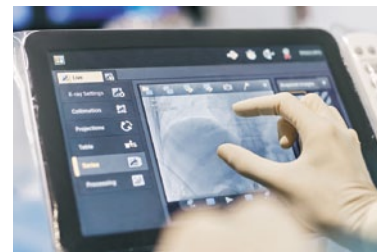
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