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Review

Breast cancer, placenta and pregnancy

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Abstract ***Background:*** Breast cancer is one of the most frequently diagnosed malignancies during pregnancy. Tumours often present characteristics of high malignancy and are hormone receptor negative/HER2 positive or triple negative. In general, pregnancy, including the postpartum period, is associated with a transiently increased risk of developing breast cancer but followed by a long-lasting protective period. Placental metastases are very rare and, thus far, breast cancer metastases in the foetal compartment have not been described. To discuss these apparently contradictory observations, this narrative review resumes immunological and hormonal alterations during pregnancy potentially affecting breast cancer risk as well as tumour growth and behaviour.

Observations: Upregulation of breast cancer–associated genes involved in immunological and reproductive processes has been observed in parous women and is potentially responsible for a transiently increased risk in pregnancy. In contrast, maternal immunisation and immunoglobulin production against antigens expressed on trophoblast cells, such as specific glycosylation patterns of mucin-1 or RCAS1-associated truncated glycans, seem to prevent breast cancer development in later years. Animal and human studies indicate that T cells are involved in these processes. Several placenta-derived factors, especially kisspeptin, have direct antitumour effects. The pregnancy-related increase of estrogen, progesterone, and other hormones influence growth and characteristics of breast cancer while the role of further placenta-secreted factors is still controversially discussed.

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Conclusion: Several factors and cells are involved in altered breast cancer risk during and after pregnancy and have potential for developing novel treatment strategies in future.

1. Breast cancer in pregnancy

Although breast cancer and pregnancy rarely coincide [1], at an incidence of 1 in 3000 to 10,000 pregnancies [2,3], mammary carcinoma seems to become the most frequent malignant disease in pregnancy because of the decrease of cervical cancer [4–6]. Pregnancy-associated breast cancer (PABC) is defined to occur during pregnancy or lactation period up to 12 months postpartum [7,8]. Studies analysing the effect of pregnancy on its prognosis extended this time period up to 2 or 10 years [9,10]. Although it remains overall low, an increasing coincidence because of the tendency of delaying family planning is expected [2,11,12].

Pregnant or breastfeeding cancer patients are often diagnosed with a delay of 2–15 months leading to a 2.5-fold higher risk for diagnosis at an advanced stage [9,13,14]. Reasons may be several factors: at first, diagnosis is more difficult at an early stage of malignancy due to physiological changes during gestation, e.g. growing of mammary glands and milk ducts [15]. Second, young women, pregnant or non-pregnant, have higher breast density and are not routinely screened by mammography [16]. Third, tumours of pregnant women present more often adverse pathological patterns, such as estrogen receptor (ER) α and progesterone receptor (PR) negativity and human epidermal growth factor receptor 2 (HER2) positivity, which are associated with higher tumour aggressiveness [17–19]. Advanced tumour stages may also be related to the comparatively young age of expectant mothers, because women below the age of 40 are generally diagnosed with more aggressive subtypes of breast cancer, associated with a worse prognosis [9,19–23].

1.1. Treatment of PABC

Although breast cancer in pregnancy is associated with a higher mortality risk, the prognosis is principally not connected with a worse outcome, if treatment schedule is identical to that in non-pregnant patients [24]. Therefore, it is important to begin chemotherapy immediately after completion of first trimester when foetal organogenesis is completed. First guidelines for breast cancer treatment during pregnancy have been developed by the German Breast Group demonstrating that pregnant breast cancer patients can be treated according to recommendations for non-pregnant women [5,25]. Anthracyclines in combination with cyclophosphamide, fluorouracil or taxanes are the most common chemotherapeutics, whereas hormonal and anti-HER2 therapies have to be avoided because cases of malformation and oligohydramnion have been reported [26,27]. Apart from this, the applied chemotherapeutic drugs seem to be well tolerated by the foetus when applied in the second or third trimester, and newborns have no higher risk for developing malformations [28–30]. This may occur because of low transport across the placental barrier because drugs as doxorubicin, paclitaxel and vincristine are substrates for different ATP-binding cassette (ABC)–transporters [31,32]. Especially, the efflux pumps ABC subfamily B member 1 (ABCB1), also known as P-glycoprotein, and ABC subfamily G member 2 (ABCG2), also known as breast cancer resistance protein (BCRP), are involved in foeto-maternal exchange processes and may support foetal protection [33–35]. For instance, the anthracycline doxorubicin is a substrate for both efflux pumps, P-glycoprotein and BCRP and is known to be well tolerated during pregnancy [32]. Nonetheless, frequently, a reduced birth weight in newborns from PABC patients has been observed [25,36], which may be a consequence of disturbed placentation, impaired placental tissue development and reduced nutrition transfer [37].

2. Influence of immunological factors on breast cancer risk

During the postpartum period, women have a transiently increased risk of developing breast cancer which turns back into a long-lasting protective period described as dual or cross-over effect [38–40]. This increased risk has been supposed to persist for 10–15 years after pregnancy [38,41–43]. If primiparous women are older than 35 years, the elevated risk may persist lifelong [44]. As placentation is accompanied by a transient maternal immunosuppressive state, the decreased immune surveillance has been discussed to worsen the outcome of breast cancer diagnosed shortly after delivery [16]. In contrast, an immunisation-like effect during gestation has been considered to lead to a long-lasting protection against breast cancer [45], which is enhanced in multiparous women [46].

2.1. Gene expression in parous women

In the breasts of parous women, regulation of several genes is changed as evidenced by an upregulation of 238 genes as well as a downregulation of 48 genes [47].

Upregulated genes are mainly related to immune responses, e.g. *CC-chemokine ligand 5 (CCL5)*, *CD48* and *interleukin-7 receptor (IL7R)* but usually decrease rapidly after delivery to the level of nulliparous women. The chemokine CCL5 affects T cells and recruits leucocytes into inflammation sites. Additionally, proliferation and activation of NK cells is induced by CCL5 in combination with cytokines [48,49]. CD48, which can be found on the surface of lymphocytes, dendritic and endothelial cells, induces their activation and differentiation [50]. IL7R is expressed on the surface of T cells and triggers their activation. Its absence or functional defects leads to immunodeficiency [51]. Activation or inactivation of these genes may be involved in the short-term increased risk of breast cancer after gestation. The activity of other upregulated genes, which are also related to immune responses, e.g. *CD38* and *CXCL10*, or to developmental processes, as mainly *DKK3* and *LAMA2*, decreases but does not return to nulliparous levels after pregnancy (long-term changing genes). For instance, CD38 is expressed on the surface of several immune cells, such as $CD4^+$ and $CD8^+$ T cells, NK cells and B lymphocytes, has activating functions [52]. CXCL10, which is secreted by monocytes, endothelial cells and fibroblasts in response to interferon γ, supports chemoattraction for different immune cells leading to anti-cancer and anti-angiogenic effects [53–55]. In summary, a set of upregulated and downregulated genes may be involved in processes explaining the described cross-over effect, but experimental studies addressing this issue remain to be performed.

2.2. Glycoprotein-induced immunomodulation

Pregnancy and breast feeding are assumed to induce protective anatomical and molecular changes in mammary glands. During these phases, the maternal immune system may get primed against pregnancy-related antigens, which are also expressed in breast cancer tumours [56–58]. In clinical observations, parous women were found to be naturally immunised against antigens on breast, ovarian and endometrial cancer cells, while nulliparous women were not [59,60]. This observation has been described first by Janerich *et al.* and termed as 'foetal antigen hypothesis' [61]. It has been suggested that a stimulation of the maternal immune system is caused by foetal antigens, which are similar to antigens on breast cancer cells, and thereby, induce protection against breast cancer [46]. Transmembrane mucin (MUC) glycoproteins, especially MUC1, have been discussed to be involved in molecular mechanisms of cancer and offer novel targets for immunotherapies [62]. MUC1 comprises a membrane-bound beta-subunit and an extracellular alpha-subunit, which are subsequently characterised by a variable number of tandem repeats (VNTRs) [63]. In these VNTRs, serine and threonine residues are strongly modified by O-linked glycans [62,64]. MUC1 is present in normal human epithelium helping to create a protective barrier against pathogens [65]. However, MUC1 is also one of the major cell surface mucins expressed in various malignancies, e.g. in breast and ovaries, and plays a key role in cell communication promoting breast cancer growth [66]. Interestingly, glycosylation patterns of MUC1 are different in both cases: in healthy tissue, MUC1 is O-glycosylated with long core-2 glycans, whereas it carries truncated O-linked glycans in cancer cells [62]. Consequently, these aberrant glycosylated mucins on cancer cell surfaces are characterised by specific antigens, which are absent in healthy tissues and therefore, can be considered as neoantigens evoking immune responses [62]. At the maternal foetal interface MUC1 is secreted by uterine cells required for blastocyst growth and development. Likewise, this glycoprotein is essential for immunological processes during implantation and prevents alloreactivity [67,68]. Aberrant glycosylation patterns are also present in the human placenta and the lactating breast with mastitis, which exhibit similarities to those on cancer cells. Hence, the human placenta is assumed to express these otherwise tumour-specific epitopes [69–71]. For example, Thomsen-Friedenreich disaccharide Galβ1–3GalNAc (TF) antigen, which is expressed in approximately 90% of cancer types and also on trophoblast cells, probably supports galectin-mediated interactions between syncytiotrophoblast and endometrium cells [72]. In general, these aberrant glycosylated mucin epitopes may induce maternal immune reactions during pregnancy helping to eliminate arising cancer cells later in life. Indeed, Croce *et al.* analysed 149 serum samples and found increased MUC1 levels in pregnant compared with non-pregnant women. Elevated values of IgM-anti-MUC1 and IgG-anti-MUC1 circulating antibodies have been detected in non-pregnant compared with pregnant women. Lactation raises IgG-anti-MUC1 significantly, but not IgM-anti-MUC1 [73]. The authors suggest that IgG antibodies are involved in the anti-carbohydrate epitope response. This hypothesis of the triggered lactation effect is further supported by two case-control studies, and one case reports of puerperal mastitis. Women suffering from mastitis had significantly higher levels of anti-MUC1 antibodies [69,74]. In conclusion, prior mastitis is associated with a significantly lower risk for ovarian cancer [74]. Especially, activated cytotoxic $CD3^+/CD8^+$ T cells (CTLs) proliferate in response to MUC1 and consequently recognise MUC1 peptide sequences exposed on tumour cells. These cytotoxic T cells are able to lyse MUC1 expressing breast tumour cells [75,76]. In a clinical study, a higher MUC1 expression on primary breast cancer tumours is associated with a better prognosis. The steroid hormones progesterone and estrogen, which are highly produced during human pregnancy, induce an upregulation of MUC1 expression on cancer cells [77].

2.3. Gender-specific aspects

The sex of the first child has been discussed to have an influence on breast cancer survival in young women, but studies reveal controversial results [78]. It has been reported that primiparous women giving birth to a boy have an increased risk of early mortality when diagnosed with breast cancer [79], but other studies could not observe any sex-dependent correlations [80]. Immunological processes have been suggested as underlying mechanisms [78].

2.4. Animal studies

Several experimental animal models have been established to investigate the interaction between breast cancer and placenta tissue. For instance, splenocytes of parous rats develop a slight cytotoxicity against mammary tumour cells resulting in a reduced tumour aggressiveness after delivery. A restimulation of these splenocytes by irradiated mammary tumour cells leads to an enhanced cytotoxic effect induced by cytotoxic T cells [81]. Owing to the ability to reactivate the cytotoxic response of splenocytes, a long-term T-cell memory has been suggested. A murine study has demonstrated that $CD44^{hi}$ T cells with long-term memory phenotype can survive *in vivo* for up to 70 days. Hence, it has been considered that repeated pregnancies stimulate already existing mammary tumour targeting T cells. This may explain a lower breast cancer risk after multiple pregnancies [82]. Additionally, antigens that are foreign or unknown to the immune system of a healthy nulliparous female have been detected in embryonic and placental cells of rats, including alpha foetoprotein, alpha-2 glycoprotein, beta-1 glycoprotein and placental lactogen [83]. Pregnancy may lead to respective immunisation and potential immunity also after delivery which may protect against similar antigens on mammary tumours.

2.5. Tumour-associated and pregnancy-associated proteins

In general, the progression of a malignancy is determined by multifactorial interaction between cancer cells and the host immune system. Cancerous cells are able to acquire the ability to escape from immunological surveillance and, moreover, to suppress immune responses [84]. Therefore, receptor-binding cancer antigen expressed on SiSo cells (RCAS1) seems to play an important role in immune-modulation of the tumour microenvironment [85–88]. It has been suggested that RCAS1 is also a determining factor in the development of immune tolerance during pregnancy. The protein has been detected in soluble as well as membrane bound forms in trophoblast, decidua and endometrium cells [89–91]. Decreased levels of RCAS1 in blood serum have been measured during labour. Its physiological function seems to be induction of apoptosis and cell cycle arrest in T cells [92–94]. Recurrence of cancer is accompanied by an increase of RCAS1 levels in blood serum, whereby preeclamptic patients, who exhibit decreased RCAS1 serum levels in general, consequently suffer less frequently from neoplasms [95]. RCAS1, also known as estrogen-responsive protein EBAG9 [85] was originally identified by monoclonal antibody (mAb) 22.1.1, which increases in mice after immunisation with the human uterine cervical adenocarcinoma cell line SiSo [96]. Subsequently, studies demonstrated that mAb 22.1.1 does not recognise RCAS1 itself but the tumour-associated O-linked glycan Tn (N-acetyl-D-galactosamine, GalNAc) [97]. As described before, aberrant expression of carbohydrate epitopes frequently occurs on malignant cells. Especially, Tn and TF are often found on tumour surfaces, but their role in tumour development remains unknown [98]. Because early embryonic tissue also expresses these glycan epitopes, it may be expected that RCAS1-associated truncated glycans may induce long-term immunity against breast cancer as described for MUC1. As RCAS1 is estrogen-inducible, the high estrogen levels during pregnancy may influence its expression and thus, the development of malignancies. RCAS1 impairs the cytotoxic activity of CTLs by formation/exocytosis of secretory lysosomes, which triggers the development of tumours [99].

The pregnancy-related placental immunoregulatory ferritin is involved in regulating immune responses against the embryo but is also expressed in breast cancer manipulating the cytokine network, immune responses and tumour microenvironment. When the protein is blocked by anti-C48 treatment in a mouse model, an inhibition of placental, foetal and tumour growth can be observed [100]. In general, enhanced activity of immunosuppressive factors based on coincidence of breast cancer and pregnancy may worsen the survival of patients.

Glycodelin (GD), initially described as progesterone-associated endometrial protein, is a glycoprotein with a molecular weight of 28 kDA consisting of 180 amino acids [101]. The GD gene (gene name *PAEP*) is located on chromosome 9q34 [102,103]. GD gene expression and GD secretion from the luteal and decidual endometrium correlate with progesterone levels [104–106]. Also relaxin and human chorionic gonadotropin (hCG) stimulate GD synthesis and secretion by endometrium cells [106]. GD exists in three isoforms differing only by glycosylation resulting in different functions. In breast cancer, the isoform GD-A contributes to cell differentiation and indicates a good prognosis [102]. Increased levels of GD-A are associated with enhanced endometrial secretory functions [107]. In an ovulatory cycle, GD-A secretion is absent during the proliferative phase [108] and starts 4–5 days after ovulation persisting until the next menstrual cycle indicating its involvement in

implantation [105,107]. The increased production of GD-A in early pregnancy is mainly effected by decidual cells [105]. Between the 6th and 12th week of pregnancy, the GD-A concentration reaches a maximum [109]. Hence, decreased expression of GD in decidual tissue indicates disturbed functions in early pregnancy [110]. In contrast, in premalignant conditions such as hydatidiform mole with upregulated hCG levels, GD expression is increased [110]. This relationship might be caused by a feedback mechanism between hCG and GD expression [110]. GD exerts immunosuppressive and immunomodulatory functions in the endometrium, especially during pregnancy, supporting implantation and maintenance of pregnancy [105,109]. These properties may also influence tumourigenesis of different malignancies [111]. GD-A induces apoptosis of NK cells, T cells, monocytes and B cells and is involved in the suppression of cell proliferation [103]. GD expression is also associated with cell differentiation and, consequently, growth reduction which might be interesting for further studies in cancer research [112]. Specific monoclonal antibodies against GD-A have been developed to further investigate its role in endometrial development, maintaining pregnancy and tumour progression [113]. These antibodies are able to detect GD-A in breast cancer tissue and may be useful for further studies in PABC research [113].

3. Effects of pregnancy-associated hormones on growth and behaviour of breast cancer cells

The placenta is the central organ for foetomaternal exchange, maintaining pregnancy and supporting the development and health of the growing foetus by providing nutrients and oxygen [114]. These functions are accompanied by the placental production of progesterone, estrogens, placental lactogen, placental growth hormone and chorionic gonadotropin (hCG) leading to a significant change of the hormonal milieu in pregnant women, which may influence growth and behaviour of breast cancer cells [115]. The main estrogen, estriol, is produced at significant amounts during pregnancy by the foetoplacental unit. However, published data on the effects of estriol on breast cancer are limited, yet some authors assume that breast cancer recurrence may be stimulated by increased levels of pregnancy-related hormones which consequently decrease the survival rate [116]. In contrast, a meta-analysis has demonstrated a significant improvement in overall survival in women, who became pregnant following breast cancer diagnosis compared with women without subsequent pregnancy [116]. This phenomenon has been called 'healthy mother effect' and was first described 1994 by Sankila *et al.* [117]. In combination with the observation of rare breast cancer metastases in the placenta, it has led to the assumption that the placenta may present a non-supportive microenvironment not only for breast cancer cells but also for cancer cells in general [118]. In fact, only 87 cases of any maternal tumours (e.g. melanomas or cervical cancer) metastasising to the placenta or even to the foetus have been reported from 1966 to 2002 [119]. In this report, 15 cases of placental breast cancer metastases have been described but none with foetal involvement. Indeed, maternal-foetal transmission of tumour cells seems to be very rare. However, in *ex vivo* one-sided perfused placentas T-cell leukaemia cells principally can cross the placental barrier [120]. A co-culture model of first trimester placental tissue and hormone-positive breast cancer cells (MCF-7/T47D) revealed a reduction of breast cancer cells closely to the placental explant, and ERα expression in cancer cells decreased [121]. In general, ERα promotes breast cancer cell proliferation, survival and motility [122]. Likewise, an extensive cross-talk between progesterone and 17beta-estradiol has been described; progesterone reduces ERα levels and exhibits some anti-estrogenic effects and vice versa [123]. Interestingly, most studies have demonstrated that ERβ acts as negative modulator of ERα indicating a good prognosis [124,125]. Even in triple negative breast cancer cells, which do not express ERα, PR and HER2, but may express ERβ [126], ERβ agonists reduce invasiveness and tumour progression [127]. Therefore, the expression of ERβ in the breast may also influence growth of breast cancer during pregnancy. Gene expression analyses of the breast showed that parous women have a significantly two-fold higher ERβ expression compared with nulliparous women [128]. hCG is one of the most important pregnancy-related hormones, mainly produced during early gestation. Its expression decreases in the second trimester but rises again towards delivery [129]. The expression of hCG in breast cancer has been assumed a sign of differentiation associated with lower malignancy [130]. A clinical study has demonstrated that hCG given as a breast cancer treatment reduces tumour proliferation and progression [131]. This anti-proliferative effect has been confirmed on breast cancer cells in experimental studies [132,133]. Therefore, hCG has been discussed to be a natural chemopreventive agent [134].

4. Anti-tumour effects of placenta-derived components

Besides the effects of immunological and hormonal factors, special cell types of the human placenta and extraembryonic tissue have been suggested to be potentially useful for inducing apoptosis in cancer cells. For instance, human amniotic epithelial (hAM) cells induce apoptosis in cancer cells and have anti-angiogenic effects [135]. In fact, hAM cells express thrombospondin-1, endostatin and heparin sulphate proteoglycan. Further, tissue inhibitors of metalloproteases (TIMP-1, TIMP-2, TIMP-3 and TIMP-4)

with a potential anti-angiogenic effect have been detected in amniotic membrane [136]. Therefore, application of amniotic epithelial cells has been considered for novel therapeutic anti-tumour strategies [135]. hAM protein extracts isolated from amniotic membrane inhibit the metabolic activity of several cancer cell lines, but the commonly used breast cancer cell line MCF-7 appears to be unaffected by this treatment [137]. These recent studies may encourage testing effects of further placental cells and factors on tumour cells. Another study revealed the inhibition of tumour growth and metastasis through application of placental extracts in cell culture and mouse models [138]. Furthermore, high expression of *KISS-1*, a human metastasis suppressor gene, has been found in placental tissue. The respective peptide kisspeptin, previously also termed metastin, has been isolated from human placenta and is an endogenous ligand of an orphan G protein–coupled receptor. Highest concentrations of kisspeptin have been detected in third trimester placenta. Five days after delivery,

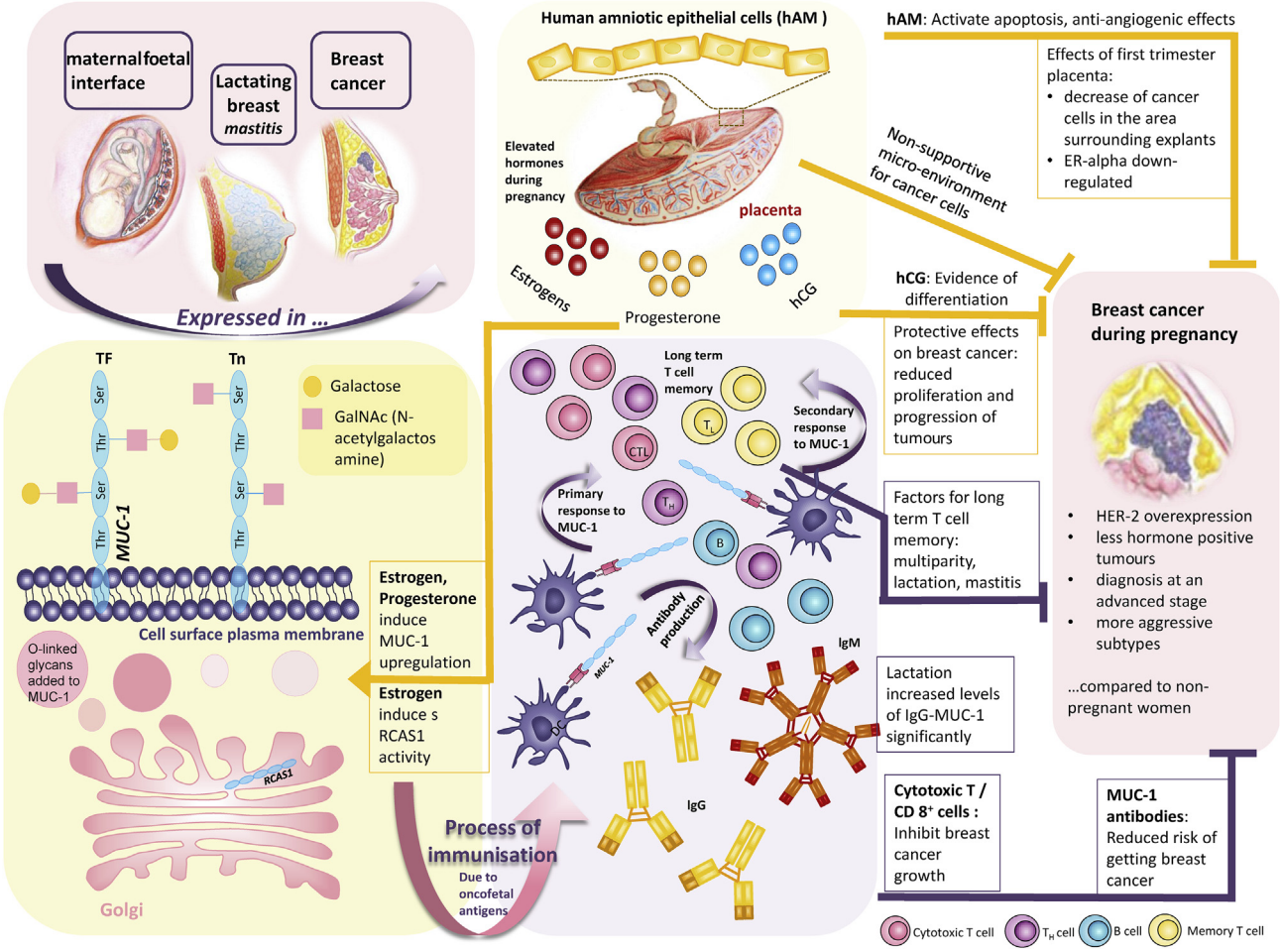

Fig. 1. Proposed anti-tumour effects of the placenta. During pregnancy, several breast cancer surface proteins are expressed on the cell surface membrane of trophoblast cells. The extracellular alpha-subunit of MUC1 is characterised by alternately repeated threonine (Thr) and serine (Ser) sequences. At these positions, O-linked glycosylation occurs constantly. These truncated O-linked glycans, such as Thomsen-Friedenreich disaccharide Galβ1–3GalNAc (TF) antigen, are present in breast cancer, trophoblast cells and mastitis. Owing to different glycosylation patterns in healthy tissue, these structures may induce immune responses. The closely related tumour-associated O-linked glycan Tn (N-acetyl-D-galactosamine) is also present on the receptor-binding cancer antigen expressed on SiSo cells (RCAS1) in the Golgi complex of trophoblast cells. Dendritic cells (DCs) present these antigens and activate cytotoxic T cells (CTLs), T_H cells and B cells leading to the secretion of IgG antibodies detectable in maternal serum. Memory T cells may be induced by multiparity, lactation and mastitis. All described immune regulatory effects might lead to a reduced breast cancer risk after pregnancy in later years of life. The placenta itself is described as non-supportive microenvironment for cancer cells with indirect and direct effects on breast cancer invasiveness. Estrogen and progesterone induce MUC-1 upregulation, whereby estrogen enhances RCAS1 activity. This might strengthen the process of immunisation. Human chorionic gonadotropin (hCG), which is secreted at high amounts by the placenta, induces differentiation and reduces proliferation and progression of breast tumours. Human amniotic epithelial cells (hAM), located at the foetal placental surface, have also anti-angiogenic effects and induce apoptosis. These direct effects of placental factors might explain the low rate of breast cancer metastases in placenta.

kisspeptin plasma levels returned to almost non-pregnant levels suggesting the placenta as major source of expression [139]. The authors concluded that kisspeptin may act as potential biomarker for aggressive metastasising tumours and may offer new therapeutic approaches against metastatic cancer [140]. Fig. 1 summarizes potential anti-tumour effects of the placenta.

5. Perspectives

Effects of pregnancy on breast cancer are still partially unknown, and reports are often contradictory. Most studies have reported an increased risk for developing breast cancer for a few years after pregnancy which, subsequently, reverses to a reduced risk [38,41–43]. The reasons for this phenomenon have not been studied intensively, yet. The hypothesis of immunisation induced by pregnancy-related antigens [61] offers a potential explanation but has not been investigated further. Studies on MUC1 have led to creation of MUC1 antigen-based vaccines for reduction of breast cancer risk [62]. Phase I/II clinical trials are currently ongoing [141], but thus far, in contrast to other tumours, no vaccine for treatment or prevention of breast cancer has been launched. It may be expected that MUC1 or other oncofoetal antigens expressed during pregnancy or lactation period may have a vaccine potential as indicated by the absence of metastases in the placenta. Current studies have shown tumour suppressive characteristics of different placenta-derived factors and placental components. Understanding their molecular mechanisms and long-term effects on development of breast cancer and its transiently increased risk during and after pregnancy may help to develop novel treatment strategies.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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