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The immune response in pregnancy and in cancer is active and supportive of placental and tumor cell growth not their destruction

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HIGHLIGHTS

- The placenta and tumor microenvironment are strikingly comparable.
- The review relates the immune responses in cancer and pregnancy.
- Placenta/tumors exploit similar immune mechanisms for growth and vascularization.
- This unique relationship provides insights into cure of cancer.

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ABSTRACT

While many investigators have described the biochemical and physiological similarities between tumor cells and trophoblast cells, in this discourse we will compare primarily their leucocytes, which constitute a large portion of the tumor and its microenvironment as well as the placenta and its microenvironment. There is a remarkable similarity between the cells that support placental growth and development and tumor growth and development. In many cases over half of the cells present in the tumor and the placenta are non-tumor or nontrophoblast cells, immune cells. Most of these immune cells are prevented from attacking the fetal derived placental cells and the self-derived tumor cells. Nevertheless, these leucocytes, in our opinion, are very active and support tumor and placental cell growth through the production of growth factors and angiogenic factors. These cells do this by activating the portion of the immune response which initiates and helps control tissue repair.

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1. Introduction

Early comparisons between the placenta in pregnancy and of tumors in cancer were based on two features. One feature of the placenta during pregnancy is the absence of expression of classical MHC class I molecules, with the exception of HLA-C, leading to a lack of recognition by self-cytotoxic T cells during pregnancy [1]. Another feature is the absence of an expected immune response to the trophoblastic foreign tissue which has been called "immune tolerance". This was thought to be due to an active immune suppressive process regulated by cells such as Treg cells that effect T cells and that regulate macrophages, neutrophils and "NK Cells". These features also are seen in many tumors, i.e., the absence in some cancers of MHC class I molecules leading to a lack of self-reactive cytotoxic T cells and the suppression of an immune process which is attempting to destroy the foreign tumor cells in the cancer [1]. However, we believe the following hypothesis should be considered, that the immune system is very active in inducing trophoblast cell development and that this same activity is important in tumor development [2].

Sir Peter Medawar noted the lack of recognition of foreign antigens on allografts and immune tolerance in his very early work on the maternal fetal interface [3]. This work suggested that immune tolerance was thought to be a key feature in pregnancy, which has dominated the investigations into the immune system and pregnancy. These investigations focused on the perceived immune suppression towards the fetal 'allograft' as a model for transplantation. While Medawar's manuscript clearly suggested other interesting avenues of research, the transplantation scientist had the most interest in immune tolerance. The findings of Warburg suggested a similarity between tumors and the placenta [4–9]. A recent study shows a direct relationship between increased lactic acid production and increased glucose utilization by both the developing placenta and the tumor [10]. Another article notes that both placenta and tumor development occur under low oxygen conditions, and both rely heavily on glycolysis for energy and cell proliferation [11].

In this review, we will compare the microenvironments, cells (especially immune cells), cytokines and growth factors in pregnancy and cancer and conclude with the possibility that similarities exist between these two conditions which may be useful to aid diagnosis and treatment.

2. Microenvironments and a2V-vacuolar ATPase

In the tumor microenvironment, metastasis of cancer cells is influenced by both "normal" and cancer derived factors. Some of these factors are related to infection and chronic inflammation. Indeed, infiltration by immune cells is observed in a majority of solid tumors; these cells release high levels of cytokines or other cancer related factors into the surrounding tissues and blood stream [12]. In a recent review, Mlecnik et al. [13] correlated the decreased presence of lymphatic vessels and reduced immune cytotoxicity with the metastatic spread of tumor cells. The hypothesis that there is a link between inflammation and cancer is now widely accepted [12]. It has been shown that many solid tumors have infiltrated immune cells and secrete cytokines into the surrounding tissues or into the blood stream. The tumor associated cytokines affect tumor growth and affect the tumor environment by inducing the growth of new blood vessels. This process leads to more inflammation which in turn induces more tumor angiogenesis leading to more tumor growth. Similar events occur during pregnancy. After implantation of the fertilized egg, the decidua must establish more blood vessels to nurture the developing fetus; this happens by the induction of angiogenesis in the developing placenta. This mechanism is induced by the immune cells that are present in the decidual and secrete pro-angiogenic and immunomodulatory cytokines [14–16].

Vacuolar-ATPase (V-ATPase) is a proton pump ubiquitous in all cells; it is required by both normal and cancer cells for growth and development [10,17]. In normal cells, V-ATPase is crucial for maintaining a homeostatic intracellular pH and is found on intracellular organelles. In contrast, in cancer cells V-ATPase is found on the plasma membrane and used by these cells to transport hydrogen ions outside of the rapidly proliferating malignant cells. This process induces an acidic extracellular environment which facilitates metastasis and drug resistance [18–20]. Vacuolar ATPases are enzymatic complexes of approximately 800 kDa consisting of two domains (V1 and V0) held together by the V0 subunit aV [21]. This subunit has four isoforms (a1V, a2V, a3V and a4V) which target these large complexes of hydrogen ion transporting enzymes to different organelles. In pregnancy, the inhibition of a2V isoform results in lack of the development of the maternal-fetal unit and subsequent loss of pregnancy and/or abortion [19]. A key difference in either successful or unsuccessful tumor or placenta growth is the level of expression and the location (intracellular or on the plasma membrane) of V-ATPase within these cells [6,22].

In our studies regarding the tumor microenvironment, we found a correlation between a2v which is found in both tumor cells and normal cells and is involved in the metastasis of the cancer. We have used an a2V mammary gland knockout (KO) mouse model to determine the effect of the microenvironment on cancer dissemination. When these a2V knockout mice, which lack a functional V-ATPase due to the lack of the a2V isoform, were transplanted with tumor cells, the tumors that developed were atypically soft and highly metastatic. This finding correlated with our finding that in human breast cancer specimens, low a2V expression levels were observed in uninvolved breast tissue of cancer patients reported with lymph node metastasis. Similarly a reduction in the growth of both the tumor cells and placental trophoblasts was observed when the expression of a2V was reduced in the placenta or in tumor cells [19,22].

An increase in a2V correlated with a unique and abundant change in cytokine expression in monocytes These cytokines included IL-1β and IL-10, which are important in promoting inflammation and immune escape by tumor cells. The secretion of inflammatory cytokine IL-1β is dependent on ATP, K(+) efflux, and reactive oxygen species, all mediators that activate the inflammasome of macrophages. These findings describe a mechanism by which tumor cells affect the maturation of tumor associated macrophages (TAMs) via a nontraditional cytokine-like signal, the a2NTD peptide, which is generated from the a2V-ATPase. These studies show the importance of the tumor microenvironment in facilitating growth and rapid metastasis of the malignant cells [23,24].

3. Characteristics of trophoblasts and tumor cells

The invasion of fetal cells into the maternal tissue is a key step in nidation (implantation) of the embryo and the establishment of a successful pregnancy. Trophoblast cells have to evade potential maternal immune system attack and persist in the presence of extreme hypoxia and the initial lack of vasculature supply [16]. These conditions are necessary to enable the fetus to grow instead of being attacked as a foreign entity by the immune system. Trophoblast cells have characteristics similar to tumor cells as they both have an invasive phenotype, a high proliferative capacity, and the ability to promote angiogenesis. Tumor cells encounter a similar environment as trophoblasts (extreme hypoxia, initial lack of vascular growth and increased glycolysis over time due to their growth-Warburg effect); they also evade immune detection while invading host tissue. The mechanisms used for invasion, proliferation, vasculature development and immunosuppression are similar for both tumor cells in cancer and trophoblast cells [25,26].

Tumor and trophoblast cells actively modulate the host immune response [7,16,27]. Trophoblast cells and tumor cells are continuously intermingling with host cells as they progress and develop. Tumor cells have the ability to actively engage host immune cells as *host inflammatory cells* and induce proteins that stimulate invasion and proliferation in tumor cells [22,28]. However, many of these cells are able to evade immune system attack. Comparable to the mechanism of evasion

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