

Mother knows best: Lessons from fetomaternal tolerance applied to cancer immunity

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1. ABSTRACT

Failure of the immune system to recognize and eradicate tumor cells has deadly consequences. It is possible that the normal host response to the inflammatory environment created by many cancers – the body’s natural attempt at wound repair and restoration of tissue integrity – is one of counter-regulation that paradoxically favors tumor growth. A physiologic condition where this situation is favorable (and even required) is that of normal pregnancy, where blastocyst implantation creates endometrial inflammation, and the maternal response in turn supports angiogenesis and tolerance required for placentation. Lack of such inflammation and resultant maternal immunologic engagement can lead to serious pregnancy complications including fetal loss, highlighting how important the fetomaternal immunologic dialogue is for survival. Here, we describe how the dynamics of fetomaternal tolerance can help disentangle complex cancer/host immunologic interactions and provide new avenues for immunologic reconstitution in patients with cancer.

2. INTRODUCTION

Cancer cells’ interaction with the microenvironment (including stromal cells and infiltrating immune cells) leading to exhausted anti-tumor immunity and cancer progression is increasingly recognized. According to the self-nonself model of immunologic interactions (for which a Nobel Prize was awarded to Burnet and Medawar in 1960), tumor cells, although not normal, are still “self” and thus would not be expected to create an immune response. We know, however, that this is not the case. It is not at first glance intuitive why a host’s immune system would recognize tumor antigens, but tumor-antigen specific cytotoxic T cells have been observed in most malignancies. Likewise, during gestation, the mother is similarly continuously exposed to fetally-derived trophoblast cells. Although the fetus is “non-self,” immunologic rejection typically does not occur. In fact, many immunologic changes occur with the maternal recognition of pregnancy that are of benefit during gestation and perhaps even beyond (1). Both cancer and

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pregnancy are situations where the self-nonsel model is inadequate to explain evidence of immunologic engagement. What then is common between the “dangerous self and the harmless foreign” (2)? In the paragraphs that follow, we will describe some of similarities in these processes but also make note of key differences that open the possibility of identifying new ways of rescuing cancer patients from immunologic exhaustion by the study of normal human pregnancy.

3. TOLERANCE AND ANTI-INFLAMMATORY THEORIES OF PREGNANCY AND CANCER

Pregnancy has previously been described as an immunologic paradox where a semi-allogeneic fetus escapes attack from the maternal immune system (3). Once considered an inert physical barrier to protect the fetus from an immunologic attack, the placenta actively recruits maternal immune cells to the fetomaternal interface to create not only a tolerogenic but also an angiogenic microenvironment. Endometrial inflammation is a crucial first step to establishing receptivity (4), and early pregnancy proceeds as a relatively inflammatory process characterized by a rich immune cell infiltration; in fact, nearly half of all cells in the decidua are of hematopoietic origin (5). Why are there so many immune cells in the gravid uterus? On the surface, it seems counterintuitive that the maternal decidua would contain so many leukocytes, especially natural killer (NK) cells – cytotoxic lymphocytes that are licensed to kill without prior activation – if a fetal allograft merely escapes maternal immune recognition.

The answer lies in the microenvironment. In the presence of factors secreted by endometrial stromal cells including transforming growth factor (TGF)-beta, NK cells that would inherently be conceived as “foes” to invading trophoblast cells are actually transformed into “friends,” providing critical angiogenic and immunomodulatory factors necessary for placentation (6, 7). NK cells recruited to the fetomaternal interface comprise up to 70% decidual immune cells and has a distinct phenotype and function from their peripheral blood counterparts (8). Classically, peripheral blood NK cells are primarily conceptualized by cytotoxic functions in two circumstances: (1) when encountering cells with downregulated major histocompatibility class I molecules on the surface (viral-infected or tumor cells), and (2) and antibody-dependent cell-mediated cytotoxicity (ADCC) when recognizing a cell with many antibodies bound to its surface via CD16, the Fc-gamma receptor. However, the adaptability of NK cells to their environment and the potential regulatory role they play in immunity has been increasingly recognized (reviewed by Vivier *et al.* (9)). NK cells “tuning” within the uterine environment is an excellent example of this phenomenon. Decidual NK cells phenotypically are CD56 bright, CD16dim/–, and CD9-positive and secrete immunomodulatory factors galectin-1 and glycodelin (7). They are also a major source of angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PGF) critical for placentation (10). Failure of these NK cells with regulatory functions to expand has been

associated with miscarriage, highlighting their important role in supporting normal pregnancy (11).

In addition to NK cells, several other cells of hematopoietic origin including macrophages (12), dendritic cells (13), and regulatory T cells (14) are also present at the fetomaternal interface and play critical roles for supporting placentation. Macrophages are felt to play a crucial anti-inflammatory role by secreting IL-10 and TGF-beta in response to the phagocytosis of apoptotic cellular debris at the fetomaternal interface (15). Additionally, in a murine model where dendritic cells are ablated, (even syngeneic) pregnancy cannot progress beyond implantation and decidual angiogenesis was severely impaired (16). Likewise, decidual regulatory T cells express high levels of CTLA-4 and contribute to peripheral tolerance to paternal alloantigens (14), and without them, pregnancy cannot progress (17).

A similar pattern of microenvironmental changes exists in tumor immunology. Like modulation of immune cell subsets during the decidualization and placentation process, tumor infiltrating immune cells can undergo phenotypic change to provide cytokines and growth factors that are paradoxically helpful for the progression of cancer within the tumor microenvironment and beyond (18). For example, infiltration of macrophages is associated with increased tumor stage and enhanced angiogenesis through increased interleukin-8 and VEGF levels in melanoma (19). As with the fetomaternal interface, immature intratumoral and peritumoral DCs predominate in primary cutaneous melanomas (20). Although cytotoxic lymphocytes can be attracted to neoplastic sites, they can be rendered anergic due to insufficient costimulation, extrinsic inhibition by regulatory T cells, by soluble negative regulatory factors such as TGF-beta (21). As observed in pregnancy, patients with advanced malignancies including metastatic melanoma demonstrate alterations in peripheral blood lymphocytes subsets; e.g., patients with metastatic melanoma have higher levels of circulating regulatory T cells than those patients with minimal disease (22). We recently identified a derangement in NK cell subsets in the peripheral blood of patients with metastatic melanoma that resulted in expansion of the CD16- pool, and a subset *also* expressed CD9, the cell adhesion molecule specific for NK cells within the female reproductive tract (23).

As we think about these host responses – the maternal acceptance of blastocyst implantation and inflammatory/down-regulatory responses within a person with cancer – we see that both conditions involve the same processes. An immunoregulatory network may be shared between the two conditions, and NK cell “tuning” is just one example of the similarities. Both trophoblasts and cancer cells might be seen as conductors of a symphony, orchestrating responses in local tissues by environmental and epigenetic mechanisms (24, 25). What is unique to pregnancy, however, is that the placenta is a short-lived organ and the immunologic privilege granted it is transient, suggesting that cancer rejection via host immunologic responses is possible. In order to explore that possibility, we must first understand the dynamics of maternal-

Table 1. Summary of human studies describing changes in immune cells in the decidua and peripheral blood during healthy pregnancies

Cell Type	Location	Early pregnancy	Midgestation	Late Pregnancy
Dendritic cells (CD45+ Lineage-HLA-DR+) (34-39)	Decidua	<2% of decidual leukocytes, phenotypically immature, ↑ myeloid DC (CD11c+CD123-) compared with lymphoid DC, significantly ↑ CD80 expression	?	Minor population still present
	Peripheral blood	Absolute numbers —, but ↑ lymphoid DC (CD11c-CD123+) compared with myeloid DC, similar CD40 and CD80 expression compared with non-pregnant women	Absolute numbers —, but ↓ CD40 and CD80 expression than non-pregnant women	Absolute numbers — to ↓, with ↓ CD40 and CD80 expression than non-pregnant women, more immature DC (30.1% vs 17.5%)
Monocytes-Macrophages (CD14+) (5, 8, 38, 40-42)	Decidua	20-30% of decidual cells at site of implantation	— compared to first trimester	Significantly ↓ in third trimester
	Peripheral blood	— to ↑	—	— to ↓, but increased expression of levels of CD14, CD11a, CD11b, CD54, CD49d, CD62L, CD64
NK cells (CD3-CD56+) (8, 38, 40, 43-46)	Decidua	Major cell population, CD16dim/- CD9+ NKs comprise ~70% of leukocytes	— compared to first trimester	Significantly ↓ in third trimester, to ~40% leukocytes
	Peripheral blood	Overall ↑ in NK cells over non-pregnant controls, CD16 significantly ↓	↓ in CD16+ NK cells	CD16+ cells similar to non-pregnant controls, although NK cytolytic function post-partum does not seem to recover until >3 months post-partum
Regulatory T lymphocytes (CD4+CD25+ Foxp3+) (8, 47, 48)	Decidua	~10% of decidual leukocytes, co-express CTLA-4 and activation marker CD69	?	~14% of decidual leukocytes
	Peripheral blood	↑ compared with non-pregnant controls (6.7% vs 4.4%), median ~25% of CD4+ cells	~11% of T cells ~20% of CD4+ cells	~8% of T cells ~15% of CD4+ cells (non-pregnant controls ~10% of CD4+ cells)
T lymphocytes (CD3+) (5, 8, 38, 40, 41, 43, 44)	Decidua	~20% of decidual leukocytes, primarily CD8+ lymphocytes	— compared to first trimester	No significant change over first trimester levels, although significant ↑ in CD3+CD161+ subset (possibly an NKT-like cell)
	Peripheral blood	↓ in CD4+ cells, ↑ in CD8+ T cells leading to decrease in CD4:CD8 ratio compared with non-pregnant controls	Relative overall lymphopenia compared with first and third trimesters, ↓ in CD4+ cells	Overall ↓ in lymphocytes compared with non-pregnant controls, CD4+ cells return to non-pregnant level, ↑ CD8+ perforin+ cells compared with non-pregnant controls and ↑ first trimester levels, ↑ in expression levels of CD11a and CD49d

trophoblast tolerance from implantation to parturition, a process that remains one of the great mysteries of human reproductive immunology.

4. IMMUNOLOGIC PHASES OF PREGNANCY

Normal pregnancy has been established as a predominantly T helper 2 cytokine-enriched state (26) with resultant tolerance toward a fetal allograft. However, pregnancy is not a monophasic immunologic event. Rather, it is a dynamic process involving inflammation during implantation, tolerance induction/maintenance to establish adequate placentation and nutrients for fetal growth, and then restoration of an inflammatory state to prepare for parturition (27). In Table 1, we summarize our current understanding of the dynamics of the maternal response to pregnancy throughout gestation. Notable are features supportive of tolerance until late pregnancy, where the return of acute inflammation and immunologic reconstitution appears to take place. Failure of adequate tolerance induction and maintenance of Th2-type immunity can be associated with severe complications such as recurrent spontaneous abortion (28) and preeclampsia (29, 30), highlighting the importance of this process for survival.

A simplified graphical depiction of the putative alterations in immune cell subsets during healthy

pregnancy is depicted in Figure 1. Much of the data that exists today, although it has been very helpful for initial description of patterns of immunity during gestation, is cross-sectional and from relatively few time points. To better understand the dynamics of immunomodulation at the systemic level (and because the risk of repeated placental biopsies is not acceptable), we are currently opening a longitudinal study of systemic immunologic changes in a cohort of healthy primigravidas. We will address some of our current knowledge gaps in changes in cellular immunity as directly related to angiogenic, hormone, and other growth factor levels in a prospective, longitudinal study that opened for enrollment in January 2011.

5. POSSIBILITIES FOR IMMUNOLOGIC RECONSTITUTION

Both pregnancy and metastatic malignancies are thought to be characterized by a Th2-polarized state of angiogenesis and chronic inflammation. While several characteristics inherent to cancer cells create interference with immunosurveillance (18), recent data suggests that the physiologic response to malignancy is also much more complex (31). As we have summarized above, pregnancy is not a static physiologic state but rather a dynamic condition associated with tolerance induction and

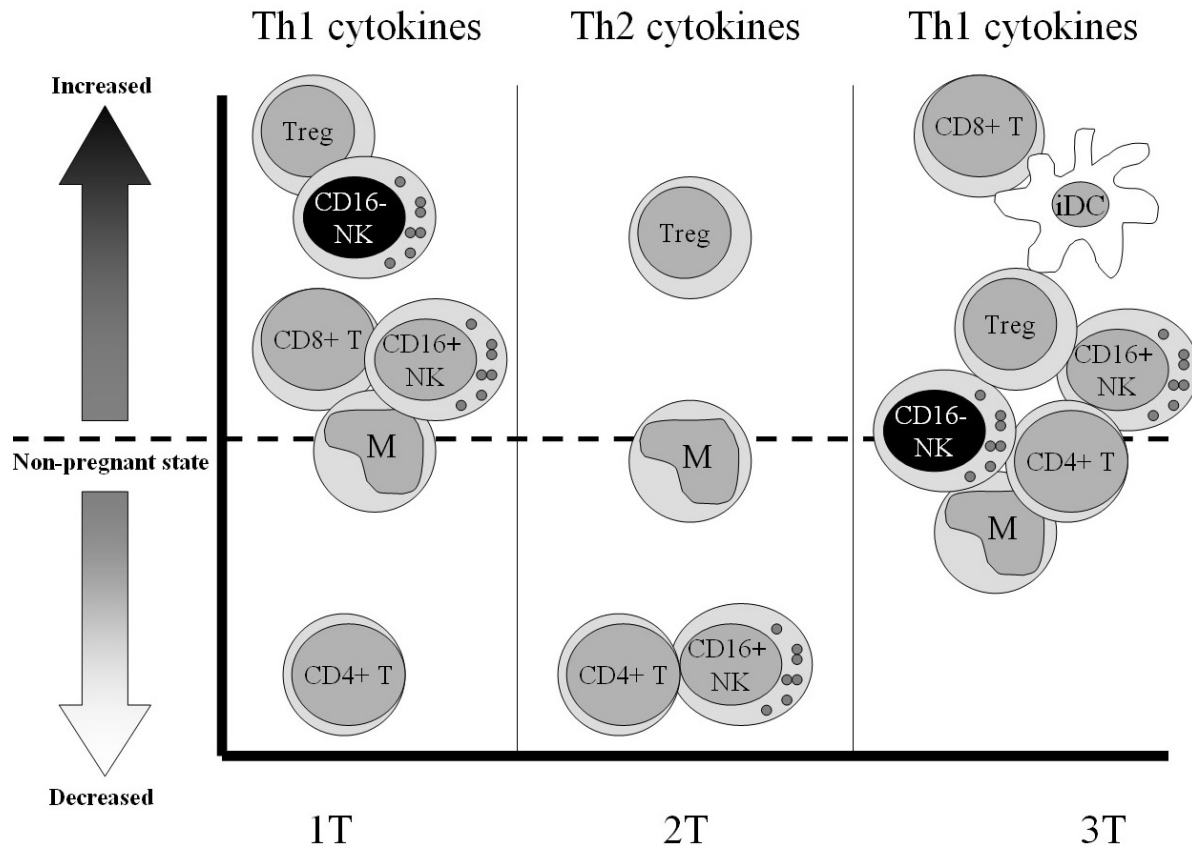


Figure 1. Graphical representation of putative changes in peripheral blood immune cell subsets and cytokine milieu according to trimester during healthy pregnancies. Abbreviations: 1T=first trimester, 2T=second trimester, 3T=third trimester, iDC=immature dendritic cell, M=monocyte, NK=natural killer cell, Treg=regulatory T cell, T=T lymphocyte.

angiogenesis in the early months followed by acute inflammation as term approaches. We hypothesize that the cellular and cytokine milieu associated with the restoration of Th1-bias toward the end of pregnancy may be a desirable state to emulate in metastatic melanoma and other cancers, as it would be associated with the greatest likelihood of reconstituting endogenous anti-tumor immunity.

Figure 2 below is a heat map of normalized cytokine and growth factor levels in plasma from 14 patients with metastatic melanoma compared with those levels in women in their third trimester of normal pregnancy and at diagnosis of preeclampsia. The normal pregnancy and preeclampsia samples (bottom two rows) were an aliquot of pooled plasma from 23 women with uncomplicated pregnancies and 23 women with preeclampsia (gift from Dr. Lynda Harris, University of Manchester, UK) (32). Pregnancy, whether normal or preeclamptic pregnancy, is associated with moderate to high levels of inflammatory cytokines and growth factors as determined by ELISA (osteoprotegerin, osteopontin, PGF, TGF, and VEGF) and multiplex cytokine array (the remainder of parameters measured). It may be no coincidence that the patient whose cytokine profile demonstrates inflammation similar to (even superseding)

that of pregnancy in the early third trimester had a complete response to immunotherapy and remains in complete remission greater than four years out from his diagnosis of metastatic melanoma. All other patients progressed within months of therapy, preliminarily indicating to us that our evaluation of inflammation and angiogenic parameters relevant to pregnancy may be both prognostic and predictive in metastatic melanoma, helping to individualize therapy for patients.

Also notable in Figure 2 are differences in cytokine and growth factor levels between the pregnancy and preeclampsia samples. Preeclampsia appears to be associated with higher levels of IL-2, epidermal growth factor, fibroblast growth factor-basic, IL-12, IL-15, MIP-1 alpha, and osteoprotegerin, and lower levels of IL-13, interferon gamma, GM-CSF, and PGF. As preeclampsia may be a failure of tolerance induction (29), this pattern may also be potentially desirable to emulate in the setting of cancer. This data is preliminary and will require replication but is consistent with our observation of bevacizumab (whose side effects completely mirror symptoms of preeclampsia – hypertension, proteinuria, and endothelial dysfunction) repolarizing immunity from Th2 to Th1-bias in metastatic melanoma (33). It is also tempting to consider that pregnancy may also be able to

Plasma cytokine/growth factor levels by time to progression (days)

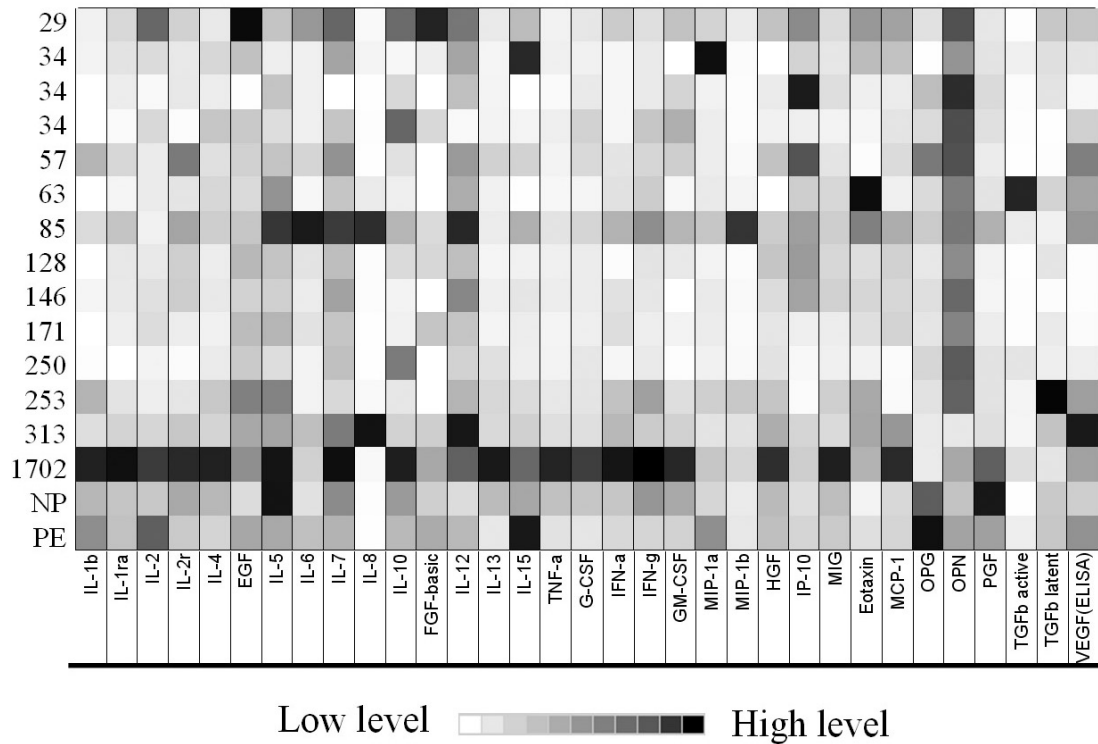


Figure 2. Heat map of plasma cytokine and growth factor levels as determined by ELISA and multiplex cytokine array. Each row represents an individual patient with previously untreated metastatic melanoma with their respective time to progression listed in days. The bottom two rows are pooled plasma from normal pregnant and preeclamptic pregnancies from women in their late second/early third trimesters (N=23 each). Abbreviations: EGF=epidermal growth factor, G-CSF=granulocyte colony stimulating factor, GM-CSF=granulocyte-macrophage stimulating factor, IFN=interferon, IL=interleukin, FGF=fibroblast growth factor, HGF=hepatocyte growth factor, MCP=macrophage chemoattractant protein, MIP=macrophage inflammatory protein, NP=normal pregnant, OPG=osteoprotegerin, OPN=osteopontin, PE=preeclampsia, PGF=placental growth factor, TGF=transforming growth factor, TNF=tumor necrosis factor, VEGF=vascular endothelial growth factor. Mig is also known as CXCL9, and IP-10 is also known as CXCL10.

teach us about therapeutic tolerance induction, for example, in the setting of allogeneic hematopoietic stem cell transplantation and graft-versus-host disease.

6. CONCLUSION

Pregnancy, a physiologic condition of transient, organ system-based immune evasion, affords a unique opportunity to identify the interplay between inflammation, tolerance, and parameters of angiogenesis in a predictable pattern. Enriching our understanding of immunity during pregnancy will help identify new targets of immunotherapy in otherwise immunologically exhausted patients with advanced malignancies and ultimately lend insight into an immunoregulatory network that appears to be reversible.

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Abbreviations: CTLA-4:cytotoxic lymphocyte T antigen-4, ELISA:enzyme-linked immunosorbent assay, GM-CSF:granulocyte macrophage stimulating factor, IL:interleukin, MIP:macrophage inflammatory protein, NK:natural killer, PGF:placental growth factor, TGF:transforming growth factor, VEGF:vascular endothelial growth factor.

Key Words: Pregnancy, Cancer, Tolerance, Angiogenesis, Inflammation, Natural Killer Cells, Review

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