



Immune Suppression in Pregnancy and Cancer: Parallels and Insights

Irina Kareva*

Computational and Modeling Sciences Center, Arizona State University, Tempe, AZ, 85287, USA

ARTICLE INFO

Article history:

Received 7 December 2019

Received in revised form 7 March 2020

Accepted 8 March 2020

Available online xxxxx

ABSTRACT

Immune system has evolved to maintain homeostatic balance between effector and regulatory immunity, which is critical to both elicit an adequate protective response to fight pathogens and disease, such as cancer, and to prevent damage to healthy tissues. Transient immune suppression can occur under normal physiological conditions, such as during wound healing to enable repair of normal tissue, or for more extended periods of time during fetal development, where the balance is shifted towards regulatory immunity to prevent fetal rejection. Interestingly, tumors can exhibit patterns of immune suppression very similar to those observed during fetal development. Here some of the key aspects of normal patterns of immune suppression during pregnancy are reviewed, followed by a discussion of parallels that exist with tumor-related immune suppression and consequent potential therapeutic implications.

© 2020 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

Introduction	1
Immune Suppression During Pregnancy and Cancer	2
Tregs and Mechanistic Insights from Animal Models	2
Potential Implications	3
Conclusions	3
Acknowledgements	4
Declaration of Competing Interest	4
References	4

Introduction

Immune cell homeostasis is critical for maintaining protection from infection and disease, as well as for preventing autoimmune disorders. There are two main arms of effector immunity: innate and adaptive. Innate immunity is largely non-specific and refers to defense mechanisms that are activated within hours of antigen encounter in order to contain and prevent the spread of foreign antigens. The key cell types involved in innate immunity are natural killer cells (NK), macrophages, neutrophils, dendritic cells, basophils and eosinophils, among others [1]. Adaptive, or acquired immune response is the second line of defense; it is specific to particular antigens and it requires several days to become activated. It is characterized by

clonal expansion of T and B lymphocytes, which increase rapidly from a few to millions of cells; upon expansion, these cells express the same antigen receptor and are primed to fight the same pathogen [1]. B lymphocytes are primarily involved in humoral (antibody-mediated) immunity, while T lymphocytes are largely involved in cell-mediated immunity, which involves increased phagocytosis and antigen-specific cytotoxic cells. Cells of the adaptive immune response mediate pathogen clearance through either direct cytotoxicity, or through secretion of inflammatory cytokines, which in turn mediate additional phagocyte-dependent inflammation and cell-mediated immunity [1].

Activated effector T lymphocytes can additionally be roughly subdivided into Th1 and Th2 cells [2]. Th1 cells are involved in production of pro-inflammatory cytokines, such as IFN-gamma and IL-2 and are understood to be primarily involved in killing external pathogens, as well as cancer cells. In contrast, Th2 cells produce interleukins (IL) -4,-5,-6,-9,-10 and -13, increasing antibody-specific responses and eosinophil accumulation

* Address all correspondence to: Irina Kareva, EMD Serono Research and Development Institute, Billerica, MA, USA.

E-mail address: ikareva@asu.edu.

[2]. While excessive Th1 responses can cause damage to the body's own tissues, Th2 response can act as a counterweight, and thus a balance between Th1 and Th2-associated cells is needed to both maintain a suitable immune response suitable and to prevent autoimmunity.

The risk of autoimmunity is additionally mitigated by regulatory immune cells, such as Tregs, which are CD25 + CD4+ cells, characterized by expression of nuclear transcription factor Forkhead box P3 (FoxP3) [3]. They can suppress proliferation of cytotoxic T cells [4,5], suppress production of cytokines, such as IL-2, by CD8+ and CD4+ cells [5], or kill responder T cells via both granzyme and perforin-dependent mechanisms [6,7]. They can also inhibit effector immunity by promoting T cell exhaustion [8].

Prevalence of immunosuppressive cells, such as Tregs, has been observed under pathological situations, such as in cancer, but they serve an additional important purpose in normal human development. Similar patterns of immune suppression are observed during fetal development. In fact, many processes that are characteristic of successful tumor establishment and growth are critical for fetal implantation and survival throughout pregnancy. These include establishment of blood supply, avoidance of destruction by the mother's immune system (fetal-maternal tolerance), cell migration, as well as recruitment and modification of tissue to support fetal development [9]. Here we focus particularly on the mechanisms of immune suppression that are common in pregnancy and cancer.

Immune Suppression During Pregnancy and Cancer

A state of temporary immune suppression is normally observed during healthy pregnancy, since from an evolutionary point of view, it is important to balance protecting the mother from infection while simultaneously protecting the fetus from the mother's immune system. Blastocyst implantation typically occurs in Th1-dominant microenvironment, which then soon becomes biased towards Th2 phenotype to enable immunological tolerance that is necessary for pregnancy to continue [10–12]. Upon delivery, the Th1/Th2 balance is typically restored within several weeks post-partum [13]. Altered balance between Th1/Th2 cell phenotypes is also observed in many tumors, favoring a more permissive Th2-polarized microenvironment; this has been observed in numerous malignancies, including glioma, melanoma and leukemic cutaneous T cell lymphoma [14–16].

Regulatory T cells (Tregs) are another important actor in maintenance of immune permissive environment in pregnancy [17]. CD4 + CD25+ cells are elevated during various stages of pregnancy, particularly during the first and second trimesters [18], and CD25 + T cell depletion can lead to gestation failure [19]; a more detailed discussion of the importance of Tregs in fetal-maternal tolerance will be given below. Similarly to pregnancy, in many cancers the ratio of effector to regulatory T cells is altered in favor of Tregs, such as in ovarian cancer [20], muscle invasive urothelial carcinoma of the bladder [21], squamous cell carcinoma of the cervix [22], colorectal cancer [23] and breast cancer [24].

To further elucidate similarities between immunological tolerance during pregnancy vs tumor development, Enninga et al. [25] compared the levels in the blood of women during and after pregnancy of soluble programmed cell death ligand-1 (sPD-L1), a checkpoint molecule that has become the target of successful immunotherapeutic interventions [25,26], and that of galectin-9, a β -galactoside binding protein that can act as a negative regulator of Th1 immune responses. The authors observed that the levels of these molecules were elevated during pregnancy compared to non-pregnant controls; they returned to normal after delivery. The authors separately showed that galectin-9 was elevated in plasma of patients with advanced melanoma compared to healthy controls, which was associated with increased Th1 cell apoptosis and promotion of Th2-biased cell phenotype [27]. Finally, the authors compared the levels of sPD-L1 and galectin-9 in pregnant women to those of patients with stage IV melanoma [28]. They found that galectin-9 was significantly increased in pregnant women's plasma (2524 pg/ml) and in plasma of cancer patients (3969 pg/ml) compared to controls (997 pg/ml). Furthermore, The levels of PD-L1 increased

throughout gestation but dropped dramatically within 6 weeks postpartum, further highlighting the transient nature of immune suppression during pregnancy.

In summary, as with Th1/Th2 balance, while in pregnancy numerous immune suppressive mechanisms, such as PD-L1 expression and Treg abundance decrease within several weeks after delivery [17,28], they remain elevated during tumor development, suggesting that similarly to angiogenesis, which commences in the same way as normal wound healing that does not terminate [29], immune suppression in tumors may commence in a way that is similar to fetal development that does not end.

Notably, the extent of immune suppression is not constant during pregnancy but in fact follows an “immune clock of human pregnancy” [13]. In an extensive study, Aghaepour and colleagues [13] used mass cytometry to map the timing of specific pregnancy-induced changes to immune system composition and function. The authors quantified abundance and functionality of all major immune cell subsets in serial blood samples that were collected during pregnancy to both confirm many known mechanisms and to identify several novel ones. Specifically, the authors confirmed overall enrichment of innate immune responses during pregnancy, as well as increase in abundance of neutrophils and increased responsiveness to a variety of cytokines, such as IFN-alpha, IL-2, and IL-6. The authors confirmed higher expression of tolerogenic surface proteins, such as PD-L1, particularly in early pregnancy, and showed that pregnancy induced progressive increase in STAT5ab signaling across multiple T cell subsets, including Tregs and CD8 + T cells. Specifically, they showed that IL-2 dependent STAT5ab activity is critical to development of CD4 + CD25 + FoxP3 + T cells; increase in IL-2 throughout pregnancy was suggested to highlight increasing importance of Tregs in human pregnancy and until delivery.

Tregs and Mechanistic Insights from Animal Models

While studies in humans allow demonstration of largely correlative relationships between immune cell activity and maternal-fetal tolerance (and subsequent parallels with mechanisms of immune evasion used by tumors), animal models allow deeper exploration of the mechanisms underlying the impact of immune system on both these processes. While the importance of regulatory immunity in fetal-maternal tolerance has been highlighted in several placental species [30,31], the most extensive work has been done in mouse models with both syngeneic and allogeneic pregnancies. In order to mechanistically assess the impact of Tregs on maternal-fetal tolerance, the following aspects needed to be evaluated: 1) whether there is a difference in Treg counts in normal vs abortion-prone mice, 2) whether Treg transfer from normal to abortion-prone mice can decrease fetal rejection, and 3) whether Treg ablation in normal mice would lead to increased fetal rejection.

The first two aspects were demonstrated experimentally by Zenclussen et al. [32], who analyzed syngeneic and allogeneic mouse pregnancy models of both normal and abortion-prone animals. The authors showed that indeed, mice with normal pregnancies showed elevated levels of CD4 + CD25+ cells in the thymus, while significantly lower Treg cell frequencies were observed in abortion-prone animals.

Next, in order to evaluate whether Tregs can rescue pregnancies in abortion-prone mice, the authors performed adoptive transfer of Tregs from both normal pregnant and normal non-pregnant mice into abortion-prone animals. They were able to show that while Tregs from both cases were able to infiltrate feto-maternal interface, only Tregs from normal pregnant mice were able to achieve fetal rescue in vivo, suggesting importance of previous exposure to paternal genetic material, and perhaps more broadly, the importance of Treg priming. Moreover, Treg transfer was successful only when done sufficiently early in the pregnancy and was not effective after 4–5 days, highlighting the importance of this particular mechanism in establishing maternal-fetal tolerance very early on.

Finally, the question of whether Treg ablation can rescue fetal rejection was evaluated by Aluvihare et al. [33], where the authors showed that depletion of CD25+ T cells indeed led to gestation failure; Darasse-Jeze et al. [34] also showed that Treg depletion leads to fetal rejection, confirming

that this mechanism is indeed critical for prevention of fetal rejection, and potentially tumor rejection as well.

Immune suppression during pregnancy also predictably correlates with increased susceptibility to infection. For instance, Engels et al. [35] demonstrated that anti-viral immune responses were diminished in pregnant allogeneic mice compared to non-pregnant ones, which mechanistically was reflected in reduced type I IFN response and diminished CD8 + T cell migration.

More broadly, it is interesting to evaluate whether changes in maternal immune system precede or supersede successful fetal and potentially tumor implantation. In cancer, several mechanisms, such as decreased oxygen flow or low pH may trigger immune suppression [36] as a consequence of normal physiological adaptations to, for instance, wound healing. However, according to Zenclussen et al. [32], the presence of Tregs is critical at early but not late stages of fetal development in order to mediate maternal tolerance to allogeneic fetus, a result also confirmed by Shima et al. [37]. It would be of interest to evaluate whether a state of transient immune suppression is in fact a necessary precursor to tumor establishment, and not only a consequence of other adaptations, perhaps through a series of experiments similar to those used to evaluate the impact of Tregs on fetal-maternal tolerance.

Another interesting question is whether mechanisms of immunosuppression during pregnancy to maintain maternal-fetal tolerance are different or similar across other placental animals. Bainbridge [31] suggests that despite placentation likely having a single evolutionary origin, it most likely evolved multiple times in other vertebrates, with different mechanisms for maternal-fetal tolerance having evolved for different species. The author hypothesizes that it is duration of gestation in different animals that may affect immunological challenges affecting the fetus, selecting for different mechanisms of tolerance.

From the point of view of life-history strategies, a connection between fertility and cancer risk has recently been proposed by Thomas et al. [38], where the authors hypothesize that poor anti-cancer defense mechanisms select for earlier pregnancy and emergence of post-fertile life span, and thus a post-fertile life stage is not expected to evolve in species with adequate cancer resistance mechanisms, such as multiple copies of p53 gene in elephants [39]. The ability of tumors to harness immunosuppressive state of the host to evade the immune system through “fetal mimicry” can be viewed as one example of less adequate anti-cancer defenses, a hypothesis that warrants further investigation and cross-species analysis.

Potential Implications

Similarities and parallels in the mechanisms of immune suppression during fetal and tumor growth could provide insights into additional avenues for immunotherapy based on what immunological events may negatively affect fetal growth (i.e., pre-eclampsia or miscarriage). A Th1 bias has been observed in women with a history of recurrent spontaneous miscarriage (RSM) [40], with higher ratios of inflammatory to anti-inflammatory cytokines of RMS groups compared to normal pregnancy [41–44]. Specifically, it has been suggested that NK cells could be releasing cytokines that are contributing to pregnancy losses [45–47] and it is the balance between cytotoxic and regulatory cells [48] that could be impacting both pregnancy complications and recurrent miscarriages [49]. Decrease in CD4 + CD25 + FoxP3+ cells in pregnancy is associated with both pre-eclampsia [51] and spontaneous miscarriage [19]. In application to cancer, this may suggest focusing not only on increasing adaptive cytotoxic immunity and dampening regulatory immunity but also developing treatment strategies that focus on innate immunity, such as NK cells [50] to increase tumor rejection.

A number of cytokines have been associated with increased rates of miscarriage, including IL-2, IFN-gamma and TNF-alpha, which are elevated in women with RSM compared to women with normal pregnancies [52]; in contrast, IL-4,-5,-6 and -10 were produced at higher levels by mitogen-stimulated peripheral lymphocytes in women with normal pregnancies compared to those with RSM [44,53–55]. Of these, tumor necrosis factor

(TNF) alpha is a particularly interesting cytokine that is involved both in pregnancy and throughout cancer disease progression. TNF-alpha was first isolated in 1975 by Carswell et al. [56] during investigation of hemorrhagic necrosis produced by this endotoxin, giving rise to the name “tumor necrosis factor”. The authors proposed that TNF mediates tumor necrosis and may be responsible for cancer cell suppression by macrophages. TNF signals through two distinct receptors, TNFR1 and TNFR2. TNFR1 is expressed in most tissues, initiating both pro-inflammatory and programmed cell death pathways [57]. TNFR2 is primarily expressed on immune cells, such as macrophages; engagement of this receptor can both induce apoptosis and promote tissue repair and angiogenesis [58]. TNF-alpha is produced predominantly by myeloid cells, as well as NK cells, neutrophils, eosinophils and neuronal cells [57,59] and is an important mediator of various immune responses. It appears to have dual function both in pregnancy and in cancer.

In pregnancy, TNF is typically associated with pregnancy loss [60–62]; however, analysis of human amniotic fluid samples from normal pregnancies, as well as samples of full term placental and decidual tissues revealed that TNF was detected in 91% of amniotic fluid samples [63]; furthermore, TNF concentrations collected during second trimester were significantly higher compared to those in third trimester, with even higher quantities detected in placental and decidual tissues, suggesting a physiological role for TNF-alpha in normal pregnancy. It is possible that the inflammatory response mediated by TNF-alpha in early pregnancy that can lead to pregnancy loss serves as an evolutionary mechanism to protect the mother even at the expense of the fetus, a hypothesis that remains to be investigated.

In cancer, TNF-alpha has also been shown to play a dual role. It has been shown to both promote apoptotic [64,65] and necrotic cell death [57,66], and to promote angiogenesis [67], tumor growth [68] and even epithelial to mesenchymal transition (EMT), contributing to metastatic disease spread [69,70]. Elevated levels of TNF-alpha have been associated both with malignancy [71–74] and with pre-eclampsia and spontaneous miscarriages [60–62,75,76], although several studies have shown that TNF-alpha levels are not predictive of pre-eclampsia [77,78], suggesting that it may be a consequence rather than a cause of pregnancy complications.

Interestingly, TNF-alpha is the same protein as cachectin, or cachexin [59], a cytokine that is frequently elevated in cachexia, a wasting syndrome that is characterized by systemic inflammation and involuntary loss of lean body mass [79] that is common in late stage cancer patients. While TNF-alpha can induce symptoms of cachexia, its inhibition has not been shown to reverse or improve symptoms of cachexia [80,81]. One can hypothesize that lack of efficacy of TNF-alpha inhibitors in cachexia lies in the fact that the cytokine's effects have both pro-and anti-inflammatory properties, and thus the effects of its inhibition may become canceled out. It is also possible that, since TNF-alpha is a characteristic of systemic inflammation, its accumulation begins from very early stages in tumor development but remains unnoticed due to other more prominent features of disease manifestation; similarly to wound healing and transient immune suppression, it may be a process that starts as a normal physiological response that does not terminate. It might be of interest to explore whether TNF-alpha blockade in early stages of disease, combined with compensatory therapy to alleviate the negative effects of such blockade can delay or prevent the onset of cachexia.

Conclusions

Numerous similarities exist between immune suppression in normal fetal development and in tumor growth. Immune suppression in pregnancy is transient, aimed at protecting the fetus from the mother's immune system until delivery; in tumor growth, same mechanisms may be activated by the tumor to gain protection from immune system, leading to disease progression. Understanding mechanisms and processes that may interfere with fetal development may provide an avenue to explore ways to similarly interfere with tumor growth.

Acknowledgements

The author would like to thank Jon Aster for careful reading of the original manuscript, as well as the two anonymous reviewers for their helpful comments and suggestions. This manuscript was written during 2018-2019 High Impact Cancer Research and Therapeutics program at Harvard Medical School in Boston, MA.

Declaration of Competing Interest

IK is an employee of EMD Serono, US subsidiary of Merck KGaA. The views expressed in this manuscript are the author's personal views and do not necessarily reflect the views of EMD Serono.

References

- [1] K. Murphy, C. Weaver, *Janeway's immunobiology*, Garland Science, 2016.
- [2] A. Berger, Th1 and Th2 responses: what are they? *Bmj, British Medical Journal Publishing Group* 321 (7258) (2000) 424.
- [3] J.D. Fontenot, A.Y. Rudensky, A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor Foxp3, *Nature immunology. Nature Publishing Group* 6 (4) (2005) 331.
- [4] T. Takahashi, Y. Kuniyasu, M. Toda, N. Sakaguchi, M. Itoh, M. Iwata, J. Shimizu, S. Sakaguchi, Immunologic self-tolerance maintained by CD25+ CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state, *Int. Immunol.* 10 (12) (1998) 1969–1980.
- [5] S. Sakaguchi, K. Wing, Y. Onishi, P. Prieto-Martin, T. Yamaguchi, Regulatory T cells: how do they suppress immune responses? *International immunology. Oxford University Press* 21 (10) (2009) 1105–1111.
- [6] D.C. Gondek, L.-F. Lu, S.A. Quezada, S. Sakaguchi, R.J. Noelle, Cutting edge: contact-mediated suppression by CD4+ CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. *The Journal of Immunology, Am Assoc Immunol* 174 (4) (2005) 1783–1786.
- [7] X. Cao, S.F. Cai, T.A. Fehniger, J. Song, L.I. Collins, D.R. Piwnica-Worms, J. Ley, Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance, *Immunity. Elsevier* 27 (4) (2007) 635–646.
- [8] S. Paust, L. Lu, N. McCarty, H. Cantor, Engagement of B7 on effector T cells by regulatory T cells prevents autoimmune disease. *Proceedings of the National Academy of Sciences, National Acad Sciences* 101 (28) (2004) 10398–10403.
- [9] S.G. Holtan, D.J. Crendon, P. Haluska, S.N. Markovic, Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. *Mayo Clinic Proceedings, Elsevier* (2009) 985–1000.
- [10] G. Chaouat, N. Ledée-Bataille, S. Dubanchet, S. Zourbas, O. Sandra, J. Martal, Th1/Th2 paradigm in pregnancy: paradigm lost? *International archives of allergy and immunology, Karger Publishers* 134 (2) (2004) 93–119.
- [11] R. Raghupathy, Th 1-type immunity is incompatible with successful pregnancy, *Immunology today. Elsevier* 18 (10) (1997) 478–482.
- [12] T.G. Wegmann, H. Lin, L. Guilbert, T.R. Mosmann, Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunology today. Elsevier* 14 (7) (1993) 353–356.
- [13] N. Aghaepour, E.A. Ganio, D. McIlwain, A.S. Tsai, M. Tingle, S. Van Gassen, D.K. Gaudilliere, Q. Baca, L. McNeil, R. Okada, et al., An immune clock of human pregnancy. *Science immunology, Science Immunology* 2 (15) (2017), eaan2946.
- [14] E. Guenova, R. Watanabe, J.E. Teague, J.A. Desimone, Y. Jiang, M. Dowlatsahi, C. Schlapbach, K. Schaeckel, A.H. Rook, M. Tawa, D.C. Fisher, T.S. Kupper, R.A. Clark, TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma. *Clinical cancer research, AACR* 19 (14) (2013) 3755–3763.
- [15] W.K. Nevala, C.M. Vachon, A.A. Leontovich, C.G. Scott, M.A. Thompson, S.N. Markovic, Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma, *Clinical Cancer Research. AACR* 15 (6) (2009) 1931–1939.
- [16] S. Shimato, L.M. Maier, R. Maier, J.N. Bruce, R.C. Anderson, D.E. Anderson, Profound tumor-specific Th2 bias in patients with malignant glioma, *BMC cancer. BioMed Central* 12 (1) (2012) 561.
- [17] D.A. Somerset, Y. Zheng, M.D. Kilby, D.M. Sansom, M.T. Drayson, Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset, *Immunology. Wiley Online Library* 112 (1) (2004) 38–43.
- [18] Heikkinen J, Mötönen M, Alanen A, Lassila O. Phenotypic characterization of regulatory T cells in the human decidua. *Clinical & Experimental Immunology. Wiley Online Library*; 2004;136(2):373–378.
- [19] Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4+ CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *MHR: Basic science of reproductive medicine. Oxford University Press*; 2004;10(5):347–353.
- [20] Preston CC, Maurer MJ, Oberg AL, Visscher DW, Kalli KR, Hartmann LC, Goode, EL, Knutson, KL. The ratios of CD8+ T cells to CD4+ CD25+ FOXP3+ and FOXP3-T cells correlate with poor clinical outcome in human serous ovarian cancer. *PLoS one. Public Libr. Sci.*; 2013;8(11).
- [21] A.S. Baras, C. Drake, J.-J. Liu, N. Gandhi, M. Kates, M.O. Hoque, et al., The ratio of CD8 to Treg tumor-infiltrating lymphocytes is associated with response to cisplatin-based neoadjuvant chemotherapy in patients with muscle invasive urothelial carcinoma of the bladder, *Oncoimmunology. Taylor & Francis* 5 (5) (2016), e1134412.
- [22] Baras AS, Drake C, Liu JJ, Gandhi N, Kates M, Hoque MO, Meeker A, Hahn N, Taube JM, Schoenberg MP, Netto G, Bivalacqua TJ. A reversed CD4/CD8 ratio of tumor-infiltrating lymphocytes and a high percentage of CD4+ FOXP3+ regulatory T cells are significantly associated with clinical outcome in squamous cell carcinoma of the cervix. *Cellular & molecular immunology. Nature Publishing Group*; 2011;8(1):59.
- [23] Salama P, Phillips M, Grieu F, Morris M, Zeps N, Joseph D, Platell C, Iacopetta B. Tumor-infiltrating FOXP3+ T regulatory cells show strong prognostic significance in colorectal cancer. *Journal of clinical oncology. American Society of Clinical Oncology*; 2009;27(2):186–192.
- [24] F. Liu, R. Lang, J. Zhao, X. Zhang, G.A. Pringle, Y. Fan, D. Yin, F. Gu, Z. Yao, L. Fu, CD8+ cytotoxic T cell and FOXP3+ regulatory T cell infiltration in relation to breast cancer survival and molecular subtypes. *Breast cancer research and treatment, Springer* 130 (2) (2011) 645–655.
- [25] Enninga EAL, Harrington SM, Creedon DJ, Ruano R, Markovic SN, Dong H, Dronca RS. Immune checkpoint molecules soluble program death ligand 1 and galectin-9 are increased in pregnancy. *American Journal of Reproductive Immunology. Wiley Online Library*; 2018;79(2):e12795.
- [26] Massard C, Gordon MS, Sharma S, Raffi S, Wainberg ZA, Luke J, Curiel TJ, Colon-Otero G, Hamid O, Sanborn RE, O'Donnell PH, Drakaki A, Tan W, Kurland JF, Rebelatto MC, Jin X, Blake-Haskins JA, Gupta A, Segal NH. Safety and efficacy of durvalumab (MED14736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *Journal of Clinical Oncology. American Society of Clinical Oncology*; 2016;34(26):3119.
- [27] E.A.L. Enninga, W.K. Nevala, S.G. Holtan, A.A. Leontovich, S.N. Markovic, Galectin-9 modulates immunity by promoting Th2/M2 differentiation and impacts survival in patients with metastatic melanoma, *Melanoma research. NIH Public Access* 26 (5) (2016) 429.
- [28] E.A. Enninga, W. Nevala, D. Creedon, T. Flotte, H. Dong, S. Markovic, Shared immunoregulatory properties of galectin-9 and PD-L1 in pregnant women and patients with stage IV melanoma, *Placenta* 100 (45) (2016) 86–87.
- [29] Kareva I, Abou-Slaybi A, Dodd O, Dashevsky O, Klement GL. Normal wound healing and tumor angiogenesis as a game of competitive inhibition. *PLOS ONE. https://doi.org/10.1371/journal.pone.0166655*; 2016;11(12):e0166655.
- [30] Dimova T, Mihaylova A, Spassova P, Georgieva R. Establishment of the porcine epitheliochorial placenta is associated with endometrial T-cell recruitment. *American Journal of Reproductive Immunology. Wiley Online Library*; 2007;57(4):250–261.
- [31] D. Bainbridge, Evolution of mammalian pregnancy in the presence of the maternal immune system. *Reviews of Reproduction. BioScientifica* 5 (2) (2000) 67–74.
- [32] A.C. Zenclussen, K. Gerlof, M.L. Zenclussen, A. Sollwedel, A.Z. Bertoja, T. Ritter, K. Kotsch, J. Leber, H.D. Volk, Abnormal T-cell reactivity against paternal antigens in spontaneous abortion: adoptive transfer of pregnancy-induced CD4+ CD25+ T regulatory cells prevents fetal rejection in a murine abortion model. *The American journal of pathology, Elsevier* 166 (3) (2005) 811–822.
- [33] V.R. Aluvihare, M. Kallikourdis, A.G. Betz, Regulatory T cells mediate maternal tolerance to the fetus, *Nature immunology. Nature Publishing Group* 5 (3) (2004) 266.
- [34] G. Darasse-Jeze, D. Klatzmann, F. Charlotte, B.L. Salomon, J.L. Cohen, CD4+ CD25+ regulatory/suppressor T cells prevent allogeneic fetus rejection in mice, *Immunology letters. Elsevier* 102 (1) (2006) 106–109.
- [35] G. Engels, A.M. Hierweiger, J. Hoffmann, R. Thieme, S. Thiele, S. Bertram, C. Dreier, P. Resa-Infante, H. Jacobsen, K. Thiele, M. Alawi, D. Indenbirken, A. Grundhoff, S. Siebels, N. Fischer, V. Stojanovska, D. Muzzio, F. Jensen, K. Karimi, H.W. Mittrücker, P.C. Arck, G. Gabriel, Pregnancy-related immune adaptation promotes the emergence of highly virulent H1N1 influenza virus strains in allogeneically pregnant mice. *Cell host & microbe, Elsevier* 21 (3) (2017) 321–333.
- [36] I. Kareva, P. Hahnfeldt, The emerging “hallmarks” of metabolic reprogramming and immune evasion: distinct or linked? *Cancer research. AACR* 73 (9) (2013) 2737–2742.
- [37] T. Shima, Y. Sasaki, M. Itoh, A. Nakashima, N. Ishii, K. Sugamura, S. Saito, Regulatory T cells are necessary for implantation and maintenance of early pregnancy but not late pregnancy in allogeneic mice. *Journal of reproductive immunology, Elsevier* 85 (2) (2010) 121–129.
- [38] F. Thomas, M. Giraudeau, F. Renaud, B. Ujvari, B. Roche, P. Pujol, M. Raymond, J.F. Lemaitre, A. Alvergne, Can postfertile life stages evolve as an anticancer mechanism? *PLoS Biology. Public Library of Science* 17 (12) (2019), e3000565.
- [39] Sulak M, Fong L, Mika K, Chigurupati S, Yon L, Mongan NP, Emes RD, Lynch VJ. TP53 copy number expansion is associated with the evolution of increased body size and an enhanced DNA damage response in elephants. *Elife. eLife Sciences Publications Limited*; 2016;5:e11994.
- [40] J.A. Hill, K. Polgar, D.J. Anderson, T-helper 1-type immunity to trophoblast in women with recurrent spontaneous abortion, *Jama. American Medical Association* 273 (24) (1995) 1933–1936.
- [41] R. Raghupathy, M. Makhsed, F. Azizieh, N. Hassan, M. Al-Azemi, E. Al-Shamali, Maternal Th1-and Th2-type reactivity to placental antigens in normal human pregnancy and unexplained recurrent spontaneous abortions, *Cellular immunology. Elsevier* 196 (2) (1999) 122–130.
- [42] M.-P. Piccinni, L. Beloni, C. Livi, E. Maggi, G. Scarselli, S. Romagnani, Defective production of both leukemia inhibitory factor and type 2 T-helper cytokines by decidual T cells in unexplained recurrent abortions, *Nature medicine. Nature Publishing Group* 4 (9) (1998) 1020.
- [43] Polgar K, Hill J. Identification of the white blood cell populations responsible for Th1 immunity to trophoblast and the timing of the response in women with recurrent pregnancy loss. *Gynecologic and obstetric investigation. Karger Publishers*; 2002;53(1): 59–64.

- [44] C. Jenkins, J. Roberts, R. Wilson, M.A. MacLean, J. Shilito, J.J. Walker, Evidence of a TH 1 type response associated with recurrent miscarriage, Fertility and sterility. Elsevier 73 (6) (2000) 1206–1208.
- [45] Sharma S. Natural killer cells and regulatory T cells in early pregnancy loss. The International journal of developmental biology. NIH Public Access; 2014;58:219.
- [46] Lachapelle M-H, Miron P, Hemmings R, Roy DC. Endometrial T, B, and NK cells in patients with recurrent spontaneous abortion. Altered profile and pregnancy outcome. The Journal of Immunology. Am Assoc Immunol; 1996;156(10):4027–4034.
- [47] I. Sargent, A. Borzychowski, C. Redman, NK cells and pre-eclampsia. Journal of reproductive immunology, Elsevier 76 (1–2) (2007) 40–44.
- [48] Yu G, Xu X, Vu MD, Kilpatrick ED, Li XC. NK cells promote transplant tolerance by killing donor antigen-presenting cells. Journal of experimental medicine. Rockefeller University Press; 2006;203(8):1851–1858.
- [49] S. Shigeru, N. Akitoshi, M.-H. Subaru, A. Shiozaki, The balance between cytotoxic NK cells and regulatory NK cells in human pregnancy. Journal of reproductive immunology, Elsevier 77 (1) (2008) 14–22.
- [50] O. Demaria, S. Cornen, M. Daéron, Y. Morel, R. Medzhitov, E. Vivier, Harnessing innate immunity in cancer therapy. Nature. Nature Publishing Group 574 (7776) (2019) 45–56.
- [51] A. Steinborn, G.M. Haensch, K. Mahnke, A. Schmitt, A. Toerner, S. Meuer, C. Sohn, Distinct subsets of regulatory T cells during pregnancy: is the imbalance of these subsets involved in the pathogenesis of preeclampsia? Clinical Immunology. Elsevier 129 (3) (2008) 401–412.
- [52] R. Raghupathy, M. Makhseed, F. Azizieh, A. Omu, M. Gupta, R. Farhat, Cytokine production by maternal lymphocytes during normal human pregnancy and in unexplained recurrent spontaneous abortion, Human Reproduction. Oxford University Press 15 (3) (2000) 713–718.
- [53] Makhseed M, Raghupathy R, Azizieh F, Al-Azemi M, Hassan N, Bandar A. Mitogen-induced cytokine responses of maternal peripheral blood lymphocytes indicate a differential Th-type bias in normal pregnancy and pregnancy failure. American journal of reproductive immunology. Wiley Online Library; 1999;42(5):273–281.
- [54] Dong M, He J, Wang Z, Xie X, Wang H. Placental imbalance of Th1 and Th2-type cytokines in preeclampsia. Acta obstetrica et gynecologica Scandinavica. Taylor & Francis; 2005;84(8):788–793.
- [55] Y. Jonsson, M. Rubè, L. Matthiesen, G. Berg, K. Nieminen, S. Sharma, J. Ernerudh, C. Ekerfelt, Cytokine mapping of sera from women with preeclampsia and normal pregnancies. Journal of reproductive immunology, Elsevier 70 (1–2) (2006) 83–91.
- [56] Carswell E, Old LJ, Kassel R, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proceedings of the National Academy of Sciences. National Acad Sciences; 1975;72(9):3666–3670.
- [57] Y. Lin, S. Choksi, H.-M. Shen, Q.-F. Yang, G.M. Hur, Y.S. Kim, J.H. Tran, S.A. Nedospasov, Z.G. Liu, Tumor necrosis factor-induced nonapoptotic cell death requires receptor-interacting protein-mediated cellular reactive oxygen species accumulation, Journal of Biological Chemistry. ASBMB 279 (11) (2004) 10822–10828.
- [58] D. Luo, Y. Luo, Y. He, H. Zhang, R. Zhang, X. Li, W.L. Dobrucki, A.J. Sinusas, W.C. Sessa, W. Min, Differential functions of tumor necrosis factor receptor 1 and 2 signaling in ischemia-mediated arteriogenesis and angiogenesis. The American journal of pathology, Elsevier 169 (5) (2006) 1886–1898.
- [59] B. Beutler, D. Greenwald, J. Hulmes, M. Chang, Y.-C. Pan, J. Mathison, R. Ulevitch, A. Cerami, Identity of tumour necrosis factor and the macrophage-secreted factor cachectin, Nature. Nature Publishing Group 316 (6028) (1985) 552.
- [60] Peraçoli JC, Rudge MVC, Peraçoli MTS. Tumor necrosis factor-alpha in gestation and puerperium of women with gestational hypertension and pre-eclampsia. American Journal of Reproductive Immunology. Wiley Online Library; 2007;57(3):177–185.
- [61] M. Cackovic, C.S. Buhimschi, G. Zhao, E.F. Funai, E.R. Norwitz, E. Kuczynski, C.J. Lockwood, I.A. Buhimschi, Fractional excretion of tumor necrosis factor- α in women with severe preeclampsia, Obstetrics and gynecology. NIH Public Access 112 (1) (2008) 93.
- [62] M.J. Kupferminc, A.M. Peaceman, T.R. Wigton, K.A. Rehnberg, M.L. Socol, Tumor necrosis factor- α is elevated in plasma and amniotic fluid of patients with severe preeclampsia. American journal of obstetrics and gynecology, Elsevier 170 (6) (1994) 1752–1759.
- [63] Jäättelä M, Kuusela P, Saksela E. Demonstration of tumor necrosis factor in human amniotic fluids and supernatants of placental and decidual tissues. Laboratory investigation; a journal of technical methods and pathology. 1988;58(1):48–52.
- [64] S.L. Petersen, L. Wang, A. Yalcin-Chin, L. Li, M. Peyton, J. Minna, P. Harran, X. Wang, Autocrine TNF α signaling renders human cancer cells susceptible to Smac-mimetic-induced apoptosis, Cancer cell. Elsevier 12 (5) (2007) 445–456.
- [65] Lin Y, Devin A, Rodriguez Y, Liu Z. Cleavage of the death domain kinase RIP by caspase-8 prompts TNF-induced apoptosis. Genes & development. Cold Spring Harbor Lab; 1999;13(19):2514–2526.
- [66] Y.-S. Kim, M.J. Morgan, S. Choksi, Z. Liu, TNF-induced activation of the Nox1 NADPH oxidase and its role in the induction of necrotic cell death, Molecular cell. Elsevier 26 (5) (2007) 675–687.
- [67] L.B. Nabors, E. Suswam, Y. Huang, X. Yang, M.J. Johnson, P.H. King, Tumor necrosis factor α induces angiogenic factor up-regulation in malignant glioma cells: a role for RNA stabilization and HuR, Cancer Research. AACR 63 (14) (2003) 4181–4187.
- [68] H. Kulbe, R. Thompson, J.L. Wilson, S. Robinson, T. Hagemann, R. Fatah, D. Gould, A. Ayhan, F. Balkwill, The inflammatory cytokine tumor necrosis factor- α generates an autocrine tumor-promoting network in epithelial ovarian cancer cells, Cancer research. AACR 67 (2) (2007) 585–592.
- [69] Bates RC, Mercurio AM. Tumor necrosis factor- α stimulates the epithelial-to-mesenchymal transition of human colonic organoids. Molecular biology of the cell. Am Soc Cell Biol; 2003;14(5):1790–1800.
- [70] M.-J. Chuang, K.-H. Sun, S.-J. Tang, M.-W. Deng, Y.-H. Wu, J.-S. Sung, T.L. Cha, G.H. Sun, Tumor-derived tumor necrosis factor-alpha promotes progression and epithelial-mesenchymal transition in renal cell carcinoma cells, Cancer science. Wiley Online Library 99 (5) (2008) 905–913.
- [71] P.W. Szlosarek, M.J. Grimshaw, H. Kulbe, J.L. Wilson, G.D. Wilbanks, F. Burke, F.R. Balkwill, Expression and regulation of tumor necrosis factor α in normal and malignant ovarian epithelium. Molecular cancer therapeutics, AACR 5 (2) (2006) 382–390.
- [72] Bel Hadj Jrad B, Chatti A, Laatiri A, Ahmed SB, Romdhane A, Ajimi S, Chouchane L. Tumor necrosis factor promoter gene polymorphism associated with increased susceptibility to non-Hodgkin's lymphomas. European journal of haematology. Wiley Online Library; 2007;78(2):117–122.
- [73] I. Duarte, A. Santos, H. Sousa, R. Catarino, D. Pinto, A. Matos, D. Pereira, J. Moutinho, P. Canedo, J.C. Machado, R. Medeiros, G-308A TNF- α polymorphism is associated with an increased risk of invasive cervical cancer. Biochemical and biophysical research communications, Elsevier 334 (2) (2005) 588–592.
- [74] C.-M. Shih, Y.-L. Lee, H.-L. Chiou, W. Chen, G.-C. Chang, M.-C. Chou, L.Y. Lin, Association of TNF- α polymorphism with susceptibility to and severity of non-small cell lung cancer, Lung cancer. Elsevier 52 (1) (2006) 15–20.
- [75] Berman J, Girardi G, Salmon JE. TNF- α is a critical effector and a target for therapy in antiphospholipid antibody-induced pregnancy loss. The Journal of Immunology. Am Assoc Immunol; 2005;174(1):485–490.
- [76] Schipper E-JI, Bolte AC, Schalkwijk CG, Van Geijn HP, Dekker GA. TNF-receptor levels in preeclampsia—results of a longitudinal study in high-risk women. The Journal of Maternal-Fetal & Neonatal Medicine. Taylor & Francis; 2005;18(5):283–287.
- [77] Ý.S. Serin, B. Özçelik, M. Babuo, H. Klç, D. Okur, R. Erez, Predictive value of tumor necrosis factor alpha (TNF- α) in preeclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology, Elsevier 100 (2) (2002) 143–145.
- [78] Heikkinen J, Möttönen M, Pulkki K, Lassila O, Alanen A. Cytokine levels in midtrimester amniotic fluid in normal pregnancy and in the prediction of pre-eclampsia. Scandinavian journal of immunology. Wiley Online Library; 2001;53(3):310–314.
- [79] K. Fearon, F. Strasser, S.D. Anker, I. Bosaeus, E. Bruera, R.L. Fainsinger, et al., Definition and classification of cancer cachexia: an international consensus. The lancet oncology, Elsevier 12 (5) (2011) 489–495.
- [80] Stone JH, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, Min Y-I, Specks U, Merkel PA, Spiera R, Davis JC, St Clair EW, McCune WJ, Ytterberg SR, Allen NB, Hoffman GS. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. Wiley Online Library; 2006;54(5):1608–1618.
- [81] I. Gueta, A. Altman, Y. Shoenfeld, The effect of blocking TNF-alpha in patients with cancer-related cachexia and anorexia, Harefuah 149 (8) (2010) 512–514.