MAYO CLINIC

Immunomodulatory Effects of Sex Hormones: Requirements for Pregnancy and Relevance in Melanoma

Elizabeth Ann L. Enninga, BS; Shernan G. Holtan, MD; Douglas J. Creedon, MD, PhD; Roxana S. Dronca, MD; Wendy K. Nevala, MS; Simona Ognjanovic, PhD; and Svetomir N. Markovic, MD, PhD

Abstract

Similarities between the pathologic progression of cancer and the physiologic process of placentation (eg, proliferation, invasion, and local/systemic tolerance) have been recognized for many years. Sex hormones such as human chorionic gonadotropin, estrogens, progesterone, and others contribute to induction of immunologic tolerance at the beginning of gestation. Sex hormones have been shown to play contributory roles in the growth of cancers such as breast cancer, prostrate cancer, endometrial cancer, and ovarian cancer, but their involvement as putative mediators of the immunologic escape of cancer is still being elucidated. Herein, we compare the emerging mechanism by which sex hormones modulate systemic immunity in pregnancy and their potentially similar role in cancer. To do this, we conducted a PubMed search using combinations of the following keywords: "immune regulation," "sex hormones," "pregnancy," "melanoma," and "cancer." We did not limit our search to specific publication dates. Mimicking the maternal immune response to pregnancy, especially in late gestation, might aid in design of better therapies to reconstitute endogenous antitumor immunity and improve survival.

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From Mayo Graduate School (E.A.L.E., S.O.), Department of Obstetrics and Gynecology (D.J.C.), Department of Oncology (R.S.D., W.K.N., S.N.M.), and Department of Medicine, Division of Hematology (S.N.M.), Mayo Clinic, Rochester, MN; and Oregon Health and Science University, Portland (S.G.H.).

In 1948, Beard and Krebs acknowledged a striking similarity between a trophoblast and a tumor, publishing their observation titled "The Unitarian or Trophoblastic Thesis of Cancer."[1-3] Since then, these similarities have been extensively studied; many shared pathways and immunologic mediators have been identified.[4,5] The purpose of this review was to take an in-depth look at existing research describing the role of sex hormones in the potentially parallel settings of reproductive and tumor immunology, with a focus on metastatic melanoma. Although imperfectly understood, sex hormones are important regulators of the immune system in both pregnancy and cancer.[6,7] It is clear that they are involved in regulation and modification of the immune system to allow invasion, proliferation, and migration of tumor cells and trophoblasts.[5] It is possible that an organ system—level view of the process of placentation as well as melanoma progression could yield additional insights into potential therapeutic targets for hormone-based immune modulation.[8]

The complexities and redundancies involved in orchestration of the maternal response to pregnancy as well as the host response to cancer are increasingly appreciated.[4,9] Importantly, however, we and others have observed that neither pregnancy nor advanced cancers are static immunologic events.[10-12] Oscillations in systemic immunity between inflammation and tolerance seen in patients with metastatic melanoma have been documented and seem to follow a biologically predictable pattern. When tolerance seen in malignant melanoma is disrupted and brought back to a state of inflammation, patients have a much better prognosis than do those whose immune systems stay in an immunologically exhausted state. Pregnancy is also characterized by many hormonal fluctuations, although the time scale for these hormonal and immunologic changes may be measured in weeks as opposed to days[13] (Figure 1) Although it seems intuitive to consider the involvement of sex hormones interacting with the maternal immune system during pregnancy, it is less obvious but just as possible that such hormones alter systemic

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immunity in the setting of cancers such as melanoma. We describe the observations and experimental evidence supporting such involvement in the following sections.

CLINICAL EVIDENCE OF HORMONAL REGULATION OF MELANOMA

The skin is capable of producing many neuroendocrine mediators such as melanin, steroids, thyroid hormones, and sex hormones such as androgen, estrogen, and progestin to maintain homeostasis; any failure to communicate between the skin, endocrine, and immune system could result in deregulation and disease.[14,15] Both melanocytes and melanoma tumors produce pigment in the melanosome that protects the skin against damaging ultraviolet rays through positive regulation by hormones such as L-tyrosine and L-dihydroxyphenylalanine.[16,17] Although the interplay between sex hormones and the immune system in melanoma remains poorly understood, several clinical observations support the role of sex hormones in melanoma development. Melanomas that are responsive to estrogens are associated with the superficial spreading melanoma subtype, a type of tumor with a much better prognosis. In addition, estrogen exerts a proliferative effect on melanocytes and can lead to the development of hyperpigmentation in women using oral contraceptives or hormonal replacement therapy.[18] Whether hormonal contraceptives increase the risk of melanoma is a matter of ongoing debate. Koomen et al[19] have reported that high levels of estrogens increase a woman's risk for developing malignant melanoma, while Lens and Bataille[20] have not observed a relevant association. It may be no coincidence that melanoma is the most common form of cancer associated with pregnancy.[21] This is believed to be due to the trophoblasts' increased need for lymphangiogenesis, which the melanoma then uses to promote its own growth. Complementary to this hypothesis, demographic characteristics and incidence may also provide an explanation as to this phenomenon. In addition, pregnant women are more likely than their nonpregnant counterparts to be diagnosed with an invasive melanoma.

We have shown that aging in healthy individuals is associated with a T_H2 bias.[22] Women are more likely than men to develop melanoma before age 40, after which the diagnosis of melanoma is observed at a much higher rate in men.[23] However, women diagnosed with melanoma have a better prognosis than do men, and premenopausal women have higher survival rates than do postmenopausal women.[24,25] Interestingly, melanoma metastasizes at a much slower rate in women than in men, and the pattern of metastatic spread is also different, with more

ARTICLE HIGHLIGHTS

- Systemic immunity in metastatic melanoma (cancer) mimics the systemic immune response of early pregnancy.
- Sex hormones promote/suppress different T cell responses during pregnancy and in melanoma.
- Metastatic melanoma and early pregnancy promote a systemic state of Th2 dominant chronic inflammation.
- Near parturition, hormones play a role in the return to cytotoxicity (Th1) of maternal immunity and the promotion of labor.
- Understanding the mechanism that causes immunity to switch from Th2 to Th1 in pregnancy may help researchers better understand how to break tolerance and improve patient outcomes in advanced cancers.

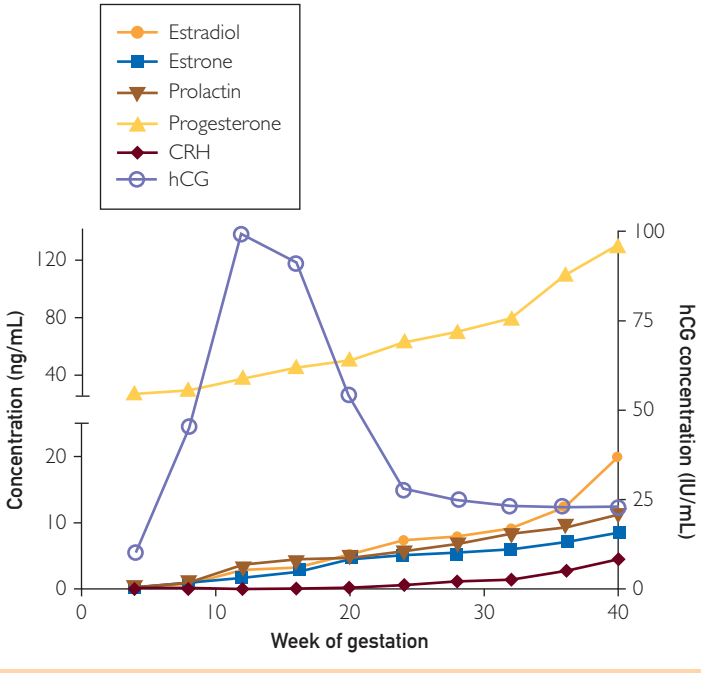

FIGURE 1. Hormonal changes (in weeks) important for the regulation of gestation in healthy pregnant women. CRH = corticotropin-releasing hormone; hCG = human chorionic gonadotropin.