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The uterine cervix - a new member of the family of immunologically exceptional sites?

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Abstract

As a bystander effect, immune responses against infectious organisms can damage normal cells. Immune privilege can protect such endangered tissues from immune destruction. One example is the eye where potentially devastating inflammatory reactions are prevented by active, counter-regulating processes that prevent lymphocyte activation. Recent epidemiological data from transplant patients in Sweden showed, surprisingly, that the frequency of cervical cancers did not increase in organ transplant recipients, in contrast to cancers of the vagina, vulva and anus. The same subtypes of HPV are known to be involved in the genesis of all these tumors. The immune surveillance mechanisms known to antagonize the outgrowth of virally-associated neoplasms would have been expected to affect them all. The special case of cervical carcinomas may reflect a site-specific immune privilege that could have evolved to protect the integrity of the reproductive function.

Secondary lymphoid organs, such as spleen and lymph nodes, are instrumental in initiating anti-viral and other immune responses. Once primed against infection, the immune system can target those sites in the body where it is most needed. Some sites, however, actively prevent immune cells from entering or from performing their effector functions after entry. Such exceptions may have evolved in places where strong immune responses against pathogens could potentially lead to organ dysfunction. The eye, a well-studied immunologically privileged site, is a case in point (1). Recent epidemiological data from Adami *et al.* (2) indirectly suggest that the uterine cervix may be another. In an extensive study based on data from the Swedish Cancer Registry, cancer incidence was analyzed in 5931 recipients of solid organ transplants performed between 1970 and 1997 in Sweden. The study shows strongly increased risks for many cancers, with non-melanoma skin cancer, lip cancer, non-Hodgkin's lymphoma, and anogenital cancers showing the most impressive increase (10 to 20-fold higher). Cancer of the uterine cervix was a surprising exception. While other tumors of the anogenital region, such as carcinoma of the vagina, vulva and anus, clearly increased in immunosuppressed patients, there was no significant increase of cervical cancers (2).

The fact that transplant recipients and other persons with immunodeficiencies develop a large excess of papillomavirus-associated tumors is not surprising (3). It has been taken as evidence that immune surveillance, conceived as the ongoing elimination of potentially neoplastic cells, plays an important role in the protection against the outgrowth of virally-transformed cells. This has been shown in several experimental tumor systems. Cells transformed by DNA tumor viruses, such as polyoma, SV40, adeno- and papillomaviruses, were particularly well recognized (4). This is understandable since the virally-encoded oncogenes, such as the SV40 and polyoma LT, the adenoviral E1A/E1B and the papillomavirus-encoded E6/E7 proteins, are essential for tumor cell growth and are also known to generate immunogenic peptides. Tumor development is restricted to genetically or experimentally immunodeficient hosts. The same theme is replayed, with only minor variations, in humans. The "extra" tumors that arise in congenital, iatrogenic, or infection- (HIV) based immunodeficient patients are mainly EBV-driven immunoblastomas, papillomavirus-associated epithelial tumors and HHV-8-related Kaposi sarcomas (3).

It was taken for granted that immune surveillance would apply to all HPV-associated tumors. The surprising finding that the incidence of cervical but not other anogenital cancers was unaffected in transplant patients could have several possible explanations. For instance, immune surveillance in the cervix could be mediated by T cell-independent mechanisms, such as natural killer cells, macrophages, or antibodies, which would not be affected by immunosuppressive treatments directed against T cell activation. We suggest another explanation. In view of the critical role of cervical physiology in facilitating the passage of spermatozoa, the cervical epithelium may be an immunologically exceptional site. The ejaculate contains many somatic cells, including lymphocytes, competent to induce allograft reactions and to generate cytotoxic T cells. Conceivably, they might damage the spermatozoa, known to express MHC class I antigens, and/or create reactive conditions that could inhibit free passage. Autoimmune reactions against the acrosomal proteins, a frequent reason of autoimmune sterility (5), is yet another.

The immune privilege we postulate does not necessarily affect all immune activity (6, 7). Impairment of immune functions involved in the rejection of antigenically foreign cells would be sufficient. Functional evidence for immune deficiencies in the uterine cervix have indeed been reported. Higher than average levels of the immunosuppressive cytokine TGF-beta was found in the most cancer-prone region of the cervix, the transformation zone (8), suggesting active downregulation of immune responses at this site. Moreover, a recent study demonstrated the presence of an eosinophilic infiltrate in cervical squamous carcinoma (9), suggesting a predominant Th2 response. This may antagonize Th1 responses associated with CTL activity and macrophage activation. Cervical carcinoma cells also express FasL. This implies that the cervical epithelium could potentially induce apoptosis in tumor-specific T cells (10). Deficiencies like these are all possible consequences of an immune privilege in the uterine cervix.

We suggest that cervical immunosuppression may play a positive role in reproductive physiology since it would reduce the risk of maternal alloresponses triggered by spermatozoa and other cells in the ejaculate. Such reactions are potentially capable of inhibiting the passage of spermatozoa and may even damage the fetus. At the same time however, immune responses against viruses carrying preneoplastic and neoplastic cells would also be impaired. This would explain the lack of any increase in the incidence of cervical (but not other anogenital) cancers in immunosuppressed transplant patients (2). Our hypothesis would predict that CD4+ and CD8+ lymphocytes isolated from normal cervical epithelium would respond less well in allo-MLC tests compared to lymphocytes from other genital regions, and/or fail to differentiate into cytotoxic and cytokine-secreting effector cells. We are currently testing this prediction.

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