Immunodeficiency, Immunosuppression, and Susceptibility to Neoplasms

Robert S. Schwartz

HISTORICAL BACKGROUND

The idea that the immune system serves as a protective barrier against the growth of neoplastic cells began to emerge at the end of the 19th century, soon after the role of immunity in the defense against infection was established. In 1908, the year he was awarded the Nobel Prize, Paul Ehrlich wrote, “...in the enormously complicated course of fetal and post-fetal development, aberrant cells become unusually common. Fortunately, in the majority of people, they remain completely latent thanks to the organism’s positive mechanisms” (1). These “positive mechanisms,” Ehrlich proposed, were grounded in the immune system, and, when they were depressed, “the rapid, parasitic growth of [neoplastic] cells” would follow. Twenty years later, in his book Heteroplastic and Homoplastic Transplantation, Georg Schoen (2) coined the term “transplantation immunity” and formulated the general laws of transplantation as we know them today: Transplantation into a foreign species or unrelated members of the same species fail, whereas autografts succeed; a second graft in a recipient that previously rejected a graft from the same donor undergoes accelerated rejection; and a close “blood relationship” between donor and recipient enhances the success of the graft.

It is notable that all these principles had been demonstrated in experimental animals with the use of grafts of tumor cells. In that same era, James B. Murphy (3) called attention to the role of the lymphocyte in the rejection of tumor grafts, and George D. Snell (4), another Nobel laureate, began his historic experiments that were to become the foundation of immunogenetics. The discovery by Peter Goris (5) of hemagglutinating antibodies in the serum of mice that had rejected a tumor allograft (containing what he called antigen II) was joined with Snell’s H locus—the genetic basis of the rejection of tumor allografts—to yield the H-2 system. For all these reasons, tumor immunology became inextricably linked to transplantation immunology and, thus, back to Ehrlich’s idea that one of the functions of the immune system is to guard against the growth of neoplastic cells. [The history of transplantation immunology is well summarized in (6).]

Despite these historic advances, the idea of protective immunity against autochthonous neoplasms remained in the backwater of immunology until 1970, when F. McFarlane Burnet aroused interest in the topic with his book Immunological Surveillance (7). In this work, Burnet presented the sweeping hypothesis that “...an important and possibly primary function of the immunological mechanisms is to eliminate cells which as a result of somatic mutation or some other inheritable change represent potential dangers to life.” Burnet assigned this function to the cellular immune system (today’s T cells) and went on to write, “...without immunological surveillance, cancer would be more frequent and occur at younger ages than it does,” and that “immuno-suppressive agents (sic) ... will increase the likelihood of neoplasia.” Thirty years after its publication, this book remains a fascinating glimpse into the thoughts of a brilliant theoretist, yet, despite his sparkling imagination, Burnet had to admit that he could not conceive of an experiment that would conclusively prove his thesis. Indeed, evidence that the immune system has a major role in defending the body against mutated (neoplastic) cells is still wanting.

NEOPLASMS IN CONGENITAL IMMUNODEFICIENCY DISEASES

One would suppose that an excellent approach to finding ways of testing Burnet’s idea is through studies of congenital immunodeficiency diseases, in which the hypothetical immunologic surveillance system would be severely impaired, hence rendering the patient susceptible to cancers of all types. But the congenital immunodeficiency diseases may not be the ideal testing ground for immunologic surveillance [see Table 1 and (8)]. For example, there is no undue susceptibility to cancer in X-linked hypogammaglobulinemia because the defect is in B cells; T-cell immunity, which is thought to be crucial for immunologic surveillance, is intact (9). Severe combined immunodeficiency disease, the DiGeorge syndrome, and congenital deficiency of major histocompatibility complex molecules are usually fatal within the first year of life unless corrected by a bone marrow or thymic transplant. There is simply insufficient time for a neoplasm to develop in children with these disorders.

In the X-linked hyperimmunoglobulin M (hyper-IgM) syndrome, common variable immunodeficiency disease, and selective immunoglobulin A (IgA) deficiency, there does seem to be an increased risk of neoplasms, but these diseases are almost always lymphomas rather than a representative sample of the variety of neoplasms that affect children (10,11). Moreover, evidence directly implicating the immunodeficiency itself as the cause of the lymphomas in these three diseases is inconclusive. Patients with X-linked hyper-IgM syndrome, common variable immunodeficiency disease, or selective IgA deficiency have a disorder of immunoregulation, often manifested clinically by enlarged lymph nodes and splenomegaly. The derangement of the immune system—and not the immunodeficiency—may be the key reason for the development of lymphomas in these patients. In the X-linked hyper-IgM syndrome, for example, the defect is a crippling mutation in the CD40 gene, which encodes a protein (CD40) that is required for the production of immunoglobulin G (IgG) antibodies (12). In addition to this property, the CD40 molecule and its ligand have anti-apoptotic properties in normal and neoplastic B cells (13–17). In common variable immunodeficiency disease and IgA deficiency, there is not only impaired immunoregulation but also chromosomal abnormalities, both of which may contribute to the susceptibility to lymphomas (18).

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An increased susceptibility to lymphomas has also been noted in the Wiskott–Aldrich syndrome of thrombocytopenia, eczema, recurrent otitis media, and susceptibility to infection by a variety of microorganisms (19). The faulty WAS gene has been mapped to chromosome Xp11.22, and the Was protein, located in the cytoplasm, is probably involved in signal transduction and the maintenance of the cytoskeleton in many kinds of cells, including all three lineages of hematopoietic cells and their precursor, the CD34+ hematopoietic stem cell (20). Many aspects of the function of the Was protein are unknown, but it is plausible that disorganization of a protein with such fundamental properties could increase the probability of the malignant transformation of a cell. Ataxia-telangiectasia, the Nijmegen breakage syndrome, and Bloom syndrome, all associated with immunodeficiency, are really diseases of chromosomal instability because of faults in the mechanism of DNA repair. This is why patients with ataxia-telangiectasia, the Nijmegen breakage syndrome, and Bloom syndrome, all associated with immunodeficiency, are actually diseases of chromosomal instability because of faults in the mechanism of DNA repair. The faulty WAS gene has been mapped (19). The reason is the way patients with ataxia-telangiectasia, and cultures of their cells are extremely susceptible to radiation (15). Malignancies, mainly lymphomas, occur in about one third of homozygotes for the ataxia-telangiectasia defect or the Nijmegen breakage syndrome (15). The cause of these neoplasms is likely to be the marked chromosomal instability, but the immunodeficiency may have a secondary role by allowing the early appearance and rapid growth of the tumors.

X-linked immunodeficiency disease (also called X-linked lymphoproliferative disease and Duncan’s disease) is of special interest because of its association with lymphomas caused by the Epstein-Barr virus (EBV) (21). Boys who carry the XLP gene are healthy until they become infected with EBV. The outcome of this infection can be a severe, often fatal form of infectious mononucleosis, a malignant lymphoma, or hypogammaglobulinemia, sometimes with increased serum levels of IgM. Lymphoma develops in about one third of patients with X-linked lymphoproliferative disease, usually around the age of 5 or 6 years (21). Griersson and Purttilo (22) have estimated that the risk of lymphoma in boys with the disease is 200 times greater than that in the general population. The lymphomas usually appear in extranodal sites, arise from B cells, and often have the histologic features of Burkitt’s lymphoma. Other types of lymphoma, including immunoblastic, large noncleaved or small cleaved, and mixed cell lymphomas, also occur in this disease (23). Before infection by EBV, boys with X-linked lymphoproliferative disease may have subtle immunologic defects, such as impaired isotype switching (IgM to IgG), but the outstanding feature after infection by the virus is the lack of anti-EBV antibodies. The XLP gene, located on chromosome Xq25, has been cloned and found to be a mutated version of a gene called SH2D1A, which encodes a protein involved in multiple intracellular signaling pathways, especially in T cells [reviewed in (24)]. This rare disease is an experiment of nature that demonstrates the importance of the immune system in the defense against a potentially oncogenic virus. It is likely that this aspect of protective immunity is the key to understanding the development of neoplasms in recipients of allografts who receive treatment with immunosuppressive drugs.

**NEOPLASMS IN RECIPIENTS OF ALLOGRAFTS**

From the very beginning of the clinical use of organ and bone marrow allografts, the possibility of a demanding test of the protective immunity of the immune system in the defense against a potentially oncogenic virus. It is likely that this aspect of protective immunity is the key to understanding the development of neoplasms in recipients of allografts who receive treatment with immunosuppressive drugs.

**Table 1. Congenital immunodeficiency diseases and susceptibility to neoplasms**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hypogammaglobulinemia</td>
<td>No</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disease</td>
<td>No</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>No</td>
</tr>
<tr>
<td>Major histocompatibility complex disease</td>
<td>No</td>
</tr>
<tr>
<td>Hyperimmunoglobulin M syndrome</td>
<td>Yes</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Yes</td>
</tr>
<tr>
<td>Selective immunoglobulin A deficiency</td>
<td>Yes</td>
</tr>
<tr>
<td>X-linked lymphoproliferative disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Yes</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Yes</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Table 2. Development of lymphomas in animal models of lymphoproliferation**

<table>
<thead>
<tr>
<th>Model</th>
<th>Affected cell</th>
<th>Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic graft-versus-host disease</td>
<td>T + B</td>
<td>Yes</td>
</tr>
<tr>
<td>Bcl-2 transgenic</td>
<td>B</td>
<td>No</td>
</tr>
<tr>
<td>CTLA-4 knockout</td>
<td>CD4 T</td>
<td>No</td>
</tr>
<tr>
<td>Lyn knockout</td>
<td>T</td>
<td>No</td>
</tr>
<tr>
<td>Fli-1 transgenic</td>
<td>B</td>
<td>No</td>
</tr>
<tr>
<td>NZB</td>
<td>B</td>
<td>No</td>
</tr>
<tr>
<td>MRL/lpr/lpr</td>
<td>T + B</td>
<td>No</td>
</tr>
<tr>
<td>Gld</td>
<td>T + B</td>
<td>No</td>
</tr>
</tbody>
</table>
immunologic surveillance theory was at hand. All recipients of such grafts, especially organ allografts, required extended treatment with immunosuppressive drugs to prevent rejection of the graft. Recipients of marrow allografts received a rigorous preparation with total-body radiation and, to prevent graft-versus-host disease, long-term immunosuppression after receiving the allogeneic marrow. In retrospect, patients who were treated with an allograft were the harbingers of things to come because of their susceptibility to virtually all of the infectious and neoplastic complications of acquired immunodeficiency syndrome (AIDS). These complications could be traced directly to the deficiency of T cells caused by the immunosuppressive therapy.

The immunologic surveillance theory predicted an increased frequency of all the common neoplasms that affect humans because the immune systems of these patients were suppressed to the point that allowed acceptance of an allograft. That prediction was not realized, however. There was, to be sure, an increased incidence of neoplasms in this population but not an increase in the incidence of cancer of the lung, breast, or bowel. Instead, there was not realized, however. There was, to be sure, an increased incidence of cancers of the skin, B-cell lymphomas, Kaposi’s sarcoma, and several unusual tumors (28–34) (Fig. 1). The risk of developing such neoplasms is related to the extent of immunosuppressive therapy (35), and, as experience with managing allograft recipients has increased, the risk of opportunistic cancer has decreased. Because recipients of allografts almost always require continuous treatment with immunosuppressive drugs, they have a life-long increased risk of neoplastic disease. For example, among patients who survived for at least 10 years with a renal allograft, the cause of death was cancer in 26% (30).

Skin cancer is among the most frequent neoplasms in recipients of organ allografts (36–38). In one study, the risk of cutaneous squamous cell carcinoma was increased 65-fold, carcinoma of the lip was increased 20-fold, and the risk of Kaposi’s sarcoma was increased 84-fold, compared with the general population. The risk of these cutaneous cancers was related to the degree of immunosuppression caused by long-term immunosuppressive therapy (37). The frequency of skin cancers in the transplanted population increases with time after transplantation, rising 40% to 70% after 10 years. The squamous cell carcinomas tend to be multiple and even life threatening (36,38).

Another category of lesions that occurs in allograft recipients is post-transplant lymphoproliferative disease. In allograft recipients, these disorders are relatively common, complex, and difficult to treat. They include polymorphic lymphoproliferative disorders, monomorphic lymphoproliferative lesions that usually arise in B cells but may also originate from T cells (39), and Hodgkin’s-like lesions (40). The polymorphic lymphoproliferative disorders consist of B cells and T cells intermingled with numerous plasma cells. They are often reversible if immunosuppressive therapy is decreased or discontinued, whereas the monomorphic lesions are usually irreversible—they are monoclonal disorders with all the features of a malignant lymphoma (40–42). There is a marked tendency for the monoclonal lymphoproliferative lesions to occur in extranodal sites, especially in the central nervous system (43).

Virtually all post-transplant lymphoproliferative disorders are linked to EBV (44–46). EBV has adapted to its host by using multiple, complex, and, some might say, ingenious tactics. After infecting a resting B cell, the virus drives the cell to proliferate. At this stage, the B cell expresses multiple EBV antigens, which provide ample targets for cytotoxic T cells. Normally, these T cells eliminate the proliferating clones of EBV-infected B cells, but in some B cells the virus escapes notice by entering a latent phase in which only the LMP2a antigen is expressed. LMP2a has the capacity to mask the expression of class I HLA antigens, through which cytotoxic T cells come into contact with virus-infected cells. In a normal adult, there are about 10⁷ non-dividing, EBV-infected memory B cells; in patients receiving immunosuppressive therapy, there is a dramatic rise in such cells. Occasionally, these B cells carrying latent EBV fortuitously become activated when they come into contact with activated T cells in germinal centers; on activation, they express only the EBNA-1 antigen, which allows the virus to replicate. The EBNA protein interferes with the ability of HLA class I molecules to transport EBNA peptides to the cell surface, so these cells, too, escape immune surveillance. Ultimately, these B cells return to the resting stage and again express only LMP2a [reviewed in (47)].

It is important to note that EBV is not the sole element in the pathogenesis of post-transplant lymphoproliferative diseases. In Burkitt’s lymphoma, for example, there is a genetic change in the cell, the c-myc translocation, which is essential for the tumor to evolve. In one study of 57 post-transplant lymphoproliferative disorders, mutations of the BCL-6 proto-oncogene were found in 43% of the polymorphic lesions and in 90% of the post-transplant lymphomas (48). Mutations of BCL-6 have also been found in lymphomas that were not associated with immunosuppressive therapy (49) and may play a key role in lymphomagenesis.

There is evidence that viral

Fig. 1. Types of cancers reported in recipients of allografts (10,787 recipients; 11,483 neoplasms). PTLD = post-transplant lymphoproliferative disease; KS = Kaposi’s sarcoma. [Data from (28).]
load is an important factor in susceptibility to post-transplant lymphoproliferative diseases (46,50). Moreover, Burkitt’s lymphoma is monoclonal, monomorphic, and irreversible at the outset, whereas the lymphoproliferative lesions in allograft recipients are initially reversible [reviewed in (51)]. Presumably, the conversion from reversible polyclonal post-transplant lymphoproliferative disease to an irreversible monoclonal lymphoma occurs when an EBV-infected B-cell (or T-cell) clone acquires a genetic lesion that gives that clone a growth advantage over other clones in the mass of cells that proliferate without hindrance in the immunosuppressed allograft recipient.

Post-transplant lymphoproliferative disease and the lymphomas in AIDS patients have similarities and differences. Both are characterized by extranodal disease and aggressive behavior, but the post-transplant lymphoproliferative disorders are uniformly infected by EBV, whereas EBV is detectable in only about half of the lymphomas in patients with AIDS (52,53). Another difference is that Burkitt-type lymphoma is relatively common in patients with AIDS but rare in allograft recipients (54). Another interesting aspect of post-transplant lymphomas is that follicular lymphoma, the commonest lymphoma among adults, is not seen in immunosuppressed patients. The reasons for these differences are unknown, but they likely depend on the immunologic status of the patient, the presence or absence of EBV, and the types of genetic changes in the tumors.

In recipients of allogeneic bone marrow, EBV-induced lymphoproliferative disease arises in B cells from the donor (55), and the risk of such a disease developing in the recipient is reduced by depleting the allogeneic marrow of B cells (55,56). Persuasive evidence that the lack of anti-EBV immunity is an essential feature of post-transplant lymphoproliferative diseases comes from experiments in which transfusions of leukocytes (not plasma) from EBV-positive donors caused regressions of the lymphoproliferative lesions (57,58).

It is likely that the susceptibility of allograft recipients to Kaposi’s sarcoma is also related to the lack of a defense against a herpesvirus—in this case, human herpesvirus 8 (HHV8). In one series of 28 cases of Kaposi’s sarcoma in transplant recipients, HHV8 was found in 27 of 28 lesions by means of the polymerase chain reaction. It is possible that latent HHV8 infection in allograft recipients becomes activated after transplantation, because titers of anti-HHV8 antibodies rise and HHV8 DNA can be found in the blood after institution of immunosuppressive therapy (59,60). Regamey et al. (61) have reported that in some cases HHV8 may be transmitted from the donor to the recipient through a renal allograft.

CONCLUSION

The advent of clinical transplantation presented a major challenge to the immunologic surveillance theory. It would appear that, in the context of transplantation, the theory is wanting because recipients of allografts are not unduly susceptible to the most common cancers in humans: lung, breast, prostate, intestinal, or ovarian cancer. Instead, there is a many-fold increased risk of the development of virus-induced neoplasms because of the inability of the recipient to suppress activation of latent herpesviruses or a new infection with these agents. Nevertheless, questions remain, and it would be premature to write off the theory. For example, skin cancers are among the commonest malignant growths in allograft recipients, yet none of these neoplasms has yet been linked to an oncogenic virus. It is plausible that skin cells in which DNA is damaged by UV radiation occur frequently in normal people, who, by an immune response, eliminate such potentially malignant cells. In the allograft recipient, this response may be lacking, thereby allowing the growth of neoplastic cutaneous cells. Another factor deserving consideration is the possibility that the immunosuppressive drugs themselves are oncogenic. Recently, Hojo et al. (62) found that cyclosporine induced phenotypic changes in cultured normal cells that allowed them to invade normal tissues when transplanted in vivo. Moreover, cyclosporine caused marked alterations associated with high-grade malignancy in cultured adenocarcinoma cells. These effects were nullified by adding monoclonal antibodies against transforming growth factor-β. Investigations of allograft recipients have been a rich source of knowledge about the immune system, microbiology, oncology, and genetics, but it is apparent that we still have much to learn from these remarkable patients.

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NOTE
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