CHAPTER 16.

# Immunosuppression

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## Introduction

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including surface antigens on tumour cells. Immunosuppression can result from killing of immune effector cells or from blockage of intracellular pathways essential for antigen recognition or of other elements of the immune response.

Persistent immunosuppression presents a risk of cancer. Individuals who are latently infected with an oncogenic virus are at greatly increased risk for developing virus-related cancers when they become immunosuppressed (Grulich et al., 2007; Schulz, 2009; Wieland et al., 2014), and there is excess risk of B-cell non-Hodgkin lymphoma (NHL) when immunosuppression is accompanied by continuing immune stimulation from exposure to non-viral antigens, such as after organ transplantation (Ponce et al., 2014).

Potentially neoplastic cells that arise naturally, or that have been transformed by carcinogens acting by a mechanism such as genotoxicity or by the various mechanisms of action associated with oncogenic viruses, may escape immune surveillance in immunosuppressed individuals. As a result, survival of these cells and their replication to form tumours is greatly facilitated.

Certain pharmaceutical drugs, ionizing and ultraviolet radiation, or infection with certain viruses and parasites can cause immunosuppression. After exposure to X-rays or other types of ionizing radiation, immunosuppression is most pronounced if the entire body, rather than a limited area, is irradiated. Immunosuppression by pharmaceutical drugs or by ionizing or ultraviolet radiation is dose-dependent – the intensity and duration of the effect increases with increasing dose or continuing exposure – and is usually transient: immune function generally recovers after cessation of exposure. In contrast, infection with certain pathogens, such as human immunodeficiency virus type 1 (HIV-1) or malaria parasites, is persistent, and the immune deficiency that results is progressive unless the infection is effectively treated.

Immunosuppression as a medical therapy is used to treat autoimmune diseases such as lupus erythematosus or rheumatoid arthritis. Immunosuppressive drugs, usually in much higher dosage, are used to maintain the functional and anatomical integrity of foreign tissues grafted onto another individual, such as a kidney or heart transplant. A graft

from any individual except oneself or an identical twin will provoke an immune reaction against the grafted tissues, the intensity of which varies with the degree of antigenic difference between graft and host. In the absence of adequate immunosuppression, the host will destroy the graft. Whole organs (e.g. kidney, heart, liver, or lung) can be transplanted with maintenance of function that may continue for a normal lifetime when appropriate levels of immunosuppression are maintained. However, the risk of primary cancer in the transplant recipient increases with increasing intensity and duration of immunosuppression (Kinlen, 1996; Yu et al., 2014).

An uncommon but potentially dangerous side effect of immunosuppression to support organ transplants is that suppression of the immune response can allow occult tumours or metastatic tumour cells within the transplanted tissues or organs to survive, grow, and metastasize in the transplant recipient. Occult metastatic melanoma in the donated organ is especially dangerous for the transplant recipient (Penn, 1996; Loren et al., 2003). Such transplanted cancers regress when immunosuppressive therapy is withdrawn (Wilson et al., 1968; Loren et al., 2003).

## Immunosuppression and genotoxicity

The fact that a carcinogen has immunosuppressive properties does not necessarily mean that this is the mechanism by which it causes human cancer. DNA-damaging agents are generally also immunosuppressants, especially at high levels of exposure; these include external ionizing radiation (X-rays and γ-rays), ultraviolet and solar radiation, and most of the chemical alkylating agents used in anticancer chemotherapy. Radiation and chemical alkylating agents are considered to cause cancer primarily by inducing DNA damage, rather than by immunosuppression.

Cyclophosphamide is an antineoplastic drug and is classified as *carcinogenic to humans* (Group 1). This drug has very marked immunosuppressive properties. In addition to its application in anticancer chemotherapy, cyclophosphamide is used clinically as an immunosuppressant to treat certain autoimmune diseases, such as severe systemic lupus erythematosus (Valeri et al., 1994). The drug, which must be metabolized to act as an alkylating agent, causes acute myeloid leukaemia and carcinoma of the urinary bladder in patients in whom it has been used as an antineoplastic agent (IARC, 2012b). All available evidence, including the organ sites of tumour development and the specific kinds of neoplasms induced, indicates that cyclophosphamide exerts its carcinogenic activity via a genotoxic mechanism (McCarroll et al., 2008), rather than via immunosuppression.

Chlorambucil, like cyclophosphamide, is a bifunctional alkylating agent that also is an antineoplastic drug and is classified as *carcinogenic to humans* (Group 1). It is used clinically as an immunosuppressant to treat childhood nephrotic syndrome (Neuhaus et al., 1994), rheumatoid arthritis, and other autoimmune diseases. It has been used to treat polycythaemia vera (a malignancy) and is used, often alone, as initial therapy for chronic lymphocytic leukaemia and in combination with other drugs to treat other cancers. Chlorambucil, like other antineoplastic alkylating agents, can cause acute myeloid leukaemia by a genotoxic mechanism after its use in anticancer chemotherapy (IARC, 2012b).

## Immunosuppressive carcinogens

Several Group 1 agents reviewed in Volume 100 of the *IARC Monographs* act entirely or largely by immunosuppression, often in concert with other Group 1 agents, especially oncogenic infectious agents. The Group 1 agents that act by immunosuppression are HIV-1 and the pharmaceutical drugs ciclosporin and azathioprine.

### *HIV-1 infection*

Infection with HIV-1 is the cause of the acquired immune deficiency syndrome (AIDS). The severe immune deficiency that is characteristic of AIDS results from a deficiency in CD4-positive T lymphocytes and a severe loss of memory B cells (IARC, 2012a). In addition to severe infections, several cancers occur at high frequency in patients with AIDS. NHL, especially primary brain NHL, as well as Kaposi sarcoma and cervical carcinoma are AIDS-defining conditions in severely immunosuppressed patients.

There is no evidence that HIV-1 causes NHL or other cancers through a direct effect. Unlike what is known about other cancer-associated viruses, there is no evidence that HIV-1 infection by itself leads to cell transformation or immortalization. The HIV-1 genome is not present in cancer cells, in contrast to what is observed with infectious agents that are directly oncogenic (IARC, 2012a).

Kaposi sarcoma, which is caused by Kaposi sarcoma herpesvirus (KSHV), is the most common cancer

in patients with HIV-1 infection. Its occurrence is highly correlated with the severity of suppression of CD4-positive T lymphocytes. The standardized incidence ratio for Kaposi sarcoma in a Swiss cohort was more than 500 in patients with a CD4-positive lymphocyte count of less than 100 cells/mm$^3$ but approximately 76 in patients with a CD4-positive lymphocyte count of greater than 500 cells/mm$^3$ (Clifford et al., 2005; IARC, 2012a).

NHL, chiefly of the B-cell type, is the second most common malignancy in patients with AIDS. In a meta-analysis of six studies, NHL had a standardized incidence ratio of 77 in patients with HIV-1 infection relative to the general population (Grulich et al., 2007), and NHL is frequently associated with Epstein–Barr virus (EBV) co-infection. The severe depletion of CD4-positive T lymphocytes induced by HIV-1 leads to dysregulated control of B lymphocytes and to the expression of co-infecting lymphotropic viruses (Engels, 2007).

The third most common malignancy in HIV-1-positive individuals, and also an AIDS-defining condition, is cervical carcinoma associated with human papillomavirus (HPV) infection. Anogenital intraepithelial neoplasms and carcinomas are also increased in frequency, and so are skin cancers associated with HPV infection (IARC, 2012a). In addition to NHL and Kaposi sarcoma, infection with HIV-1 causes cancer of the cervix, anus, and conjunctiva, as well as of the vulva, vagina, and penis (IARC, 2012a). The primary cause of these squamous epithelial neoplasms is co-infection with HPV. Finally, individuals with HIV-1 infection have a greatly increased incidence of infection with hepatitis B virus and hepatitis C virus, and are therefore at elevated risk for hepatocellular carcinoma (Grulich et al., 2007).

### *Therapeutic immunosuppression*

Therapeutic immunosuppression, generally by various combinations of drugs such as ciclosporin and azathioprine, is administered to organ transplant recipients to maintain their transplanted organ or organs. Recipients are at high risk for some of the same cancers that occur in patients with AIDS. A comparison of AIDS-related and transplantation-associated tumours, from which this text is excerpted, is presented in IARC (2012a).

Although individuals with AIDS and those with iatrogenic immunosuppression after organ transplantation have immunodeficiency in common, the immunological abnormalities appear to differ considerably between these two conditions. However, the spectra of neoplasms that occur in patients with AIDS and in organ transplant recipients largely overlap. An obvious similarity between organ transplant recipients and patients with AIDS is the increased incidence of B-cell NHL associated with EBV infection. Specific differences include more frequent high-grade lymphomas in patients with AIDS and a more frequent EBV association and polymorphic lesions in organ transplant recipients.

The second important malignancy that is greatly increased in incidence in both individuals with HIV-1 infection and transplant recipients is Kaposi sarcoma (Zattra et al., 2014). A study of renal transplant recipients reported a more than 20-fold increase in the incidence of Kaposi sarcoma compared with the general population (Kasiske et al., 2004). Non-melanoma skin cancers other than Kaposi sarcoma also occur at high frequency in organ transplant recipients (Forchetti et al., 2014). There is a 65-fold increase in the incidence of squamous cell carcinoma and a 10-fold increase in the incidence of basal cell carcinoma in organ transplant recipients relative to the general population (Yu et al., 2014).

#### *Ciclosporin*

Ciclosporin, a cyclic lipophilic undecapeptide, is a calcineurin inhibitor and a potent immunosuppressant that is virtually non-myelotoxic but is markedly nephrotoxic. It is used in organ and tissue transplantation to prevent graft rejection after bone marrow, kidney, liver, pancreas, heart, lung, and heart–lung transplantation, and for prophylaxis and treatment of graft-versus-host disease (IARC, 2012b).

The immunosuppressive activity of ciclosporin is consistent with an increased risk of cancer as a result of impaired immune surveillance, particularly for virus-related cancers such as EBV-related NHL and HPV-related cervical cancer (IARC, 2012b). Patients who receive ciclosporin also are at increased risk for squamous cell tumours of the skin, which may be due in part to effects of the drug other than immunosuppression. Ciclosporin has the ability to generate reactive oxygen species, and this is probably relevant to its carcinogenicity (IARC, 2012b).

#### *Azathioprine*

Azathioprine, a substituted 6-mercaptopurine, is used in immunosuppressive treatments to prevent rejection of kidney allografts. The drug is usually used in conjunction with

other immunosuppressive therapy, including local radiation therapy and treatment with corticosteroids and other cytotoxic agents.

One large prospective cohort study (Kinlen et al., 1979) on renal transplant recipients who received azathioprine examined the incidence of and mortality from different types of cancer compared with the numbers expected on the basis of the incidence and mortality rates for the relevant country (Australia, New Zealand, and the United Kingdom). An almost 60-fold increase in the risk of NHL was observed for all countries combined (34 observed, 0.58 expected), as well as a 30-fold increase in the risk of squamous cell skin cancer in patients from the United Kingdom (3 observed, 0.13 expected) (IARC, 2012b).

Azathioprine is used more often in individuals with autoimmune conditions than in transplant recipients. For example, azathioprine is given for management of the signs and symptoms of rheumatoid arthritis in adults (IARC, 2012b). Excesses in the risk of NHL (relative risk, 10.9) and of squamous cell skin cancer (relative risk, 5.0) were found in non-transplant patients receiving azathioprine, although these excesses are smaller than those in transplant recipients (Kinlen, 1985). Azathioprine is carcinogenic via two mechanisms: (i) as an immunosuppressant, it is associated with post-transplant lymphoproliferative disorders that generally have a viral etiology; and (ii) because it causes 6-thioguanine to accumulate in patients' DNA, it also contributes to cancer development by induction of DNA damage (IARC, 2012b).

Often, milder therapy and less potently immunosuppressive drugs (e.g. steroids such as prednisone) are used for autoimmune conditions than for maintenance of organ transplants. Prednisone and related immunosuppressive steroid drugs have not been shown to be carcinogenic.

## Malaria, a probable human carcinogen

In addition to the IARC Group 1 agents that are carcinogenic largely or entirely by an immunosuppressive mechanism, infection with *Plasmodium falciparum* malaria in holoendemic areas is *probably carcinogenic to humans* (Group 2A), at least in part by immunosuppression (Bouvard et al., 2012; IARC, 2014). Infection with *P. falciparum* malaria has immunosuppressive effects, as reflected by impairment of macrophage function and antigen presentation (dendritic cell inhibition), reduction in specific T-cell response, induction of regulatory T cells, and high plasma levels of pro-inflammatory cytokines (interleukin 6 [IL-6] and tumour necrosis factor alpha [TNF-α]) and regulatory cytokines (IL-10 and tumour growth factor beta [TGF-β]) (reviewed by Cunnington and Riley, 2010). Impaired humoral immune protection associated with prenatal or chronic exposure to *P. falciparum* is common in children living in malaria-endemic regions (Chelimo et al., 2005; Scott et al., 2005).

Children in certain regions of Africa become infected with EBV early in life, and nearly all have seroconverted by age 3 years (Biggar et al., 1978). EBV is activated when the immune system is compromised (reviewed by Hopwood and Crawford, 2000). Endemic Burkitt lymphoma (eBL), the most common paediatric cancer in sub-Saharan Africa, is a high-grade B-cell lymphoma characterized by the consistent presence of EBV (Epstein et al., 1964, 1965; zur Hausen et al., 1970). eBL occurs only where malaria transmission intensity is high, for example in the so-called lymphoma belt of sub-Saharan Africa and in the high-transmission areas of Papua New Guinea. Furthermore, within areas and countries where eBL occurs, it arises only among those living in regions with the highest transmission intensity, the so-called holoendemic or hyperendemic areas. *P. falciparum* can disturb the immature immune system in young children by expanding the B-cell pool in which eBL arises, and can reactivate latent EBV. Infection with both EBV and *P. falciparum* is required for the development of eBL (Bouvard et al., 2012; IARC, 2012a).

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