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Editorial

Donor leukaemia: perhaps a more common occurrence than we thought!

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Although allogeneic stem cell transplantation (SCT) has been a very successful treatment for many patients with haematological malignancies and bone marrow failure syndromes, relapse of the original disease remains a problem. In acute leukaemias, a number of factors appear to influence the incidence of relapse including the stage of disease at the time of SCT,[1] the conditioning regimen[2] and the type of graft versus host disease (GvHD) prophylaxis used.[3] In patients transplanted for acute myeloid leukaemia in first remission relapse rates are very low,[4] whereas patients transplanted for acute lymphoblastic leukaemia in second remission have a high rate of relapse, especially if the t(9;22) translocation is present.[5] In chronic myeloid leukaemia (CML), SCT performed in first chronic phase is associated with a greater than 60% long-term disease-free survival, but relapses may occur many years after the original transplant.[6] The use of T cell depletion as GvHD prophylaxis in patients undergoing SCT for CML was particularly associated with an unacceptably high rate of leukaemia relapse.[7] The administration of donor lymphocytes to patients relapsing after SCT for CML is commonly associated with long-term second remissions and in some cases 'molecular remission' may be achieved.[8] In patients with bone marrow failure syndromes, especially severe aplastic anaemia, early or late graft rejection may occur. This may be a reflection of relapse of the original disease. Rarely, autologous recovery occurs, in patients receiving SCT for leukaemia or severe aplastic anaemia.

When leukaemia relapse occurs, it is commonly assumed to be a re-emergence of the original leukaemia, however, in a number of thoroughly investigated cases, the leukaemia has been clearly demonstrated to occur in cells of donor origin.[9–11] The incidence of 'donor leukaemia' is unknown because many physicians do not investigate the origin of the relapsed leukaemia cells. Rare cases of donor leukaemia occurring after bone marrow transplantation for severe aplastic anaemia have been reported.[12]

The mechanisms underlying 'donor leukaemia' remain unknown. Rare cases of occult transmission of leukaemia from the donor have been described but appear to be very uncommon.[13] Putative explanations, which range from residual radiation-induced damage to stromal cells in the recipient to abnormal levels of growth factors in stromal cells in the blast crisis of CML, remain speculative. Recent radiobiological evidence of a bystander effect on nonirradiated progenitors and variations in response to radiation in different animal strains may enhance our understanding of the possible explanations for the phenomenon of 'donor leukaemia'.

Chromosome aberrations and gene mutations induced by ionizing radiation are conventionally attributed to the DNA being irreversibly changed immediately after exposure, either during the processing and enzymatic repair of the damage or during DNA replication. However, this paradigm of genetic alterations being restricted to direct DNA damage has been challenged by the induction of mutations and chromosome aberrations in cells that are not themselves irradiated but in the neighbourhood of irradiated cells or exposed to medium in which cells have been irradiated. Such untargeted effects are collectively termed radiation-induced bystander effects.[14,15] Recent investigations have revealed that genetic instability expressed in the progeny of haemopoietic stem cells can be induced by an indirect bystander-type mechanism both *in vitro*[16] and *in vivo*[17] in a manner consistent with an inflammatory-type mechanism involving superoxide and nitric oxide production.[18,19] However, the level of induced damage is strongly influenced by genetic factors[20] that may be attributed to the genotype-dependent differences in the efficiency of apoptotic response and phagocytic clearance of damaged cells in haemopoietic tissues.[19] These differences may also be relevant to the genotype-dependent differences in susceptibility to radiation leukaemogenesis,[21] as a more effective apoptotic response would eliminate a greater number of unstable and potentially leukaemic cells.

Prior to the recent studies of bystander effects, there are reports that superoxide radicals may induce genotoxic effects by indirect mechanisms, involving the formation of more long-lived, secondary chromosome breakage factors or clastogenic factors. These factors are present in the plasma of therapeutically or accidentally irradiated individuals, but there is considerable inter-individual variation in both production and response.[22–28] The clastogenic factors are able to stimulate further superoxide production by competent cells and this may be the explanation for their persistence over many years. The vicious circle of formation and action shifts the pro-oxidant/anti-oxidant balance in cells towards the pro-oxidant state, and the genotoxic effects are brought about by the formation of lipid peroxidation products,[29] inosine nucleotides[30] and cyto-

Correspondence: Professor S McCann, Department of Haematology, Durkan Building, Trinity Centre, St James's Hospital, Dublin 8, Ireland; E-mail: smccann@stjames.ie

toxic cytokines.[31] Potentially related findings are that irradiated bone marrow stromal cells release cytokines[32,33] and/or nitric oxide [34] and that the frequency of transformation of haemopoietic growth factor-dependent cells is enhanced if cocultured with irradiated bone marrow stromal cell lines[35,36] or transplanted into irradiated syngeneic mice.[37] There is also experimental evidence that induction of inflammatory responses in mice increases the incidence of radiation-induced acute myeloid leukaemia[38] and that germ-free mice have a lower incidence of radiation-induced AML but transferring mice housed and irradiated in germ free conditions to conventional conditions increases their AML incidence.[39]

Overall, there is a growing body of experimental evidence that there are indirect or bystander mechanisms of radiation damage that involve oxidative stress and inflammatory-type responses to radiation-induced injury. This conclusion is consistent with the recent report of a persistent subclinical inflammation among Japanese A-bomb survivors and the suggestion that 'radiation-induced enhancement of inflammatory reactions might contribute as an epigenetic and/or bystander effect to the development of several radiation-induced disorders'.[40] While it is not yet clear how bystander effects contribute to overall cellular radiation responses *in vivo*, they have opened up avenues of investigation with potential relevance to understanding leukaemic relapse in donor cells.

S McCann[1]
E Wright[2]

[1]*Department of Haematology, St James's Hospital and University of Dublin, Trinity College, Ireland; and*
[2]*University of Dundee, Ninewells Hospital and Medical School, Scotland, UK*

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