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New drugs protect against radiation damage

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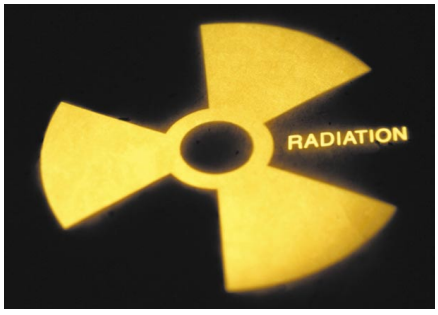
Two naturally occurring steroid hormones, androstenetriol (AET) and androstenediol (AED), could boost immunity and prevent infection and tumour formation following radiotherapy. AET and AED have previously been shown to protect mice from lethal radiation exposure[1]. Such exposure damages the immune response and leaves the animals vulnerable to lethal infections. Moreover, Roger Loria (Commonwealth University of Virginia, Richmond, VA, USA) says that, 'Both drugs counteract the immunosuppressive effects of corticosteroids and could have major uses in rheumatic diseases and asthma, as well as in diseases in which prolonged use of corticosteroids produces toxicity and problematic side-effects.'

Fast dividing cells such as lymphocytes are particularly vulnerable to radiation exposure, either during radiotherapy or a nuclear attack. The degree of toxicity, says Loria, depends in part on the radiation dose and on the type of cells exposed, as some cells survive higher doses than others. Focusing radiation on specific target tissues limits systemic injury, as does limiting exposure to radiation.

The ability of the haematopoietic system to recover following a course of radiotherapy is diminished, explains Loria, even if it has had time to recover after an earlier round of treatment. 'Recovery after the second round will be slower and more difficult,' he adds. Moreover, like radiation, corticosteroids (such as hydrocortisone and prednisolone) also suppress immunity by altering protein synthesis and redistributing the circulation of lymphocytes. Once the immune system is damaged, either by radiation or other forms of attack, individuals are highly susceptible to infection. As the immune system also keeps tumours in check, says Loria, 'any significantly impaired immune resistance could result in new tumours being expressed and cancer developing.'



Natural protectors

The adrenal steroid hormone dehydroepiandrosterone (DHEA) is metabolized first to AED and then to AET. All three hormones protect mice against bacterial and viral infection but AET is the most potent and is effective at concentrations more than tenfold lower than those of AED, which itself is 10,000-fold more potent than the parent molecule[1–3]. As Loria and colleagues knew that AED could protect against radiation exposure, their next logical step was to examine the protective effects of AET[1,4].

Mouse model

Both AET and AED protect mice against lethal doses of radiation (8 Gy)[1]. To investigate the effects of the two drugs on the immune system, Loria and colleagues exposed mice to sub-lethal doses of radiation (6 Gy) and coxsackievirus B4, a combination that normally kills 50% of mice[1]. Treatment with AED and AET reduced mortality to 12% and 25%, respectively. Moreover, the concentrations of AET required to protect the mice were approximately tenfold lower than those of AED. AET also restored spleen cell counts diminished by irradiation, including $CD4^+$ and $CD8^+$ cell counts.

'The experiment demonstrates that following 90% loss of host immune cells, AET induces a rapid proliferation of the surviving immune cells, leading to restoration of normal immune cell counts,' says Loria. The protective action of AET and AED is, says Loria, 'partly achieved by the stimulation of cytokines, such as interleukins IL-2 and IL-3, and counteraction of the immunosuppressant effects of indigenous corticosteroids that are produced during infection, irradiation and stress.' He adds: 'AET and AED mediate a rapid restoration of all haematopoietic precursors, which include neutrophils, monocytes, the $CD4^+$ and $CD8^+$ lymphocytes (the key combatants in most infections) and platelets.'

Both AED and AET are licensed for further development and AET, the more potent of the two drugs, should enter clinical trials later this year.

References

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