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Mistletoe therapy and immunological research

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In early preclinical and clinical trials, *Viscum album* L. (mistletoe) extracts and purified components such as the mistletoe lectin-I showed both impressive activity against murine and human tumour cells at higher drug concentrations, and also stimulation of immunocompetent cells at lower concentrations. Further study of mistletoe disclosed several novel mechanisms of action. Mistletoe exerts its cytotoxic activity by an induction of apoptosis mediated by the mistletoe lectins (at present it is unclear whether this is a direct consequence of protein biosynthesis inhibition or an independent killing pathway) and by stimulation of natural killer cells and macrophages by mistletoe lectins, oligosaccharides and polysaccharides from mistletoe. Surprisingly, plasma of mistletoe-treated mice increased the sensitivity of melanoma cells to cytotoxicity of lymphocytes, indicating the presence of certain growth modifying humoral factors of the host.

While mistletoe lectin I preferentially stimulates monocytes and natural killer cells, application of mistletoe, specifically the vesicles, results in an oligoclonal expansion of T-helper cells from treated cancer patients. In other experiments, however, only a fermented drug extract from mistletoes grown on pine trees stimulated T-helper cells and monocytes/macrophages from healthy and especially allergic donors. Furthermore, lymphocytes from untreated donors responded with a γδ T-cell expansion to heat-treated mistletoe extracts. These results indicate that responses of the non-specific as well as the specific immune system are elicited by several antigens from mistletoe. Although it has never been shown in detail, the mistletoe lectins are probably processed by antigen-presenting cells in response to an *in vivo* application of mistletoe. Consequently, a response of T-helper cells and B cells with subsequent production of anti-mistletoe lectin antibodies is recognized in treated cancer patients. It is obvious that the immune system responds to foreign antigens, but this may not imply effective antitumour activity. However, several studies indicate that the mistletoe-associated killing of tumour cells is mediated by an activation of non-specific immune cells rather than being a specific killing.

Another aspect of the mistletoe mechanism is particularly interesting, since mistletoe exerts antimutagenic and tumour-preventing effects in *in vitro* experiments and in animal models. Whatever the exact mechanisms are, the results indicate that mistletoe can modify the DNA damaging effect of carcinogens and probably inhibits the development of tumours, as shown by an inhibition of lung metastasis induced by B16F10 melanoma cells in mice and protection even against methylcholanthrene-induced sarcoma formation. This may be particularly relevant clinically, as the side effects of current chemotherapy have resulted in reservations about treating patients with advanced disease.

Taking the popularity of mistletoe treatment into account, one may not ignore the fact that mistletoe, specifically the mistletoe lectin, is a very potent drug that may suppress immune responses by an inadequate application (prolonged application of initially high drug concentrations). Furthermore, a non-critical use in the case of lymphomas and leukaemias may risk propagation of the malignant process. Thus, the responses of treated cancer patients have to be carefully monitored. Nevertheless, since anti-mistletoe lectin antibodies and glycoproteins/lipids from the serum strongly reduce the toxicity of the mistletoe lectins, even an intravenous application of high drug concentrations is tolerated without any signs of toxicity.

Obviously, we are far from understanding the complex interactions of the drug components and we do not know how to influence the immune system to efficiently kill cancer cells. Further investigation of this exciting drug is required so that its role in cancer therapy can be fully defined and efficacy optimized, both as a single agent and in combination with conventional therapy.