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Potential Therapeutic Application of the Plant Toxin Saporin-S6

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In a recent review, we focused on possible applications of the plant toxin saporin-S6 in cancer therapy [1]. However, this protein's therapeutic potential has been demonstrated in many other fields. Saporin-S6 belongs to the Ribosome-Inactivating Protein (RIP) family, a class of enzymes widely distributed amongst plants that damage ribosomes in an irreversible manner causing protein synthesis arrest and cell death. RIPs are mainly classified as type 1, single chain proteins with enzymatic activity, or type 2, consisting of an active A chain coupled by a disulphide bond to a lectin B chain [2]. RIPs cleave a specific adenine essential for the binding of elongation-factors to the ribosomal large subunit. *In vitro*, RIPs also deadenilate different substrates, such as mRNA, tRNA, DNA and poly (A); for this reason, RIPs' enzymatic activity has been afterwards defined as Polynucleotide: Adenosine Glycosylase (PNAG) [3].

RIPs are utilised in experimental medicine as toxic component of conjugates, which are hybrid molecules characterised by very high and selective toxicity towards target cells. Antibodies and their fragments are the most utilised carriers, but other molecules have also been employed, such as hormones, growth factors, antigens, cytokines and others. The term "Immunotoxin" (IT) generally refers to toxin-antibody conjugates. IT efficiency in killing target cells mainly depends on cell type, surface antigen density, IT binding affinity and intracellular routing. Clinical results have demonstrated the efficacy of ITs in cancer patients who were refractory to traditional modalities of treatment, including surgery, radiation therapy and chemotherapy. IT specificity is based upon characteristics (surface antigens) that are completely independent from the parameters that affect the chemo- and radiotherapy efficacy. This difference allows for a non-superimposition of side effects and for unimpaired cytotoxicity towards cell clones that are resistant to chemo- and radiotherapy [4].

Saporin-S6 (also known as saporin) is a type 1 RIP that was isolated from *Saponaria officinalis* L. seeds. The properties and mechanisms of action of saporin-S6 are well characterised, and this RIP has been extensively studied because of its potential therapeutic application in a variety of human diseases. Indeed, the high enzymatic activity of saporin-S6, its stability and resistance to blood proteases and to conjugation procedures make this molecule an ideal toxic component of conjugates for the selective killing of target cells [1].

Saporin-S6 has a low cytotoxicity because of its poor ability to enter the cell. However, if targeted inside the cell, saporin-S6 is very efficient in killing cells. After conjugation, saporin-S6 can be specifically delivered toward unwanted cells responsible for disease. The best results have been obtained in cancer therapy, mainly against haematological malignancies [1,5]. To date, saporin-S6-containing ITs have provided excellent results in hundreds of different models in pre-clinical studies in both *in vitro* and *in vivo* experiments. In mice bearing human tumours, saporin-S6-containing ITs were able to strongly reduce the size of transplanted tumours and completely eliminate tumour masses in several models. Moreover, saporin-S6-containing immunotoxins have demonstrated good efficacy in several clinical trials [5].

Saporin-S6's PNAG activity triggers multiple cell death pathways, with apoptosis being the main pathway [6]. Recently, the protein and its enzymatic activity on DNA were detected in the nuclei of intoxicated cells. These findings suggest that DNA damage may be one of the mechanisms used by this protein, and possibly other RIPs, to kill the cell, specifically by inducing DNA-dependent apoptotic death [7]. The redundancy of the cell killing mechanisms strongly reduces the possibility of selecting RIP-resistant mutants during cancer therapy. In clinical trials, efficacy was obtained at saporin-S6-containing immunotoxin doses that induced only mild and transient side effects, which were mainly fever, myalgias, hepatotoxicity, thrombocytopenia and vascular leak syndrome [1,5]. The use of ITs to treat haematological tumours has often revealed a certain grade of toxicity for bone marrow due to the expression of the targeted antigen on various normal, haematopoietic progenitor cells. However, different studies have demonstrated that although the ITs may be cytotoxic against committed progenitor cells, these cells can be repopulated by the pluripotent progenitors that are not affected by the treatment.

Some efforts have been made to enhance the toxicity of saporin-S6 alone or as an IT to develop new therapeutic approaches to treat neoplasms, especially solid tumours. These modifications include 1) augmenting IT cytotoxicity by photochemical internalization, 2) encapsulating the toxin into targeted nanoparticles, and 3) combining the IT with saponins, which are in general tenside-like compounds able to interact with cholesterol within membranes (reviewed in [1]).

Saporin-S6-containing ITs have also shown promising results in different pathological conditions in which the control of immune system can be helpful, such as the prevention and control of transplant rejection and GVHD and the treatment of autoimmune diseases [8,9]. Another therapeutic application of saporin-S6-containing ITs is in nano-surgery, e.g., to induce a permanent correction of oculo-facial dystonias or some forms of ocular motility disorders, as an alternative to botulinum toxin [10]. Additionally, saporin-S6 has been utilised in neuroscience studies; the protein has been conjugated to specific molecules (e.g., substance P, anti-NGFR antibodies) for the purpose of selectively destroying neurons. Permanent and selective killing of neurons is an important tool for research on the central nervous system, (e.g., in studies of behaviour, pain, neurodegenerative diseases, etc.) [11].

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