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Mistletoe lectins: telomerase inhibitors in alternative cancer therapy ▼

For decades, standardized mistletoe extract (*Viscum album* L.) such as Iscador® has been used as complementary treatment for benign and malignant tumors, especially in German speaking areas since the Austrian anthroposophist Rudolf Steiner (1861–1925) and the physician Ita Wegman (1876–1943) suggested the use of a *Viscum* extract as a natural anticancer drug in 1920 [1,2]. Mistletoes are semi-parasite plants, which contain chlorophyll and photosynthesize but which take water and salts from their host trees, such as apple, acer, robinia, polar, willow and oak. Unlike other plants, mistletoe does not follow a 12-month vegetation period, never touches the earth and blooms during winter. Mistletoe lectins I–III, type 2 ribosome-inactivating proteins (RIPs), which are present in commercially available mistletoe preparations, have been proved to possess anticancer activity [3,4] and are considered to be the major active components.

Previously, the antitumor effect of mistletoe lectins was thought to induce the death of tumor cells via binding of the B-chain of mistletoe lectin to the cell surface and inhibition of protein synthesis by the A-chain [5]. Later, mistletoe lectins were reported to induce apoptosis – a process generally associated with the mitochondria release of cytochrome *c* – and to induce caspase activation by a mitochondria-controlled pathway [6,7]. In addition, lectin II from the Korean mistletoe, *V. album* var. *coloratum*, was found to specifically induce apoptotic cell death in cancer cells, but not in normal lymphocytes [8,9]. A further breakthrough of mistletoe study has been reported in a recent paper, which provides direct evidence of the antitumor potential of mistletoe lectins, by inhibition of telomerase and the consequent induction of apoptosis [10].

Telomerase is a cellular holoenzyme that is responsible for the maintenance of telomeres, the protein–nucleic acid complexes at the ends of eukaryotic chromosomes that serve to maintain chromosomal stability and integrity. Telomerase maintains the telomere stability by adding hexameric (TTAGGG) repeats to the telomeric ends of the chromosomes, thus compensating for the continued erosion of telomeres, a biological process known as the end-replication problem [11,12]. Human telomerase has two major components; (1) a functional or template RNA, the human telomerase RNA (hTR), which contains an 11 base-pair sequence that serves as the template on which telomeric repeats are added to the chromosome, and (2) a human telomerase reverse transcriptase (hTERT) catalytic subunit. The ability of cells to express telomerase activity is limited by the presence or absence of hTERT because all human somatic cells constitutively contain hTR. Telomerase activity has been found in ~85–90% of all human tumors and tumor-derived cell lines but not in adjacent normal cells, which implies that telomerase inhibition could restore mortality in tumor cells. This makes telomerase an interesting target not only for cancer diagnosis but also for the development of potentially highly specific anticancer chemotherapeutics, although there have been no clinical trials of inhibitors to date [12,13].

The elegant telomere repeat amplification protocol (the TRAP assay) was used by Lyu *et al.* [10] to detect the telomerase activities of hepatocarcinoma cells, both SK-Hep-1 (*p53*-positive) and Hep 3B (*p53*-negative) cell lines. With 10 ng ml^{-1} of the Korean mistletoe lectin II at each time point (0, 6, 12 and 24 h), telomerase activity was greatly reduced in a time-dependent manner in SK-Hep-1 cells 24 h after treatment, and was gradually reduced in Hep 3B cells 48 h after treatment. This result provides fresh insights into anticancer mechanisms of the Korean mistletoe lectin II, particularly into its reported selective induction of tumor-cell apoptosis [8,9], suggesting that the mistletoe preparations employed in alternative cancer therapy could target the telomearse in tumor cells by a *p53*-independent mechanism.

The observation of different patterns of telomerase inhibition in *p53*-positive and *p53*-negative tumor cells indicates that the regulation of *p53* in mistletoe lectin-induced apoptosis could be associated with the inhibition of telomerase. At present, it is not clear whether the telomerase inhibition of mistletoe lectin results from a direct interaction with the telomerase complex or a down-regulated effect of the

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induced apoptotic pathway in the tumor cells. To demonstrate direct telomerase inhibition, it would be crucial to further test whether telomere erosion or eventual growth arrest of cells can be observed by prolonging exposure of the tumor cells to these lectins.

This study represents a major step towards understanding the therapeutic pathways of mistletoe extract treatment in complementary cancer medicine. It has been suggested that the telomerase inhibitors could be better used as adjuvant therapies, in combination with surgery, radiation treatment and chemotherapy with standard agents, because inhibition of the enzyme would require a lag phase before any detrimental effects on the tumor cells. Considering the mistletoe lectin as a telomerase inhibitor, the recommended strategy has been apparently practised for a long time in alternative cancer therapy.

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Gaps in text-based knowledge discovery for biology ▼

In the post-genomic era, the emphasis on the use of bioinformatic technology in pharmaceutical research is increasingly shifting from target identification to target ranking and due diligence [1]. New kinds of databases that contain information beyond simple sequences are needed, such as information on subcellular localization, protein interactions, gene regulation and the context of these interactions.

The forerunners of such databases include the Kyoto Encyclopedia of Genes and Genomes (KEGG, http://www.genome.ad.jp/kegg), the Database of Interacting Proteins (DIP, http://www.dip.doe-mbi.ucla.edu) and the Biomolecular Interaction Network Database (BIND, http://bind.ca). These databases are still small in size and are largely curated by hand. The development of reliable text-based knowledge discovery or literature data-mining technologies can accelerate their growth.

Many example applications of text-based knowledge discovery technologies in biology have been described [2,3]. These examples demonstrated significant progress in terms of both depth and breadth. Text-based knowledge discovery in biology has advanced from the simple recognition of terms to the extraction of interaction relationships from complex sentences. It has also broadened from the recognition of protein interactions to a range of problems, such as improving homology searches, identifying subcellular locations or recognizing themes in the literature. The techniques employed have spanned from word co-occurrence statistics, to pattern matching of linguistic constructs in limited contexts, to powerful natural language processing techniques capable of extracting relations that span multiple sentences through the use of co-reference. These results mark this as an emerging field that provides a synergistic combination of bioinformatics and natural language processing.

Despite the enormous potential for the application of text-based knowledge discovery techniques to biology, few of these techniques have made it into routine use to help manage biological information. We list below some issues that need to be addressed to accelerate the progress and acceptance of this field:

- Abstracts can generally be obtained for free, whereas full papers can generally only be obtained following payment. It is thus tempting to consider applying a literature-mining tool to abstracts. It is crucial to assess, for each type of information that is to be extracted from the literature, whether there is a significant loss if only abstracts are processed, compared with full papers. To date, it appears that no single group has investigated this issue to any great extent.
- Several papers [4,5] focused on extracting the interactions of proteins,

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