ANTICANCER PROPERTIES OF
NATURAL AND SYNTHETIC PLANT ALKALOIDS

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Natural products are of crucial importance in medicine especially in the cancer arena. Many drugs that are currently used in cancer chemotherapy originated from or were inspired by nature. The aim of our study was to analyze current data from scientific sources to determine possible mechanisms involved in anticancer properties of lamellarins and related pyrrole-derived marine alkaloids. Many pentacyclic derivatives of lamellarin D have been characterized, such as lamellarins T, U, and V from an unidentified ascidian from the Arabian Sea. In parallel, pyrrole tri-substituted open forms were also discovered.Mitochondrial metabolic pathways are potential routes to design new anti-cancer drugs but these pathways play a crucial role in normal cells, maintenance of tissue homeostasis, the regulation of the immune system, and other key functions in normal tissues.

The objective would not be to target mitochondria per se, but to induce a selective impact on cancer-specific mitochondrial abnormalities (e.g., functional alterations, impaired biogenesis). Perhaps and in this case lamellarins may become useful molecular tools.

Significant efforts have been devoted to create novel structures as well as to improve synthetic methods, leading to lamellarins and related pyrrole-derived marine alkaloids. Preliminary antiproliferative assays revealed that more than 50 lamellarins have been inventoried and numerous derivatives synthesized and tested as antiviral or anticancer agents.The lead compound in the family is lamellarin D, characterized as a potent inhibitor of both nuclear and mitochondrial topoisomerase I but also capable of directly interfering with mitochondria to trigger cancer cell death. How exactly the alkaloid perturbs the mitochondrial metabolism is still a matter of debate but a very elegant metabolic study showed that lamellarin D alters the Glu-Asp mitochondrial-cytosolic transport, in particular the malate-aspartate shuttle involving two tandem-functioning enzymes, aspartate aminotransferase and malate dehydrogenase. Treatment of MCF7 breast cancer cells with lamellarin D induces an accumulation of Glu and Asp metabolites, probably reflecting the inhibition of the malate-aspartate shuttle. One more another fascinating aspect of lamellarin D was discovered: its capacity to damage mitochondrial topoisomerase I. Lamellarin D slows down relaxation of mitochondrial topoisomerase I and strongly inhibits DNA relegation by this mitochondrial enzyme. Mitochondrial topoisomerase I is a genetically distinct mitochondria-dedicated enzyme with a crucial role in the homeostasis of mitochondrial DNA metabolism. Cells treated with lamellarin D exhibit dysfunctional mitochondrial respiration, probably as a consequence of the inhibition of mitochondrial topoisomerase I (and other direct effects). Poisoning of mitochondrial topoisomerase I triggers oxidative stress and DNA damage. A link has now been established between the molecular action of lamellarin D on mitochondrial topoisomerase I and the mitochondrial cascade of events (inhibition of respiratory chain, swelling of mitochondrial matrix, etc.). Lamellarin D is the first drug to target mitochondrial DNA by trapping mitochondrial topoisomerase I-DNA intermediates.Over the past years, the vast majority of topoisomerase I inhibitors developed as anticancer drugs have failed in the clinic, and as a result the enthusiasm for this class of cytotoxic drugs has been attenuated. The dual action of lamellarin D on nuclear and mitochondrial topoisomerase I constitutes a new angle to this field of research. These findings advocate continued development of to lamellarins and related pyrrole-derived marine alkaloids as a potential chemotherapeutic agent.