HAMLET – from serendipity to the clinic

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HAMLET (Human α-lactalbumin made lethal to tumor cells) is a protein-lipid complex composed of two major human milk constituents. It is formed by the major whey protein α-lactalbumin after partial unfolding and binding to oleic acid, the most abundant fatty acid in human milk triglycerides. HAMLET induces apoptosis in tumor cells, but leaves fully differentiated cells unaffected. The lecture will summarize our information on the molecular characteristics of the complex, the mechanisms of tumor cell death and the effects of HAMLET in patients and tumor models.

a) Structure. HAMLET is formed when α-lactalbumin unfolds by releasing the strongly bound Ca2+ ion. The unfolded protein exposes new fatty acid binding sites that fit oleic acid and is stabilized in a partially unfolded state by the lipid cofactor. The well-known function of α-lactalbumin is as a substrate specifier in lactose synthase, required for the formation of lactose and expression of milk from the mammary gland. Surprisingly, our data shows that this milk protein can gain yet another important function by undergoing this change in tertiary structure and binding the lipid cofactor. Relevance of this process for the breast-fed child is suggested by the acid pH in the stomach, which unfolds α-lactalbumin and releases oleic acid from milk triglycerides. The findings suggesting that HAMLET might be formed in vivo, and benefit the breast-fed child.

b) Mechanism of action. HAMLET kills >40 different lymphoma and carcinoma cell lines in vitro. The broad anti-tumor activity is due to a new mechanism of cell death. The dying cells show apoptosis-like features, but tumor cell death is independent of caspases and the p53 or bcl-2 genotype of the cells. HAMLET enters the cytoplasm of tumor cells, and translocates to the nuclei, where it accumulates. In the cytoplasm, HAMLET targets proteasomes and mitochondria. In the nuclei, HAMLET binds strongly to histones and disrupts the chromatin. Microarray studies have shown marked response differences between tumor cells and healthy cells, and have identified potential effector mechanisms of cell death, which are being explored. HAMLET thus activates unifying death response pathways that remain active in and shared by tumor cells.

c) Therapeutic effects. HAMLET limits the progression of human glioblastomas, bladder cancer and colon cancer in relevant animal models. Therapeutic efficacy against skin papillomas was demonstrated in a placebo-controlled study, and in patients with bladder cancer, HAMLET triggers a rapid death response, leading to cell detachment and release into the urine.

HAMLET thus shows great promise as a new anti-cancer agent.
The lack of tumor specific therapies remains a significant problem in oncology and many attempts are being made to identify new, more selective therapeutic targets. HAMLET is an interesting tool to understand conserved cell death mechanisms in tumor cells, and a new tool in tumor therapy.

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