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Meeting abstract

HAMLET, a tumoricidal molecular complex from human milk

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HAMLET (Human a-lactalbumin made lethal to tumor cells) is a protein-lipid complex that kills tumor cells and immature cells but spares healthy, differentiated cells. The complex is formed from partially unfolded a-lactalbumin and oleic acid, both of which are abundant constituents of human milk. The folding change occurs after removal of Ca^{2+} from native a-lactalbumin, and the partially unfolded protein exposes new fatty acid binding domains, which fit oleic acid. The fatty acid is needed for the tumoricidal activity of the complex, as the unfolded protein alone does not kill tumor cells.

HAMLET shows broad anti-tumor activity (>40 different lymphoma and carcinoma cell lines *in vitro*), suggesting that very basic cell death pathways are activated in tumor cells. The mechanism of cell death is complex but our studies have identified several death pathways activated by HAMLET in tumor cells, including apoptosis, anoikis and autophagy. The complex is internalized and causes rapid mitochondrial destruction. After translocation to the nuclei, HAMLET impairs the transcriptional machinery by high affinity binding to histones and nucleosomes.

We have compared the transcriptomes of carcinoma cells and healthy cells of the same tissue origin and the differences in cellular responses to HAMLET will be discussed. The resistance of healthy, differentiated cells to HAMLET is paradoxical, but healthy cells take up little HAMLET, there is no detectable translocation of HAMLET to the nuclei or evidence of DNA damage.

New tumour treatments should aim to destroy cancer cells without harming healthy tissues. Few molecules possess such selectivity, however, and due to their toxicity, current cancer therapies often cause severe side effects. *In vivo* studies have shown that HAMLET delays the progression of human brain tumor xenografts in a rat model. HAMLET was shown to efficiently remove/reduce human skin papillomas in a placebo-controlled clinical study. Finally, intra-vesical injection of HAMLET killed human bladder cancer tissue, while sparing surrounding healthy tissue. HAMLET thus shows great promise as a new anti-cancer agent. The possible usefulness in breast cancer will be discussed.