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THERAPY

HAMLET takes a leading role on the colorectal cancer stage

Prologue. "Diseases desperate grown, by desperate appliance are relieved, or not at all." An up-to-date translation of these words implies that a serious disease requires drastic treatment, which could endanger the patient, as the only alternative to abandoning treatment entirely. Now, refuting Shakespeare's axiom, HAMLET (human α-lactalbumin made lethal to tumour cells) could save lives by providing a novel, safe way of preventing and treating colon cancer.

Act I. Setting the scene. Colorectal cancer remains a major therapeutic challenge with ~600,000 deaths per year worldwide. A substantial number of colon cancers—all familial forms of colon cancer and >80% of sporadic colorectal tumours—are caused by a loss-of-function mutation in the *APC* gene. *APC* encodes a tumour suppressor that triggers β-catenin proteolytic destruction, regulating Wnt–β-catenin signalling. Now, researchers from Lund University, Sweden, have found a new actor to target this pathway.

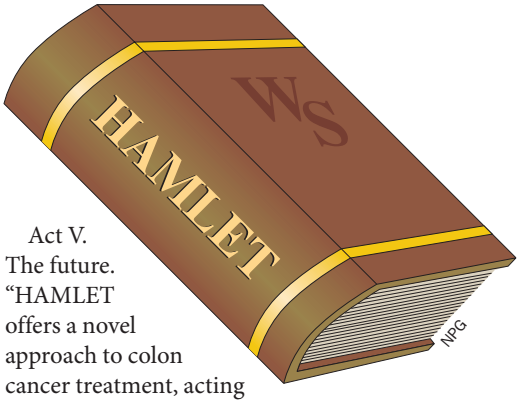
Act II. Enter HAMLET. HAMLET, the first member of a new family of naturally tumoricidal protein–lipid complexes, is formed from human milk constituents; at low pH levels (such as in the human stomach), α-lactalbumin (protein) partially unfolds, enabling oleic acid (lipid) to bind. This complex is then active and has been shown in previous research to effectively kill multiple types of tumour cell *in vitro* by a natural, non-toxic mechanism. "HAMLET was also effective and had tumour-cell selectivity in two clinical trials (for skin papillomas and bladder cancer, respectively), as well as in animal models of various human cancers," explain two authors from the study, Catharina Svanborg and Manoj Puthia. Here, the investigators aimed to determine if this agent could be given perorally to effectively treat and prevent colon cancer in $APC^{Min/+}$ male mice—a model of human familial and sporadic colorectal cancer, which develop multiple intestinal polyps.

Act III. HAMLET takes the lead. Peroral HAMLET administration reduced intestinal tumour burden (number of polyps reduced by 58%, $P<0.0001$) and increased survival ($P=0.01$) in $APC^{Min/+}$ mice compared with those that were sham fed. Tissue analysis revealed that HAMLET accumulated in intestinal tumours, but not in healthy tissue. Furthermore, HAMLET reduced β-catenin expression and that of other tumour markers in the mouse tissue, inhibiting tumour proliferation.

The researchers also defined the mechanisms of this agent using the human colon cancer cell line DLD1 (which has a homozygous mutation that inactivates *APC*) and found that HAMLET acts through two routes. First, it suppresses β-catenin-dependent transcription. Second, via an ion-channel-dependent mechanism, HAMLET modulates β-catenin integrity by promoting its proteolytic cleavage.

Surprisingly, providing HAMLET (10 mg per mouse daily) as a prophylactic agent in drinking water—from the time of mouse weaning until 15 weeks of age—also substantially reduced tumour development, showing the potential of this agent in cancer prevention.

Act IV. Understanding HAMLET. The researchers then went back to mice and characterized the whole-genome transcriptional profile of HAMLET-treated mice and compared it with sham-fed mice. HAMLET significantly decreased expression of genes in the β-catenin signalling pathway ($P=0.002$) and those involved in DNA replication ($P=0.002$). By contrast, HAMLET triggered upregulation of genes required for aerobic glycolysis. Moreover, these changes in gene expression, induced by peroral administration of HAMLET, seem to be long-lasting.



Act V. The future. "HAMLET offers a novel approach to colon cancer treatment, acting by removing established tumour cells and preventing tumour development in the intestinal mucosa," state Svanborg and Puthia. Treatments for colon cancer that have high levels of specificity for tumour tissue are required. The authors report that "there was no evidence of toxicity or inflammatory changes in healthy tissue, suggesting that side effects to peroral HAMLET may be limited." Professor Sankar Nath Sanyal and Vivek Vaish, experts in the field, note that "further work is needed to characterize the effect of HAMLET in female mice and humans."

HAMLET has the potential to be a new approach for treatment in families with hereditary colon cancer, although much more research is needed before it can be considered for clinical practice. The researchers advocate for the clinical testing of peroral HAMLET administration, especially in families with mutations in *APC*. Sanyal and Vaish caution, however, that "as HAMLET is formed from human milk protein, it could face ethical problems in vegans that could affect its global acceptance; perhaps an *in vitro* system could be used for HAMLET generation that would meet ethical approval."

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Original article Puthia, M. *et al.* Prevention and treatment of colon cancer by peroral administration of HAMLET (human α-lactalbumin made lethal to tumour cells). *Gut* doi.10.1136/gutjnl-2012-303715