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Conserved features of cancer cells definetheirsensitivityto HAMLET-induceddeath; c-Myc and glycolysis

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HAMLET is the firstmember of a new family of tumoricidal protein–lipid complexesthatkill cancer cells broadly, whilesparinghealthy, differentiated cells. Many and diverse tumor cell typesare sensitive to the lethaleffect, suggestingthat HAMLET identifies and activatesconserveddeathpathways in cancer cells. Here, weinvestigated the molecular basis for the difference in sensitivitybetween cancer cells and healthy cells. Using a combination of small-hairpin RNA (shRNA) inhibition, proteomic and metabolomictechnology, weidentified the c-Myc oncogene as oneessential determinant of HAMLET sensitivity. Increased c-Myc expression levelspromotedsensitivityto HAMLET and shRNA knockdown of c-Myc suppressed the lethalresponse, suggestingthatoncogenic transformation with c-Myc creates a HAMLET-sensitive phenotype. Furthermore, HAMLET sensitivitywasmodified by the glycolyticstate of tumor cells. Glucose deprivation sensitizedtumor cells to HAMLET-induced cell death and in the shRNA screen, hexokinase 1 (HK1), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1 and hypoxia-induciblefactor 1α modified HAMLET sensitivity. HK1 wasshownto bind HAMLET in a protein arraycontaining ~8000 targets, and HK activitydecreasedwithin 15 min of HAMLET treatment, beforemorphologicalsigns of tumor cell death. In parallel, HAMLET triggered rapid metabolic paralysis in carcinoma cells. Tumor cells werealsoshowntocontainlargeamounts of oleicacid and itsderivativesalreadyafter 15 min. The resultsidentify HAMLET as a novel anti-cancer agent thatkillstumor cells by exploitingunifying features of cancer cells such as oncogeneaddiction or the Warburg effect.

Biography

Petter Storm is a PhD student studying the effects of HAMLET on tumor cell metabolism usingvariousomicstechniquesincludingmicroarrays and massspectrometry/metabolomics.