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**Author:** Lanz, Henriette Leonore  
**Title:** Cancer-related targets sensed by apoptin  
**Issue Date:** 2012-10-24
Chapter 1

Thesis Outline
Cancer is one of the most life-threatening diseases worldwide. Many anticancer treatments fail because they are not efficient or reveal too high side effects. Cancer cells develop due to unbalances in cell proliferation, cell cycle regulation and/or cell death. Identification of these aberrant molecular processes will reveal the essential processes leading to tumor formation and allows the generation of potential novel anticancer therapies. Interestingly, a group of viral and cellular proteins has been identified that harbors tumor-selective apoptosis activity. They are named Proteins Killing Tumor Cells (PKTCs).

The aim of this thesis is to search for cellular processes sensed by the original PKTC, apoptin, which distinguish tumor cells from normal cells. Various tumor-related processes that are of importance for the tumor-selective activation of apoptin are reported. They range from proteasome activity and mitotic regulation to protein kinase and phosphatase action. Chapter 2 introduces our current knowledge on the hallmarks of cancer as well as an overview of the growing family of PKTCs. We argue that PKTCs might recognize the transformed state of a tumor cell via detection of one or more hallmarks of cancer. This biological capability of the various PKTCs might be at the base of the switch from cell growth to cell death.

Chapter 3 describes two independent lines of research revealing that deregulation of the normal function of protein phosphatase 2A (PP2A) is a sufficient step in activating apoptin-induced cell death. Derailed PP2A activity is increasingly linked to oncogenic transformation and especially its involvement during mitosis might be relevant for activation of apoptin. Chapter 4 shows that in cancer cells apoptin is insensitive to proteasomal degradation, a process that still takes place in normal cells. This cancer-related loss of proteasomal susceptibility appears to be specific for apoptin as it is not found for the tumor suppressor protein p53. In Chapter 5 the biochemical characterization of the tumor-selective apoptin kinase activity implies the existence in tumor cells of a constitutive endogenous kinase that is present in both the nuclear and cytoplasmic compartments. Weak inaccuracies in mitotic checkpoints are linked to aneuploidy and genetic instability, which are essential for cancer development. In Chapter 6 it is shown that apoptin likely senses these inaccuracies during cell division and disrupts a cancerous process by inducing mitotic catastrophe and cell death.
All data obtained in this study are discussed in Chapter 7. The systematic analysis of both apoptin and other PKTCs reflects various differences between normal and tumor cells. Linking-up the various hallmarks of cancer with the aberrant processes sensed by apoptin and other PKTCs in cancer cells will hopefully contribute to a better understanding of tumor development as well as the generation of efficient and safe anticancer therapies.