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## **Apoptin : oncogenic transformation & tumor-selective apoptosis**

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# Chapter 1

## Thesis outline





Cancer is one of the leading causes of death worldwide. Treatment is hampered by an incomplete understanding of the mechanisms underlying carcinogenesis and, consequently, by the absence of therapies to specifically eradicate cancer cells without harming normal, healthy cells. Intriguingly, the avian-virus derived protein apoptin was found to selectively induce apoptosis in transformed and tumor cells, heralding the advent of a new era in cancer treatment.

The aim of this thesis was to discover the path followed by apoptin to distinguish between normal and cancer cells, and selectively kill the latter, in order to a) get to the root of the problem that is cancer, and b) provide the knowledge which is necessary to design novel, more selective, more effective, safe anti-tumor therapies. To this end, we identified a number of apoptin-interacting proteins, and studied their roles in tumor-selective apoptin-induced apoptosis.

**Chapter 2** summarizes current knowledge on normal regulation of cellular proliferation and the derailments thereof leading to malignant transformation, as well as novel strategies in cancer treatment. Since the discovery of apoptin, a number of other cellular and viral proteins have also been shown to induce tumor-selective cytotoxicity; in **chapter 3**, an overview is presented of apoptin, and these other proteins killing tumor cells (PKTC).

**Chapter 4** introduces a novel apoptin-interacting protein, FAM96B. Functional analysis implicates FAM96B in the regulation of the cell cycle, including the processes of sensing DNA damage and establishing sister chromatid cohesion. In **chapter 5**, apoptin's activities in the tumor cell nucleus are investigated, and chromatin-bound apoptin is found to associate with various nucleolar proteins that are involved in the regulation of ribosome biogenesis, the DNA damage response and cell cycle regulation. The data suggest that apoptin coordinates tumor-selective apoptosis at least partially from

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within the nucleolus. **Chapter 6** analyzes the roles of the apoptin-interacting breast cancer associated protein BCA3 and that of the major tumor suppressor protein phosphatase 2A (PP2A) in the phosphorylation of apoptin.

Finally, the data are compiled in **chapter 7**, where novel insights into the cancer blueprint, the path taken by apoptin to sense it and effectuate cancer cell death, as well as the relevance for the design of future cancer therapies are discussed.



