



Samenvatting van het proefschrift Frederik J.H. Hoogwater

"Death Receptors and Colorectal Liver Metastases CD95/FAS as a pro-tumorigenic receptor"

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Death receptors are a unique class of cell-surface receptors which are best known for their ability to induce apoptosis upon binding their respective ligands. Among the best studied death receptors are CD95 and TNF-related apoptosis-inducing ligand (TRAIL) receptors. Apoptosis has long been thought to be the primary outcome of death receptor activation and this has led to the development of death receptor-stimulating agents as anti-tumor therapeutics. However, more recent data suggest that CD95 and TRAIL receptors can also act in a pro-tumorigenic fashion by stimulating tumor cell proliferation, survival and invasion. Identification of the factors and molecular mechanisms that determine these various outcomes in death receptor signaling may lead to new therapeutic strategies targeting death receptors in (surgical) cancer therapy.

Colorectal carcinoma (CRC) poses a serious threat to public health as it is one of the most common malignancies in the Western world with over one million new cases each year. The KRAS oncogene is one of the most frequently mutated oncogenes in human cancer with a prevalence of approximately 35-45% in colorectal cancer. It is known that a mutation in the KRAS oncogene contributes to the formation of colorectal tumors, however the role of KRAS in metastasis formation is less known. The presence of liver metastases is the major determinant of survival in patients with colorectal cancer. Approximately 25% of the patients with colorectal cancer already have liver metastases at diagnosis. Only a subgroup of patients with these synchronous colorectal liver metastases benefits from liver surgery. Currently, there are no reliable tools to identify such patients.

This thesis describes the role of death receptors in the development and outgrowth of colorectal liver metastases. The key findings in this thesis are that (1) death receptors can be switched into metastasis-promoting receptors

by the single common oncogene K-Ras and this is important for survival of metastatic tumor cells and their outgrowth in the liver. An immediate implication of the finding that oncogenic K-Ras alters CD95 signaling output is that therapeutic targeting of death receptors by CD95/TRAIL could have adverse effects on disease progression by promoting invasion and dissemination of micrometastases instead of clearing them. This is a major concern, at least when considering such compounds in the treatment of tumors harboring activating mutations in the K-Ras gene. In addition, (2) CD95 plays an important role in surgery-stimulated outgrowth of colorectal micrometastases in the liver. Therapy antagonizing death receptor signaling could therefore be of interest in the reduction of accelerated outgrowth. Furthermore, (3) preliminary results indicate that circulating CD95L might be usefull as a prognostic factor contributing to the selection of patients for liver surgery. ◀