# ABSTRACT

Cells continuously experience various forms of exogenous and endogenous stress stimuli. Cellular senescence, a state of permanent cell-cycle arrest, is a physiological response that prevents proliferation of damaged cells. It is an important tumor suppressive mechanism, because evading senescence in pre-malignant tumors leads to cancer progression. However, in the long term, senescence can also contribute to tissue aging. Our understanding of the causes and consequences of senescence can provide important insights into processes such as cancer development and aging and may help us design new therapeutic approaches.

In the first part of my thesis, we investigated a relationship between two known tumor suppressor pathways, the DNA Damage Response (DDR) and the Alternative Reading Frame (ARF), in response to oncogenic insults. By using several mouse models, human clinical samples and cell culture models we showed, that ARF activation occurs at a later stage of tumor progression than activation of the DDR. Moreover, ARF activation requires a higher level (threshold) of oncogenic stress than DDR. Therefore, we proposed, that ARF represents a delayed and complementary barrier to tumor progression.

Senescence-associated heterochromatin foci (SAHF) formation, representing pronounced changes in chromatin, has been previously established as a mechanism contributing to maintenance of the senescence phenotype in oncogene-induced and replicative senescence. In the second part of this thesis, we thus analyzed to what extent does SAHF formation represent a universal feature of the senescence program. We concluded that SAHF are dispensable for some types of cellular senescence and occur in an insult- and cell type-dependent manner.

Next, we investigated cytokine expression and signaling in cellular senescence evoked in tumor cells by diverse genotoxic drugs. We found, that senescent cells secrete a broad spectrum of cytokines/chemokines and persistently activate the JAK/STAT signaling pathway. Our data thus suggest autocrine/paracrine effects of cytokine signaling on senescence-associated gene expression, a phenomenon that is likely highly relevant to the outcome of cancer chemotherapy.

Finally, we provide novel insights into our current knowledge about regulation of the tumor suppressor PML in drug-induced senescence. According to our data, transcriptional upregulation of PML is independent of the p53 tumor suppressor pathway and is controlled by JAK/STAT signaling, via binding of the transcription factor STAT to the ISRE element in the PML gene promoter.

**Keywords:** ARF, cytokine, DNA damage response, oncogene, PML, SAHF, senescence