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Summary

Cancer is caused by the accumulation of genetic alterations in cells. These mutations can result in unlimited cell division and continued survival, both contributing to the formation of a primary tumor. When tumor cells are able to invade, they can grow out to produce secondary tumors at distant sites. This process, called metastasis, comprises multiple steps in which tumor cells have to overcome numerous barriers in order to fully grow out into a secondary tumor. One barrier is formed by the basement membrane, lining epithelial cell layers. A key process involved in overcoming this barrier is epithelial-mesenchymal transition (EMT). EMT is a process in which epithelial cells acquire more migratory and invasive properties reminiscent of those of mesenchymal cells. By undergoing EMT, tumor cells can cross the basement membrane and invade surrounding tissues and the bloodstream. Another barrier that tumor cells have to overcome is anoikis. Non-tumorigenic epithelial cells commonly undergo anoikis (=apoptosis caused by loss of cell adhesion) when exposed to unfamiliar environments, like the bloodstream. Tumor cells that have metastatic capabilities have to overcome this barrier and are anoikis resistant. In chapter 1, we describe the regulation of these two processes, EMT and anoikis resistance, and their involvement in metastasis.

Previously, in a genome-wide screen to identify novel metastasis genes based on anoikis suppression, we identified the neurotrophic receptor kinase TrkB. TrkB induces anoikis resistance and in line with the hypothesis that anoikis can be used as a readout for metastasis, cells expressing active TrkB can form metastatic tumors in mice. Interestingly, TrkB may be overexpressed in several cancers. In this thesis, we aimed to unravel the mechanism of TrkB-induced metastasis. In chapter 2, we show that TrkB promotes metastasis by inducing EMT in rat epithelial cells. The main regulator of EMT, E-cadherin, was important for TrkB-induced EMT and anoikis resistance. Furthermore, we show that TrkB downregulates E-cadherin via the MAPK pathway. Searching for more downstream factors revealed that three transcription factors, Twist, Snail and Zeb1, key EMT regulators that can suppress E-cadherin transcription, are critical for TrkB-induced EMT, anoikis resistance and metastasis. Furthermore, we show that TrkB induces metastasis via a MAPK-Twist-Snail-Zeb1-E-cadherin axis, with Twist and Snail acting upstream of Zeb1 (chapters 2 & 3).

Another process important for cancer progression is senescence. Senescent cells retain metabolic activity, but fail to proliferate. In contrast to the cancer-promoting role of EMT, senescence acts as a failsafe program, inhibiting cancer progression. Senescence can be induced by a variety of stress factors, including oncogenes. Oncogene-induced senescence (OIS), as this phenomenon is called, is characterized by mostly a flattened cell morphology, upregulation of the tumor suppressor $p16^{INK4A}$ and increased activity of senescence-associated β galactosidase. Recently, others have found a link between two processes, EMT and senescence. Whereas

overexpression of an oncogene leads to senescence, overexpression of both the oncogene and Twist leads to senescence bypass and EMT. In chapter 4, we describe this link and discuss the role of multiple factors playing dominant role in both processes.

We were intrigued by the link between EMT and senescence and set out to find out the differences in the pathways between these two processes. In chapter 5, we show that two oncogenes, Ras and Raf, can induce EMT in epithelial cells and senescence in fibroblasts. Whereas the MAPK pathway was activated in both cell systems, the difference in response was characterized by upregulation of Twist and Zeb1 upon EMT induction, and their downregulation upon senescence induction. Although the reason for the difference is not yet completely understood, as the used cell lines harbor different genetic alterations, this implies that Twist and Zeb1 have a double impact on cancer progression: by promoting EMT and inhibiting senescence.

In chapter 6, we show that a Twist-Snail-Zeb1 axis is critical for TrkB functions. Although transcription factors are not easy to target, our evidence shows that blocking one of these transcription factors is sufficient to block metastasis, at least in our experimental systems. Furthermore, we show Twist and Zeb1 are regulated differently upon EMT and senescence induction. We believe that studies like those described in this thesis not only increase our understanding of the fundamental processes underlying cancer, but may eventually also point us to the development of novel cancer targets.