

TGF β signaling in cancer progression Liu, S.

Citation

Liu, S. (2020, May 28). $TGF\beta$ signaling in cancer progression. Retrieved from https://hdl.handle.net/1887/92349

Version:	Publisher's Version
License:	<u>Licence agreement concerning inclusion of doctoral thesis in the</u> <u>Institutional Repository of the University of Leiden</u>
Downloaded from:	https://hdl.handle.net/1887/92349

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <u>http://hdl.handle.net/1887/92349</u> holds various files of this Leiden University dissertation.

Author: Liu, S. **Title:** TGFβ signaling in cancer progression **Issue Date:** 2020-05-28

Appendix

English Summary Nederlandse Samenvatting Abbreviations List of Publications Curriculum Vitae Acknowledgements

English Summary

In cancer cells, aberrant TGF β signaling can lead to loss of growth inhibition and increase in epithelial to mesenchymal transition (EMT), migration and metastasis. Targeting TGF β is currently being explored as a potential therapy against certain invasive and metastatic cancer types. However, current drugs tested in clinical trials inhibit all TGF β (good and bad) responses and suffer from unwanted side effects. The ubiquitin system is emerging as an important post-translational regulatory mechanism for the TGF β pathway. Targeting of E3 ubiquitin ligases and deubiquitinating enzymes that are highly active in aggressive cancer and promote tumor promoting functions of TGF β might offer new therapeutic opportunities. In **Chapter 2**, we summarized the role of DUBs that contribute to the regulation of TGF β signaling in cancer, and discussed the DUB inhibitors in preclinical trials for cancer treatment.

Metastasis is the underlying cause of death for majority of cancer patients. Numerous rodent models are available for investigating cancer metastasis, but to enable a quick assessment of the potential effect of (epi)genetic changes or pharmacological compounds we need more efficient, reliable, low-cost *in vivo* models. In **Chapter 3**, we describe the possibility of using zebrafish xenograft models to study the metastasis progression of breast cancer cells.

Among all the breast cancer cases, TNBC remains the most challenging subtype to treat. To discovery new targets, in **Chapter 4**, we profiled global DUB activities in breast cancer cell lines and tumor samples, and identified UCHL1 as a candidate oncoprotein. Mechanistically, we found that UCHL1 facilitates TGF β signaling-induced metastasis by protecting T β RI and SMAD2 from ubiquitination. We further found a UCHL1 covalent activity inhibitor 6RK73 that specifically inhibited UCHL1 activity and blocked metastasis in TNBC. Significantly, we observed that TNBC patient sera contained high UCHL1 levels, which may represent a potential blood-based biomarker for diagnosis of metastatic TNBC.

In order to better study the activity of UCHL1 *in vivo*, we developed a cell permeable fluorescent activity-based probe for UCHL1 in **Chapter 5**. This probe 8RK59 binds to the active-site cysteine residue of UCHL1 in an activity-dependent manner and irreversibly. Its application was demonstrated by labelling UCHL1 activity *in vitro* and in cells. Furthermore, we applied the probe in monitoring UCHL1 activity in zebrafish embryos during development. This small molecule probe may have potential other targets, such as PARK7. Additional studies are needed to increase the selectivity of the probe.

For metastatic melanoma, the median survival of BRAF(V600E) patients has improved by treatment with BRAF inhibitors, but drug resistance remains a problem for a significant fraction (about 40%) of melanoma patients. Recent studies showed that TGF β signaling is increased in BRAF inhibitor resistance melanoma. In **Chapter 6**, we investigated the potential for targeting TGF β signaling in the treatment of drug resistance melanoma. We found that pharmacologic or genetic inhibition of T β RI blocked BRAF mutant melanoma cells metastasis in xenograft zebrafish model.

In summary, this thesis focused on the understanding the underlying mechanisms driving TNBC metastatic progression. We established DUB activity profiling methods and identified UCHL1 as a candidate oncoprotein that promotes TGF β -induced breast cancer metastasis. Importantly, we found UCHL1 activity inhibitor as a potential drug for TNBC therapy and

developed UCHL1 activity-based probe. For vemurafenib-resistance melanoma, we provided insights that targeting TGF β signaling may help to overcome drug resistant phenotype.

I hope that all the fundamental and translational studies in my PhD thesis may contribute to increased survival and improved quality of life for cancer patients.