Advancing precision oncology: insights from C-terminal FGFR2/3 truncations and MYC-driven mTOR inhibitor resistance

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APPENDICES

ENGLISH SUMMARY

Precision oncology seeks to deliver the right treatment to the right patient at the right time by integrating the molecular characteristics of individual tumors with patient-specific factors. Despite major advances in genomic profiling and the development of targeted therapies, significant challenges remain. One key challenge is the accurate distinction between genomic alterations that function as oncogenic drivers—shaping tumor behavior and therapeutic response—and those that represent passenger events with little or no functional relevance to disease progression or treatment outcome. Another important challenge is to anticipate resistance mechanisms that may pre-exist or emerge during treatment and influence therapeutic response. This thesis contributes to addressing these challenges by investigating the functional and clinical relevance of genomic alterations in the fibroblast growth factor receptor (FGFR) family—particularly in FGFR2 and FGFR3—and by elucidating mechanisms of therapeutic resistance within the PI3K–AKT–mTOR signaling pathway.

The first part of this thesis focuses on *FGFR* alterations, which are increasingly recognized as important therapeutic targets across multiple cancer types. While *FGFR* amplifications and common hotspot mutations are relatively well characterized, another important class remains underexplored: *FGFR* rearrangements, including both canonical in-frame fusions and complex noncanonical variants. In **Chapter 2**, we review the biological and clinical relevance of both canonical FGFR fusions and non-canonical structural variants, with a particular focus on their oncogenic mechanisms, biomarker potential, and therapeutic implications. A key concept discussed in this chapter is the critical role of C-terminal exon 18 (E18) truncations in *FGFR2* and *FGFR3* as drivers of oncogenic activation.

As investigated in **Chapter 3**, C-terminal truncation of *FGFR2* constitutes a potent oncogenic event. Using functional genomic approaches, *in vivo* tumor modeling, and analysis of human oncogenomic datasets, we show that these truncations arise through diverse genomic mechanisms—including rearrangements, partial amplifications, and truncating mutations—all converging on the production of oncogenic *FGFR2* transcripts lacking the E18-encoded C-terminal tail. In contrast, amplification of full-length *FGFR2* alone is insufficient to drive tumorigenesis without additional cooperating alterations. Importantly, the presence of E18-truncated *FGFR2* predicts sensitivity to FGFR-targeted therapies, highlighting its potential as a clinically actionable biomarker. The mechanistic basis of this oncogenic activation is elucidated in **Chapter 4**, where we identify a previously unrecognized regulatory function of the FGFR2 C-terminal tail. Specifically, we uncover a critical motif that mediates autoinhibition of the kinase domain under physiological conditions. Loss or disruption of this motif abolishes this regulatory constraint, resulting in constitutive activation of FGFR2 and downstream signaling pathways, including PI3K–

AKT–mTOR and STAT3. These findings provide a structural explanation for how C-terminal truncations drive oncogenic signaling and suggest potential therapeutic strategies, including combined inhibition of FGFR2 and downstream pathways to overcome resistance to FGFR-targeted therapies.

In **Chapter 5**, we examine whether similar mechanisms apply to FGFR3 and reveal important functional differences between these closely related receptors. In contrast to FGFR2, we show that C-terminal truncation alone is insufficient for full oncogenic activation of FGFR3 and that fusion to a partner gene providing a dimerization domain is required. We further validate the oncogenic potential of several previously uncharacterized C-terminally truncated *FGFR3* fusions involving partner genes containing dimerization domains. These alterations confer resistance to certain receptor tyrosine kinase inhibitors, yet remain sensitive to pharmacological FGFR inhibition. Together, these findings refine our understanding of FGFR3-driven cancers and have important implications for the future interpretation of genomic alterations in clinical settings.

The second part of this thesis focuses on mechanisms of resistance to targeted therapies within the PI3K–AKT–mTOR pathway. In **Chapter 6**, we investigate resistance to mTOR inhibitors in breast cancer using multi-omic profiling of treatment-naïve and resistant tumor models. We identify activation of the MYC oncogene as a key driver of resistance, demonstrating that MYC sustains protein synthesis and tumor growth despite mTOR inhibition. Importantly, resistant tumors remain dependent on MYC activity, and combined inhibition of mTOR and MYC restores treatment sensitivity. These findings are supported by clinical data showing that MYC activation is associated with poor response to the mTOR inhibitor everolimus in patients with metastatic breast cancer. Together, these results establish MYC as both a mediator of resistance and a potential biomarker for patient stratification, suggesting that combination therapeutic strategies may improve clinical outcomes.

Finally, in **Chapter 7**, the main findings of this thesis are discussed in a broader context, highlighting their implications for precision oncology, remaining challenges, and directions for future research.

In summary, this thesis provides new insights into the molecular mechanisms underlying FGFR-driven oncogenesis and resistance to mTOR inhibition. By identifying functionally relevant genomic alterations and uncovering key regulatory processes, this work contributes to a more precise definition of actionable cancer drivers and resistance mechanisms, while highlighting new opportunities for therapeutic intervention. Ultimately, these findings may improve patient selection for targeted therapies and inform strategies to overcome drug resistance, thereby advancing the goals of precision oncology.