Mutation-driven modulation of GPCR pharmacology in cancer: insights from adenosine and serotonin receptors

Feng, C.

Stellingen

Behorende bij het proefschrift

Mutation-Driven Modulation of GPCR Pharmacology in Cancer:

Insights from Adenosine and Serotonin Receptors

1. Assessing GPCR variants should be an important step in the design and interpretation of clinical trial studies, as making these pharmacogenomics considerations at a much earlier stage can minimize adverse effects. (*Hauser A.S., et al. Cell.* 2018;172(1-2), 41-54)
2. The comprehensive mapping of the immune GPCRome in both healthy and tumor-infiltrating immune cells will pave the way for new therapeutic strategies with the goal of using GPCRs to treat a wide spectrum of diseases, from autoimmune disorders to cancer. (*Stagg J., Gutkind J.S. Annu Rev Pharmacol Toxicol.* 2025; 65(1), 315-331)
3. Strikingly, all the GPCR drugs that have been reported to significantly hamper cancer cell line growth in a recent systematic screen indeed target receptors of axes significantly correlated with patient survival, with a particular emphasis on receptors for neurotransmitters and adenosine. (*Arora C., et al. Cell Genom.* 2024; 4(5), 100557)
4. The experimental characterization of mutant phenotypes in cells remains essential to distinguish mutations that are causal for observed clinical phenotypes versus those observed in the background of other biological processes. (*Lyczek A., et al. Proc Natl Acad Sci U S A.* 2021; 118(46), 2111451118)
5. Understanding the mutation-driven modulation of GPCR function is not only critical for dissecting cancer signaling networks, but also for refining therapeutic strategies that leverage GPCRs as drug targets. (*this thesis, chapter 1*)
6. The absence of clearly defined structural hotspot mutations in GPCRs imply that targeting GPCRs in cancer is more challenging than the well-studied approaches targeting kinases. (*this thesis, chapter 2*)
7. For somatic mutations of cancer drug targets which lead to poor response and resistance to current treatment, exploiting drug binding kinetics holds great promises in personalized drug use. (*this thesis, chapter 4*)
8. Cancer-associated GPCR mutations alter receptor pharmacology in a context-dependent manner, with changes in ligand binding, receptor conformation, downstream coupling and receptor occupancy all contributing to their effects. (*this thesis, chapter 7*)
9. To know what you know and to know what you don't know, that is true wisdom. (adapted from *Confucius*)
10. Science is the acceptance of what works and the rejection of what does not. That needs more courage than we might think. (*Jacob Bronowski*)
11. To cure sometimes, To relieve often, To comfort always. (*E. L. Trudeau*)

Chenlin Feng

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