This study aims to delve into the dysregulation of G-protein-coupled receptor (GPCR) ligand signaling systems within cancer transcriptomics datasets. The primary motivation is to uncover novel therapeutic prospects in oncology through a meticulous examination of GPCR signaling networks. Specifically, the study endeavors to elucidate the rewiring of GPCR axes and shed light on the distinct regulation of GPCRs and their upstream partners across diverse cancer subtypes.

Methods

The study utilizes a comprehensive methodology to construct an innovative interaction network encompassing receptors, ligands, and their biosynthetic enzymes. Through rigorous analysis, the varied regulation of multiple GPCR axes across different cancer subtypes is delineated. Additionally, biosynthetic pathway enrichment, derived from enzyme expression, is leveraged to discern pathway activity signatures from metabolomics datasets. This approach furnishes surrogate information elucidating how GPCRs respond to organic ligands. Furthermore, the association of GPCR signaling components with patient survival is explored, underscoring the collaborative role of GPCR networks in modulating cancer phenotypes. Large-scale cancer cell drug screens are also employed to identify potential GPCR axes, with recognized GPCRs being targets of multiple drugs exhibiting anti-growth effects.

Results

The investigation unveils a nuanced interplay of GPCR signaling axes in cancer, highlighting the distinct regulation of GPCRs and their upstream partners across diverse cancer subtypes. Significantly, several GPCR signaling components exhibit associations with patient survival in a cancer type-specific manner, emphasizing the synergistic role of GPCR networks in modulating cancer phenotypes. Notably, actionable GPCR axes are identified across various cancer molecular subtypes, including muscarinic, adenosine, 5-hydroxytryptamine, and chemokine receptors. These GPCRs, recognized as targets for multiple growth-inhibitory drugs, are experimentally validated. The results of the study have been disseminated through a web app, enhancing accessibility for further research in the field (gpcrcanceraxes.bioinfolab.sns.it).

Info

The manuscript related to this work has been accepted to be published in Cell Genomics May 2024 issue

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Unveiling Cancer’s Molecular Conversations: Our latest research delves deep into the intricate world of cancer cell communication. By studying how G-protein-coupled receptor (GPCR) signaling systems go awry in cancer, we’re uncovering potential new avenues for treatment. Using cutting-edge methods, we’ve mapped out the complex networks of receptors, ligands, and enzymes involved. Our findings shed light on how different types of cancer hijack these signaling pathways, influencing tumor growth and patient outcomes. Excitingly, we’ve identified specific GPCR targets that could be key to developing personalized cancer therapies.

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