COMMENTARY

Using peptides to investigate GPCR dimerization

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INTRODUCTION

G Protein-Coupled Receptors (GPCRs) are the most common and extensively studied class of membrane proteins, as well as the most common and extensively studied pharmacological target. Numerous studies over the last decade have confirmed that GPCRs not only exist and function in their monomeric form, but can also form dimers or higher order oligomers with other GPCRs and other receptor classes. GPCR oligomers have grown in popularity due to their ability to modulate the pharmacological responses of receptors, which could play important functional roles in diseases such as cancer and a variety of neurological and neuropsychiatric disorders.

Despite mounting evidence in the field of GPCR oligomerisation, a lack of structural information, as well as difficulties in targeting the 'undruggable' Protein-Protein Interactions (PPIs) involved in these complexes, has posed challenges. Targeting PPIs has received a lot of attention outside of the field of GPCRs, with a variety of techniques being investigated, ranging from small-molecule inhibitors to disrupting peptides. In this review, we will show several physiologically relevant GPCR dimers and discuss a variety of strategies and techniques for targeting these complexes, as well as provide ideas for future research.

G Protein-Coupled Receptors (GPCRs) are involved in a variety of physiological and signaling processes, with approximately 30% of currently marketed drugs targeting them, highlighting their pharmacological importance. GPCRs are classified into six classes based on functional similarity and sequence homology: Class A (Rhodopsin-like receptors), Class B (Secretin family), Class C (Metabotropic Glutamate receptors), Class D (Fungal Mating Pheromone receptors), Class E (Cyclic Adenosine Monophosphate receptors), and Class F (Cyclic Adenosine Monophosphate receptors) (Frizzled and Smoothened receptors). Because the majority of marketed therapeutics targets the Rhodopsin-like family, this class of GPCRs will be the focus of this review, with the recognition that parallels can be drawn between classes. The traditional view of GPCRs as monomeric entities has been challenged by evidence that they can also form oligomeric complexes such as homo and heterodimers. It has been demonstrated that the formation of oligomers can affect receptor trafficking, signaling, ligand binding, and overall function, allowing these high order complexes to be studied further.

Protein-Protein Interactions (PPIs) are a growing and evolving area of interest in the field of drug discovery. When two or more protein molecules come together as a result of a biochemical incident, interactions such as hydrogen bonding, electrostatic forces, or hydrophobic interactions occur; these interactions are referred to as PPIs.

PPIs are the protagonists in a wide range of biological processes and play an important role in the cellular systems of living organisms. When inside a living organism, 80% of proteins are known to function in complexes, revealing only a small number of proteins that can function alone. PPIs have some essential properties that have previously been highlighted by Phizicky and Fields, such as: 1) the ability to deactivate proteins, 2) the ability to create new binding sites for small effector molecules, 3) the ability to permit substrate channeling, 4) the ability to adapt kinetic characteristics of enzymes, 5) the ability to be regularly involved in downstream or upstream signaling, and 6) the ability to react with alternative binding partners, thereby changing the specificity of proteins for the substrates.

PPIs regulate essential biological processes such as cell proliferation, apoptosis, protein transcription and translation, and with approximately 130,000 reported binary PPIs being responsible for the progression of diseases such as cancer and cardiovascular disease, PPIs are an appealing pharmacological target. Modulation of these PPIs involved in such pathologies is being targeted with drugs that have made it to the clinic, many of which are used to treat cancer. Checkpoint inhibitors, PD-1/PD-L1 inhibitors, and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are some examples. Individual proteins are thought to have up to five interacting partners on average, but when acting as hubs, these interacting partners can increase to over a hundred. As a result, larger drugs and biologics have been investigated in an attempt to overcome some of the challenges that small-molecule ligands face when attempting to target these expansive and dynamic surfaces. This presents its own set of challenges, such as biologics not being orally available like small-molecule drugs, making them more difficult to administer and thus more expensive overall. However, research over the last 20 years has made it possible to target such surfaces, with many of these targets being small molecules. Because the interfaces of PPIs are less conserved than those of active sites on protein surfaces, drugs inhibiting PPIs are expected to be selective. Oligomeric complexes are commonly studied as homodimers (composed of two of the same protein molecules) and

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heterodimers (referring to two differing protein molecules forming a complex). GPCR dimerization has emerged as an emerging topic in recent years as evidence suggests that they do not function solely as monomeric entities. The growing interest in GPCR oligomerisation has resulted in the prevalence of high-resolution structural information, which aids in drug development. These findings have been aided by techniques such as Bioluminescence Energy Transfer (BRET), Fluorescence Resonance Energy Transfer (FRET), Proximity Ligation Assays (PLAs), Homogenous Time-Resolved Fluorescence Energy Transfer (HTRF), atomic microscopy, and molecular modelling. In addition to homodimerization, GPCRs can form complexes with other types of receptors, such as the receptor tyrosine-protein kinase family. Heterodimeric complexes have pharmacological functions that differ from homodimers, resulting in unique properties that make them an emerging pharmacological target for a variety of disease states. PPIs are arguably one of the most difficult therapeutic interactions to target. The size and nature of these interactions have raised a slew of issues regarding how these surfaces can be targeted. Over the last decade, there have been some pivotal discoveries in this field, owing primarily to a better understanding of the nature of PPIs and how they can be targeted. The discovery of GPCRs as oligomeric complexes necessitated the detection of PPIs and thus the need for drugs that target these interactions. We have shown in this review that using peptides as drugs is an important method for targeting PPIs for GPCRs.

These are some of the ongoing challenges that we face; however, with the developing technologies and approaches to these issues, as well as the pioneering work that has already been performed and discovered, the future for the use of peptides as therapeutics agents for targeting GPCR PPIs looks promising.