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Databases and ontologies

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GPCR-OKB: the G Protein Coupled Receptor Oligomer Knowledge Base

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ABSTRACT

Summary: Rapid expansion of available data about G Protein Coupled Receptor (GPCR) dimers/oligomers over the past few years requires an effective system to organize this information electronically. Based on an ontology derived from a community dialog involving colleagues using experimental and computational methodologies, we developed the GPCR-Oligomerization Knowledge Base (GPCR-OKB). GPCR-OKB is a system that supports browsing and searching for GPCR oligomer data. Such data were manually derived from the literature. While focused on GPCR oligomers, GPCR-OKB is seamlessly connected to GPCRDB, facilitating the correlation of information about GPCR protomers and oligomers.

Availability and Implementation: The GPCR-OKB web application is freely available at http://www.gpcr-okb.org

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

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1 INTRODUCTION

G protein-coupled receptors (GPCRs) are transmembrane (TM) helical proteins that are implicated in many biological responses, and thus serve as targets for a variety of therapeutic compounds (Hopkins and Groom, 2002). Although still a matter of controversy for some GPCR subtypes, the very close proximity of two or more receptors has been demonstrated unambiguously in heterologous cell systems for several GPCRs using biochemical and biophysical techniques (Milligan and Bouvier, 2005). The challenge now is to determine whether all GPCR complexes have functional significance in native tissues, as already demonstrated for a few pairs (Panetta and Greenwood, 2008).

Information supporting the existence of functionally relevant GPCR dimers/oligomers is described in multiple articles published in the literature. This creates a challenge to researchers trying to gather experimental evidence and/or computational predictions about any given oligomer. Our previous work focused on the design of an ontology (Skrabanek *et al.*, 2007) to organize information about GPCR oligomerization, and its functional consequences *in vitro* and *in vivo*. The ontology was well received (Simpson *et al.*, 2010), demonstrating significant interest in an electronic system to access GPCR oligomer information. In this article, we describe the GPCR-OKB system, which implements the GPCR-OKB ontology and an electronic front-end to organize information about GPCR

oligomerization obtained from 167 published articles (as of January 2010).

2 METHODS

Data acquisition: the content provided in GPCR-OKB was extracted from articles published primarily during the past decade, and was recorded in the system in a format as close to the raw experimental data as possible to preserve objectivity. In cases where published evidence varied, the option 'Evidence Varies' highlighted the controversy. Thus, only original research papers were annotated; review articles were excluded. The latter, however, were checked to ensure that data from referenced original research articles were included in the GPCR-OKB.

System design: the GPCR-OKB web application was developed with the Grails web application framework, and supports both browsing and structured searches. Information is stored in XML files that follow the GPCR-OKB XML schema designed in agreement with the GPCR-OKB ontology (Skrabanek *et al*., 2007; see http://www.gpcr-okb.org, The Ontology and Figure 1 in Supplementary Data for a summary of the types of information captured, and the relationships between them). XML files are versioned with the Subversion version-control system, and can be downloaded directly (see FAQ for download instructions). The GPCR-OKB web application loads these XML files at startup, indexes text fields, and starts serving web pages. The system has been tested with a variety of modern web browsers and has no specific requirements (see FAQ for a list of recommended browsers).

For easy access to detailed information about individual subunits forming a GPCR oligomer, GPCR-OKB is linked to the latest release of the GPCRDB (Horn *et al*., 2003). Data are exchanged between GPCRDB and GPCR-OKB in XML format with an agreed-upon XML schema.

Browsing: information contained in GPCR-OKB can be browsed starting from any of the following titles: 'Oligomers', 'Protomers', 'Methods', 'Phenotypic Changes', '*In Vivo* Evidence', 'Evidence for Physiological Relevance' and/or 'All Publications'. For simplicity, the GPCR-OKB only refers to GPCR oligomers, although the majority of published experimental studies cannot discriminate between dimers, tetramers or higher order oligomers. Oligomer names are derived from the names of their constituent protomers, separated by a hyphen, in alphabetic and numerical order, following the recommendations of Ferre *et al*. (2009), and with the organism in which they were characterized and the GPCR family name specified. When the same combination of protomers has been studied in different species, the GPCR-OKB lists these combinations as different entries. Tables of data offer an option to download information in a tab delimited format (see 'Export to TSV' button at the bottom of each table).

Structured searches: the 'Search' tool at the top right side of each page (see Supplementary Figure 2) provides keyword searches across different types of information. To search for a certain oligomer, the user specifies the name of the oligomer constituent protomers in the input box. Initially configured to search only 'Oligomers', the search tool also allows to search for protomers (only those that are part of stored oligomers), methods, or to restrict oligomer searches to specific types of oligomers. The latter are oligomers (i) with demonstrated phenotypic changes with respect to the constituent protomers (e.g. specific signaling or ligand binding cooperativity events), (ii) with published information about predicted interfaces of dimerization/oligomerization and (iii) with at least one or two of the following conditions satisfied: (a) evidence for physical association in native tissue or primary cells; (b) knowledge of specific functional properties in native tissue; and/or (c) information from knockout animals or RNAi technology. These conditions are NC-IUPHAR recommendations for recognition of a bona fide functional GPCR oligomer, according to a recent report (Pin *et al*., 2007).

Related systems: we are aware of at least two databases under development that provide information about GPCR oligomerization, i.e. the GRIP-DB system (Nemoto *et al*., 2009) and the gpDB relationship database (Theodoropoulou *et al*., 2008). These systems, however, are primarily focused on predicting or storing knowledge pertaining to protein–protein interactions between GPCR subtypes, GPCRs with partner G-proteins and/or GPCRs with effector molecules.

3 CONCLUSIONS

In addition to information about protein–protein interfaces, the GPCR-OKB stores detailed biochemical, pharmacological and functional information about GPCR oligomers, including phenotypic changes, evidence for physiological/clinical relevance, effects of oligomer-specific ligands and proposed mechanisms of activation. The system was designed to integrate seamlessly with the widely used GPCRDB for receptor protomers. The information included in GPCR-OKB was collected and presented in an objective manner to encourage productive and substantiated communication among the domain experts. The GPCR-OKB is expected to be very useful to the GPCR scientific community.

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