G-protein Coupled Receptors as Novel Therapeutic and Diagnostic Targets in B-Cell Chronic Lymphocytic Leukemia

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BACKGROUND

CLL is the most common form of adult leukemia in the Western world. It is characterized by the accumulation of CD5+, CD 19+ and CD23+ B-cells due to decreased apoptosis. CLL shows a highly variable clinical course spanning from indolent, slow growing, to aggressive, which requires immediate treatment. A clinical problem for many heterogeneous diseases, such as chronic lymphocytic leukemia, is the lack of identification of molecular and cellular markers that can predict progression.

G protein-coupled receptors (GPCR) are guanine nucleotide exchange factors for heterotrimeric G-proteins, whose α and βy subunits dissociate and regulate effectors. $G\alpha_S$ stimulates adenylyl cyclase, and $G\alpha_i$ inhibits adenylyl cyclase. GPCRs are the largest receptor family (-3% of genome) and are the largest class of attractive drug targets in disease since they are expressed on the plasma membrane and are tissue specific.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have an invention that provides diagnostic and therapeutic agents for CLL. Individual biomarkers and a biomarker panel comprising G-protein coupled receptors (GPCR) specifically expressed by CLL cells are provided. Methods for diagnosing a disease stage of a CLL patient, progression, or prediction of clinical course and drug selection for said CLL patient, as well as methods for treating CLL, by targeting these GPCR biomarkers are also provided.

The invention consists of a novel biomarker panel of diagnostic and therapeutic targets for CLL. Moreover, the invention provides that certain GPCRs provide novel biomarker panels to diagnose, predict (as biomarkers) and serve as therapeutic targets for CLL. In certain cases, the invention provides expression of GPCRs that are unique or altered in either or both indolent and/or aggressive CLL cells showing different expression levels of GPCRs in different disease stages. In other examples, the invention provides that normal B-cells expressed 200 GPCRs, 84 of which were orphan receptors. In contrast, indolent CLL (slow growing CLL form not requiring treatment) expressed 170 GPCR's, 72 of which were orphans and aggressive CLL (CLL form requiring immediate treatment) expressed 117 GPCR' s, 51 of which were orphan

APPLICATIONS

The invention provides a novel biomarker panel of diagnostic and therapeutic targets for CLL. More specifically, the invention provides that GPCRs, which are previously untested entities expressed in CLL cells, provide novel biomarker panels to diagnose, predict (as biomarkers) and serve as therapeutic targets for CLL. In addition, the invention provides that expression of GPCRs is unique or altered in either or both indolent and/or aggressive CLL cells showing different expression levels of GPCRs in different disease stages

ADVANTAGES

The invention provides an identification of G-protein-coupled receptors (GPCRs) expressed by chronic lymphocytic leukemia (CLL) cells, and in turn, define effects of agonists and antagonists of particular GPCRs on cell growth and cell death and formation of second messengers by CLL cells.

STATE OF DEVELOPMENT

The GPCR array was tested on samples from patients with indolent and aggressive CLL which led them to find novel profiles (including individual and multiple GPCRs) in these patient samples. Validation of the array by independent real-time PCR analyses confirms their expression, as does protein expression (in some cases), followed by assessment of effects of receptor activation and blockade on second messenger generation and CLL cell growth and death.

RELATED MATERIALS

▶ Insel PA, Sriram K, Wiley SZ, et al. GPCRomics: GPCR Expression in Cancer Cells and Tumors Identifies New, Potential Biomarkers and Therapeutic Targets. Front Pharmacol. 2018;9:431. 2018 May 22. doi:10.3389/fphar.2018.00431 - 05/22/2018

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,107,816	10/23/2018	2012-369

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OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
  - Health
- **Medical**
  - Diagnostics
  - Disease: Cancer
  - Screening

RELATED CASES

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