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A Short Note on Systematic Approach in Biological Research and Drug Discovery

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Abstract

Traditional biological research and natural product drug discovery to a systematic operation in genomics and target-specific drug design and selection. Small, cell-permeable and target-specific chemical ligands are particularly useful in systematic genomic approaches to study biological questions. On the other hand, genomic sequence information, comparative and structural genomics, when combined with the cutting edge technologies in synthetic chemistry and ligand screening/identification, provide a powerful way to produce target-specific and/or function-specific chemical ligands and drugs. Chemical genomics or chemo genomics is a new term that describes the development of target-specific chemical ligands and the use of such chemical ligands to globally study gene and protein functions. We anticipate that chemical genomics plays a critical role in the genomic age of biological research and drug discovery.

Keywords: Chemo genomics; Drug; Mutagen

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Introduction

The turn of this century marks significant progress in biology. We have advanced from knowing very little about our genetic makeup to now having complete knowledge of our genome [1].Essential to process enormous genomic information. In this regard, chemical ligand-based approaches are especially powerful toward global understanding of gene and protein functions. Presently, the process of discovering target-specific chemical ligands using synthetic chemistry has become a practical means, which largely attributes to technological advances in target specific and diversity-based organic synthesis. Since the seminal study of pea genetics by Mendal in 1865, genetic analysis has been the benchmark for understanding gene or protein functions. In classical genetics or forward genetics, the genomic DNA of a model organism or cell is randomly mutagenized to generate large numbers of mutants, which are screened for a desirable phenotype or trait, such as alteration in growth, appearance or behavior. The phenotypes are then used to identify the responsible genes [2]. However, these approaches require complex genetic manipulation, which is often tedious and time-consuming. Moreover, they are based on blockage of steps leading to translation, which make them ineffective toward studying proteins with long half-lives. They can rapidly penetrate into the cells, bind to their target proteins and create loss-of-function (or gain-of-function) phenotypes. In recent years, drug discovery has shifted from predominantly screening for natural products to target oriented synthesis/screening of chemical ligands, which in large part is due to the realization that targeting the disease-causing genes/proteins and biological pathways is fundamentally important for successful development of highly effective drugs .In a typical chemical genetics approach, a cell permeable, target-specific chemical ligand is added to the cells of interest, which binds to and causes loss-of-function or gain-of-function of its protein target. Chemical ligands may bind to the enzyme's catalytic site by mimicking natural substrates of the enzyme, as exemplified by the drug lovastatin/mevinolin.

Description

Chemical ligands can be easily administrated at any time during the cell cycle or developmental stages, and any desired location of the cell or organism [3]. Therefore, chemical ligands pose unparalleled temporal and spatial control over their protein targets. Classical examples include the proteasome inhibitor lactacystin and the immunosuppressant rapamycin (Schreiber 1991). Both drugs are microbial natural products that inhibit cell proliferation and interfere with normal cellular functions (Martel et al. 1977; Omura et al. 1991). Lactacystin specifically

binds to and inhibits the 20S proteasome (Fenteany et al. 1995). Knowledge of the target proteins has advanced chemical genetics to a stage that parallels the classical reverse genetics, i.e., the use of the compound to study the biological functions of the drug target protein. For example, as a result of the use of lactacystin, the proteasome is found to be important for diverse biological pathways and processes, including antigen presentation, cell cycle control and cell fate determination (Fenteany and Schreiber 1998). An alternative approach has been developed to use a combination of protein and chemical engineering to modulate the functions of proteins and genes (Bishop et al. 2000) [4]. An early example of this is the use of a synthetic chemical dimerizer, called FK1012 that is derived from FK506 with two FKBP12-binding moieties. Only the engineered enzyme, but not the native enzyme modified ligand can recognize the modified ligand. Belshaw et al. first described this approach in the study of cyclophilin and its ligand cyclosporin A. Target-specific chemical ligands are pivotal for studying biological questions and drug development. Natural products have been traditionally the source for novel ligand screening and discovery, primarily because of their unparalleled range in mode of action and chemical diversity. Combinatorial organic synthesis has increasingly been used to generate small molecule libraries for ligand screening and drug discovery. It stems from the original solid-phase oligonucleotide and peptide synthesis, which provides a way to synthesize and purify peptides with defined sequences. Another concept in chemical ligand synthesis that has emerged in recent years is to change the chirality of the compounds. Biological molecules often contain chiral or asymmetric carbon atoms, at which the carbon atom is bonded to four different moieties. Such molecules exist in two forms, known as enantiomers. . To develop successful lead compounds against diverse protein targets, a designer approach is needed. This is when the in silico approach comes into play, owning to significant advances in computational power and the development of artificial intelligence. They can be readily integrated into the existing genomic approaches and tools. A significant advantage of using chemical ligands is that there is no limit on the developmental stage of the organisms or the conditions the cells and organisms are in. In addition, chemical ligands can be easily used in high throughput analyses. . It is now possible to simultaneously compare the drug-induced profiles with the existing gene expression databases, thereby identifying relevant biological pathway or functions for the drug target [5]. Proteomics or protein profiling is a field dedicated to studying the complete protein complement of a cell, tissue or organism. Posttranslational modifications play crucial roles in regulation of diverse cellular processes such as signal transduction, cell cycle control, development, cytoskeleton networks and metabolism.

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Conflict of interest

No conflict of interest

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