Cellular Signalling 26 (2014) 2834–2842

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

A molecular signaling map and its application

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ARTICLE INFO

Article history:
Received 30 July 2014
Accepted 17 August 2014
Available online 2 September 2014

Keywords:
Molecular modeling
Signaling pathway
Targeted therapy
Cancer hallmark
Comparative flux analysis
Drug discovery

ABSTRACT

Cancer research over the past decades has revealed a number of molecular, biochemical, and cellular events that reflect progressive transformation of normal human cells into their malignant derivatives. These findings help to better understand the complexity of human tumorigenesis. In our study, molecular information is organized to chart a comprehensive map of the signaling network for human cancer. It includes transcriptional and translational regulation and diverse feedback-control loops. It is demonstrated that applying this signaling network map allows predicting the effect of targeted therapy before it can be applied into practice to reduce clinical trial risks. Hence, the proposed map with prognosticating potential effect might become part of drug discovery programs for targeted therapy. Applied in individual patient care it helps to reduce the current reliance of cancer treatment on chemotherapies with low therapeutic indices. This study also demonstrates that continuing elucidation of tumorigenesis will not only need heterotypic organ culture systems *in vitro* and increasingly refined animal models *in vivo*, but also computationally calculable virtual cell models *in silico*.

1. Introduction

The fundamental trait of living cells is to sense and respond to internal as well as external stimuli and perturbations in order to carefully control a homeostasis within a cell and maintain the function and architecture of the cellular system [1]. These abilities are mainly linked to the "signaling network", which functions as an interface between the environment, the genome and the metabolism [2]. Over the past decades, cancer research developed the knowledge of human tumorigenesis based on the fundamental ability of cancer cells for sustaining chronic proliferation and twisting mitogenic signaling within the cellular system [3–6]. Elucidating the deregulated signaling events responsible for neoplastic transformation led to rationally designed targeted therapies, which resulted in launching a large number of drug discovery programs. The central issue of drug discovery programs is to identify the key molecular target in the right pathway. Unfortunately, as drug discovery programs advance, many types of preclinical cancer models *in vitro* and *in vivo* fail to provide reliable prediction and verification [7,8]. In order to address this challenge, a comprehensive molecular signaling map of a human cell is constructed, which includes different signaling pathways associated with diverse transcriptional, translation regulations and feedback-control mechanisms. During this study, this molecular signaling map has been applied for predicting drug responses of different types of cancer cell lines and the results are promising.

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2. Results

2.1. The construction of the molecular signaling map (MSM)

The complex MSM is constructed by a curated activity considering different levels of definitions and is made available. The level of node definition includes component creation representing gene, RNA, protein, compound and others. Within the MSM, each node (biological component) is uniquely labeled using Ensembl-Id (gene, RNA), UniProt-Id (protein), ChEBI-Id (compound) and MSM-Id (complex, pseudo-object). Subsequently, the definition of edge between nodes represents corresponding biochemical reactions. For instance, an edge representing a transcription reaction is defined by linking a node of gene to a mRNA node. An edge representing a phosphorylation reaction is defined as a link between a protein node and a further protein node representing the phosphorylation-modification (Fig. 1A). The MSM also contains positive and negative feedback loops (Fig. 1B; Supplementary information 1). They ensure a homeostatic regulation of signal-transduction such as signal amplification and signal desensitization [9].

Finally, signaling pathways (EGF-, mTor-, Notch-, BMP-signaling) are defined (Fig. 1C; Supplementary information 2). Each pathway generally contains three stages: signal initialization, signal amplification, and signal transduction. For the EGF-signaling pathway, signal initialization contains biochemical reactions including the creation of an EGF ligand through corresponding transcription and translation; the specifical binding of an EGF ligand with its cellular receptor (EGFR), which promotes the dimerization of a ligand receptor complex.

http://dx.doi.org/10.1016/j.cellsig.2014.08.022

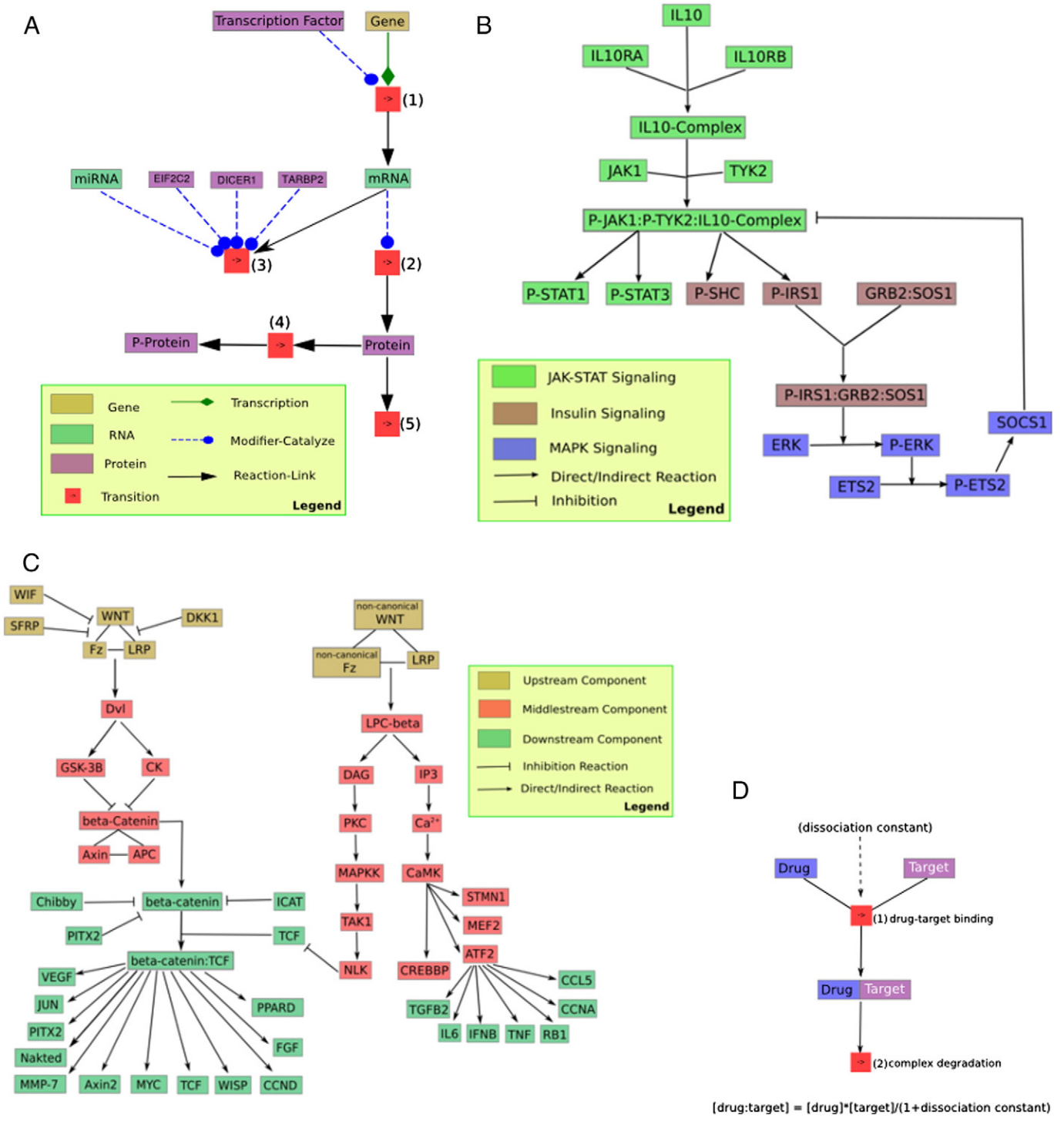

Fig. 1. (A) Node and edge definition in the MSM. A node in the MSM presents a basic component of the cellular system. An edge in the MSM presents a biochemical reaction which can happen in the cellular system. There are 5 different types of edges shown here: (1) transcription; (2) translation; (3) miRNA regulation; (4) phosphorylation; and (5) degradation. Therefore, the definition of edge means not only the linkage of different nodes to form a molecular network, but also contains the underlying biological meaning. (B) The feedback loop in the MSM. A feedback loop is an important part of a signaling network. Because of its feedback control function, the dynamics could be bestowed on a signaling network. Here is a simplified negative feedback loop visualized. This loop presents crosstalk between three different signaling pathways: JAK-STAT-, Insulin- and MAPK-signaling (Supplementary information 1 shows all possible feedback loops within the MSM). (C) The definition of a signaling pathway in MSM. The MSM contains 51 signaling pathways. Here is the simplified Wnt signaling pathway visualized, which is focused on the protein and complex level. For the sake of simplicity, all genes, RNAs and their related transcriptions, translations and miRNA regulations in this signaling pathway are not shown here. (D) Modeling the drug inhibition effect. The kinetics of drug–target binding reaction is defined by applying the mass action law. The concentration of the drug and target complex is dependent on the concentration of the drug and target and the corresponding dissociation constant.

Signal amplification includes adapter protein (Grb2, Sos) recruitment by an activated dimerized EGF ligand receptor complex, which subsequently leads invoking the activation of MAPK signaling. Signal transduction starts from the activation of different downstream targets (such as AXL1, FOS, CREB, ATF, TP53, CEBPA) and ends with the transactivation of diverse target-genes [10]. The transcriptional regulation of microRNA (miR) is integrated into the MSM using information from the TransmiR database (version 1.2) [11], which provides detailed