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Identification of cluster of proteins in the network of MAPK pathways as cancer drug targets

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ABSTRACT

The quest to develop computational drug target identification methods in complex diseases like cancer is growing in recent years. Feedback, feed-forward loops and cross-talks observed among the MAPK pathways led to the definition of a network of MAPK pathways and considered for single or multiple therapeutic interventions. We developed a computational method to identify clusters of drug targets by analysing the directed network's topological properties and the individual node's functional roles. We aim to identify the primary drug target nodes possessing more cancerous properties and less number of cellular functional roles. For every primary drug targets, we collect the alternate substrate activating nodes for local resistance analysis. Alternate substrate activation free nodes identified as single drug target are SOS, ATF1, BAD, GAB1, LAD, NFAT4, ATF2, MEF2, eEF2K, 4EBP1 and HSP27. Among the remaining identified nodes and their corresponding alternate substrate activating nodes with their cancer retaining and side effects causing properties studied as three different classes-single, multiple and dangerous targets. C-Raf1 and MAPKAP-K observed as a single efficient target due to the absence of resistance mechanism. Due to the resistance mechanism observed among the targeted M3/6, GADD45, and MKK6 multiple target intervention of their corresponding alternate nodes might prove to be the efficient targets. Targeted effect on MLK3, ZAK, DLK and MLTKa/b will impair the network due to intertwined and proximity nature among themselves.

1. Introduction

Effective therapeutic target strategy for the complex disease like cancer challenged in recent years due to late-stage failure in clinical trials [1]. Cancer is well known as “signaling disease”, and therapeutic inhibition of signal transduction network in human malignancies is gaining remarkable success. Intervention with the multiple drug targets is found to be more efficient than single target strategy [2–4]. Aiming to elucidate single/multiple targets in addicted signal transduction by a mutation in disease network is more complicated. Side effects are caused due to loss of functional properties of the targeted proteins. Computational approaches have attempted a systematic search of the pharmacological inhibitors playing vital role in controlling intracellular signaling event [5]. One such an approach is the development of an algorithm for multiple target optimal intervention (MTOI) in an arachidonic acid metabolic network using its structure and dynamics [2]. In this work, we develop a computational method to identify clusters of drug targets using topological and functional properties of the complex directed signaling network. Here, we confined to the network of MAPK pathways whose deregulation is the cause of cancer [6].

Understanding of cancer mechanism and the search for drug targets in MAPK pathways are dates back to 3 decades [7–9]. Disrupting the signal transduction that abnormally regulates cell growth and programmed cell death (apoptosis) are the therapeutic strategy. MAPK pathways uniquely form complex network due to the cross-talks among them [10]. Upstream and downstream of the pathways are involved in making cross-talks with each other, and there is no cross-talk observed at the MAPK level. Furthermore, drug resistance attained in MAPK pathways is due to the synergistic activation of them through cross-talks [11,12]. Tackling the problem of drug resistance in MAPK pathways [13–15] considered in this work.

We build a “Tailored” drug target identification method for the network of MAPK pathways by exploring topological and functional properties. The topological structure of the network is analysed to choose the best centrality. For instance, efficient and destructive free nodes are isolated in a topological sense. Functional and pathological properties of

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the nodes in a network of MAPK pathways were derived from the Gene Ontology domain Biological Process (GO: BP) to cluster the proteins. Aiming to collect the nodes which are having more number of cancerous properties and less number of cellular functional roles. Causes of resistance mechanism prevailed in the network of MAPK pathways are identified and analysed to overcome them. The nodes in the clusters are analysed to determine the drug resistance mechanism acquired through the alternative activations of their substrates. Furthermore functional and cancerous properties of the identified drug target nodes and their corresponding alternate nodes are used to study the causes of retaining cancer and side effects.

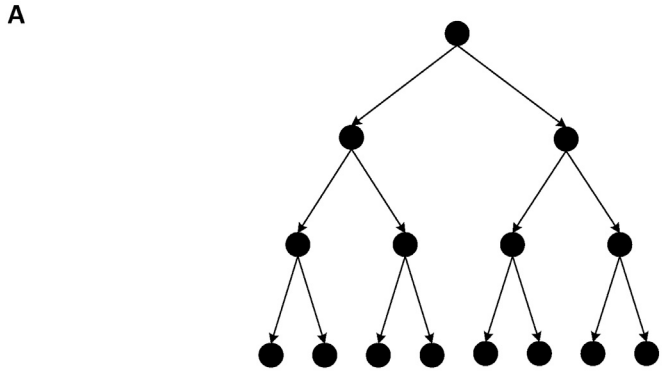
2. Results

2.1. Topology of the network of MAPK pathways

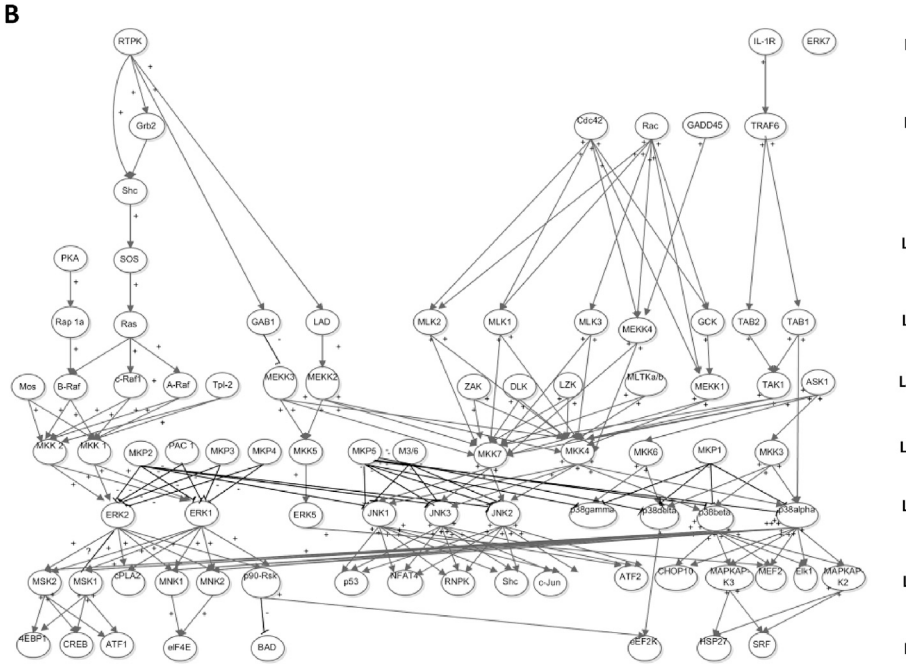
Topological properties based analysis carried out to identify the efficient and destruction free centrality nodes as drug targets. The network of MAPK pathways is directed network due to a chain of activation from receptor to transcription factors (Fig. 1). We assume the network of MAPK pathways as directed ordered network on activation time of the proteins. Directed ordered networks was first introduced by Pavel et al. [15] in the food web network by ordered nodes based on animal's body size. In this work, layer wise (9 layers) analysis carried out by considering the directed order (Fig. 1). The

Table 1
Some of the nodes observed as skipping the immediate substrate layer to activate the more further layers.

Signal events starts from node(layer) substrate node(layer)
RTPK (layer 1) substrate GAB1, LAD (layer 4)
Cdc42, Rac, GADD45, TRAF6 (layer 2) substrate MLK2, MLK1, MLK3, MEKK4, GCK, TAB2, TAB1(layer 4)
Cdc42, Rac (layer 2) substrate MEKK1(layer 5)
MLK2, MLK1, MLK3, MEKK4 (layer 4) substrate MKK7, MKK4 (layer 6)
TAB1(layer 4) substrate P38alpha(layer 7)
P38delta (layer 7) substrate eEF2K (layer 9)



Layer	Number of nodes	Average in degree	Average out degree
1	1	0	2
2	2	1	2
3	4	1	2
4	8	1	0



Layer	Number of nodes	Average in degree	Average out degree
1	2	0	2.5
2	6	1.166667	2.833333
3	2	0.5	1
4	11	1.5	1.6
5	14	0.785714	2.428571
6	14	3	3.071429
7	10	4.4	5
8	16	2.875	0.875
9	8	1.875	0

Fig. 1. A) Model hierarchal network with increasing number of nodes with 2^{n-1} order contains increasing number of nodes in the layers. Average in and out degrees are 1 and 2 respectively. B) Network of MAPK pathways found to be hierarchical up to 6 layers, converge at a 7th layer and diverges further. Average in and out degree at a 7th layer is 4.4 and 5 respectively. Network properties reveal to be small world having network diameter 9 with average number of neighbours 4.410.