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Mini-review

Organ-specific gene modulation: Principles and applications in cancer research

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ABSTRACT

Microarray and next generation sequencing has led to the exploration of correlated gene patterns and their shared functions. Gene modulators are proteins that alter the activity of transcription factors and influence the expression of their target genes. It is assumed that modulators are dependent on transcription factors. Several algorithms have been developed for the detection of gene modulators. On the other hand, it is becoming increasingly evident that modulators play a crucial role in carcinogenesis by interfering with fundamental biologic processes. Therapeutic gene modulation that is based on artificial modification of endogenous gene functions by designer molecules is an exciting new field of investigation.

Introduction

The establishment and maintenance of tissue-specific programs of gene expression remains one of the major questions in developmental biology. Organ-specificity is defined as differential expressions of the same gene across different organs. These patterns of gene expression can provide important information about gene function and organ characteristics. Gene expression profiling in different tissues has emerged as a useful tool and has led to the understanding of the complex regulatory networks between genes. Based on combined correlation of gene expression profiles, gene regulatory networks have been constructed, using engineering methods, such as statistical models, correlation coefficient and machine learning [1,2]. Genetic regulatory network approaches (GRN) are used to examine thoroughly abnormalities in regulation between biologic procedures or tumor types.

Interaction between different genes is a complex procedure in molecular biology. In GRN, regulatory genes serve either as activators or suppressors of the function of a given (target) gene. Any gene can be a target or a regulatory gene at a given time [3]. On the other hand, it is known that modulation of gene expression can occur at any time through transcription and translation. Modulators are proteins that can modify the endogenous function of a gene by binding to transcription factors; their dependency on the transcription factor in order to exert their effect is a characteristic feature [4]. Elucidation of the role of gene modulation is fundamental for the understanding of the biologic processes that govern the cell at the gene expression level. Furthermore, it constitutes the biological equivalent of therapeutic gene modulation, which refers to the design of therapeutic agents that alter the endogenous function of a gene; these agents would be valuable tools in the case where a function of a particular gene triggers the development of a disease including cancer. This review article describes the current methods of detection of gene modulators, as well as the principles and applications of therapeutic gene modulation in cancer research.

Modulator detection algorithms

Through the past years, several algorithms for the identification of gene modulators have been developed. Based on the dependency of the gene modulator on the transcription factor and its gene target, it is assumed that in a large genome profile database, expression levels of the candidate modulator will be correlated with the expression levels of the transcription factor and its gene target.

MINDy (Modulator Inference by Network Dynamics) is an information-theoretic algorithm for the identification of gene modulators that has been proposed by Wang et al. and validated as a detection tool for the identification of the modulators of MYC protooncogene, using a large collection of gene expression profiles representing cellular phenotypes from normal and neoplastic cells. MINDy has also been used to infer signaling modulators of all transcription factors in human B cells [5], and to identify the ubiquitin conjugating ligase HUWE1 as a modulator of N-MYC turnover in neural stem cells [6]. This tool estimates a theoretic measure known as the Conditional Mutual Information (CMI) between the expression profile of a transcription factor and the target gene, and its dependency on the modulator candidate [5]. It considers only two modulator expression states (up and down expression) and tests

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the difference in the expression levels of the transcription factor-target gene in correlation with up versus down expression [3,5].

Based on the same principles, GEM (Gene Expression Modulation) is a detection method that has been developed in detail by Babur et al. [4]. For a modulator/transcription factor/target assembly, GEM improves over MINDy by predicting how a modulator–factor interaction will affect the expression of the target gene. It therefore hypothesizes that the correlation between the expression of a modulator and a target will change, as expression of transcription factor changes. GEM has been used to identify modulators of the androgen receptor (AR) expression.

Mimosa has been also suggested by Hansen et al. to identify modulated transcription factor–target pairs. Instead of modulator preselection, it aims to search for the modulators. Similarly to MINDy, it hypothesizes that the modulator has only two expression states, absence (=0) and presence (=1) of expression. Furthermore, the transcription factor–target pair is assumed to be correlated only in the presence of the modulator [7]. Complex mathematic equations (Gaussian distributions) are used to model different modulated regulator–target relationships. Mimosa sets out to fit the samples of every pair of potential regulator target with the mixture model. The paired expression samples that have a correlated–uncorrelated partition are considered to be modulated; afterwards, a weighted *t* test is used to identify genes whose expressions are differentially expressed in the correlated partition versus the uncorrelated partition [3]. Mimosa has been validated for the detection of modulators of signal transducer and activator of transcription-1 (STAT1) [7].

Finally, Hermes is an extension of MINDy in terms of enabling the identification of candidate modulators genes of miRNA activity from large sets of expression profiles of genes and miRNAs of the same samples [8]. Hermes estimates MI and CMI and uses a mathematic equation to study the difference between the CMI of regulator and target genes in the presence of the modulator and the MI of the regulator and target gene in the absence of a modulator; the quantities can be computed from collections of expression of genes [3].

Table 1 summarizes modulator detection algorithms, advantages and disadvantages and examples in cancer research.

Gene modulation and cancer

Cancer is defined as the uncontrolled growth of abnormal cells in the body and is caused by abnormalities in genetic material. Gene mutations are considered as the initial step in carcinogenesis resulting in aberrant gene regulation. Furthermore, in preclinical cancer models, several molecules have been found to act as modulators of endogenous functions of several genes in specific malignancies.

In breast cancer (BC), effects of estrogens are mediated by estrogen receptors α and β (ERα, ERβ). Upon estrogen stimulation, dynamic changes in gene expression of ERs define response of BC cells to estrogen. Several transcription or growth factors, such as nuclear factor kB (NF-κB), Sp1, EGFR, and IGFR mediate changes in ERα phosphorylation and alter ERα function on target genes [9]. In a study by Shen et al., modifications in the regulatory network of transcription factors were found in a MCF7 BC cell line upon estradiol stimulation [10]. Furthermore, Estrogen Receptor 1 (ESR1) has been found to modulate coexpression among a number of genes [11]. More recently, ESR1 was shown to jointly work with other modulators, such as Human Epidermal Growth Factor Receptor 2 (HER2/*neu*) and ADAM metallopeptidase domain 12 (ADAM12) [12].

In addition, DNA-binding 2 (DDB2), most commonly known for its role in DNA repair, is a protein found to be overexpressed only in non invasive breast cancer (BC) cells. Interestingly, in a preclinical study, DBB2 was found to serve as a negative regulatory factor in the invasive abilities of BC cells via decreasing NF-κB activity, by upregulating expression of IκBα after binding to the proximal IκBα promoter. More specifically, DDB2 overexpression attenuated the activity of NF-κB transcription factor and the expression of its target matrix metalloprotease 9 (MMP9). Knockdown of DDB2-induced IκBα gene expression restored NF-κB activity and MMP9 expression, along with the invasive properties of BC cells [13]. DDB2 has also been found to decrease cell adhesion in BC cells, an event occurring early in cancer progression and metastasis [14]. More recently, Reprimo (RPRM), a protein involved in p53-induced cell cycle arrest at the G2/M checkpoint, has been shown to be involved in decreased cell migration and invasion in BC cell lines [15]. Moreover, STAT3 and STAT5 have been shown to antagonistically modulate BCL6 expression, a transcription factor implicated in breast cancer pathogenesis [16].

Interestingly, cytokine IL-6 has been shown to act as a modulator in HOXB13-mediated tamoxifen resistance. HOXB13 belongs to the HOX family of genes, and has been shown to evoke tamoxifen resistance through induction of IL-6 secretion [17]. Inhibition of IL-6 by IL-6 antibodies reduces cell growth in HOXB13-overexpressing cells [18].

In colon cancer, activated KRAS signaling plays a major role in malignant transformation by promoting cell proliferation and angiogenesis. Using a wild type (WT) KRAS colon cancer cell line with HIF-1α and HIF-2α losses, Chun et al. has shown that oncogenic KRAS modulates colon cancer metabolism by altering HIF-1α and HIF-2α target genes; absence of both KRAS and HIF-1α/HIF-2α lead to decreased mitochondrial respiration efficiency [19]. Furthermore, KRAS acts as an epigenetic modulator in RAS-mediated malignant transformation by downregulating TET enzymes that participate in DNA demethylation; as a result, increase in DNA methylation contributes to inactivation of tumor-suppressor genes [20]. In addition, NK-κB, induced by chronic inflammation has been found to modulate epigenetic phenomena observed in early colon cancer [21]. On the other hand, MAP3K ZAK (Sterile alpha motif and leucine zipper-containing kinase) is another important protein that has been shown to be upregulated in colorectal carcinoma and adenoma. ZAK is a proapoptotic factor and positive regulator of epidermal growth factor (EGFR) that modulates extracellular signal regulated kinase (ERK)-dependent migration. ZAK+ colorectal premalignant lesions significantly correlate with gene sets belonging to the MAPK/ERK and motility-related signaling pathways [22].

In addition, ERK1/2 and Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathways have been shown to be modulators of the claudin 2 and 3 induced growth in colon cancer cells. Claudin 2 and 3 are the main proteins that regulate functions of tight junctions, which constitute structural components in the epithelium [23,24]. The αvβ6 integrin might also be a key modulator in colon cancer. Integrins are cell surface receptors involved in adhesion and migration of cells. Avβ6 is upregulated in colon cancer and functions by activating TGF-β, a cytokine that plays a major role in tissue regeneration and immune system regulation [25].

In prostate cancer, testicular nuclear receptor 4 (TR4) has emerged as a key modulator involved in prostate cancer progression. TR4 modulates tumor suppressor gene ATM to reduce DNA damage in order to prevent prostate cancer evolution. However, in the absence of peroxisome proliferator-activated receptor gamma (PPARγ) gene, TR4 acts as a modulator of CCL2, Oct4, EZH2, and miRNA-373-3p expression, leading to increase in cancer stem cell population and epithelial–mesenchymal transition (EMT) and carcinogenesis [26,27]. TR4 also promotes prostate cancer metastasis via modulation of CCL2 signaling [28].

In hepatocellular carcinoma (HCC), a malignancy characterized by multiple genetic and epigenetic alterations, des-gamma carboxyprothrombin (DCP) and glypican proteoglycan-3 (GPC-3) have been shown to act as gene modulators. DCP is an abnormal prothrombin generated by lack of vitamin K in HCC patients, which