Functional hallmarks in clear cell renal cell carcinoma grade and stage progression revealed by changes in signalling circuit activities.

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Abstract

The acquisition of the cancer phenotype is a process largely dominated by changes in cell signalling that can hardly be interpreted as the consequence of isolated changes in gene activity but rather as the results of complex interactions among these. Here we propose the use of a transformation of individual gene expression data into numerical descriptors of signalling pathway activities that are further used to understand the evolution of the disease across the different tumour grades. We have studied the clear cell renal cell carcinoma (ccRCC) data from the ICGC Cancer Genome Consortium Challenge.

Introduction

Complex traits, including most diseases, are associated with complex changes in biological pathways rather than being the direct consequence of single gene alterations. In particular, the hallmarks of cancer, which include sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [1] are all directly or indirectly related to pathologically altered signalling processes. The idea of using the information contained in different biological pathways to understand complex traits, such as diseases, is recently gaining acceptance [2]. Signaling pathways provide a formal representation of the processes by which the cell triggers actions in response to stimulus through a network of intermediate gene products that configure signaling circuits. Interestingly, such circuits can directly be related to cell functionalities. Recently some methods have developed that focus particularly on the estimation of the activity of these stimulus-response signaling circuits from gene expression data [3, 4]. Here we show how to use gene expression values in the context of signaling circuits to understand the molecular mechanisms underlying the evolution of tumor grade and tumor stage.

Method

We evaluated the pathological signal transduction changes in ccRCC by analysing the TCGA ccRCC samples (https://dcc.icgc.org/repository/release_18/Projects/KIRC-US) [5] over a set of selected previously cancer related pathways that includes PI(3)K/AKT and mTOR signalling pathways taken from KEGG. The pathways are decomposed into elementary signalling circuits that connect receptor proteins with effector proteins, whose mission in the cell is triggering functional responses to the stimuli received by the receptors (see [4] for details). Activation-inactivation relationships between nodes (proteins) along the circuits enabled us to use a graph traversal methodology for updating signal intensity at each visited node and finally computing a global value of signal transduction for the circuit (thereinafter signalling circuit activity or SCA).
Both tumour grade (TG) and tumour stage (TS) status per sample were obtained from clinical data from the ccRCC page. Patients were stratified according to their status (TG and TS) and normal samples were grouped into a single initial state (s0). Then, a chronogram with the precise sequence of pathologic events that occurs after reaching each tumour status was reconstructed by comparing SCA at each stage or grade against all the precedent ones (eg. G3 against G2, G1 and G0). Here we focused only into monotonically increasing or decreasing behaviours and only significant differences were reported.

Results and discussion

When samples are clustered on the basis of their SCA patterns a clear separation between cases and controls is observed (Figure 1) which provides an initial evidence of the relationship of these values to the biological progression of cancer.

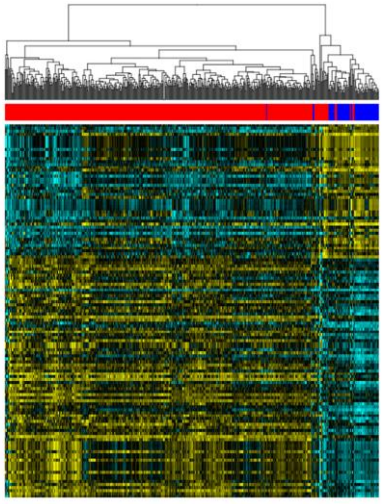

Figure 1. *Hierarchical clustering of SCA values. Normal samples are coloured in blue and cases in red*

When the SCA values are compared across tumour developmental phases, several systematic activations or deactivations of signalling circuits across TGs and TSs is observed.

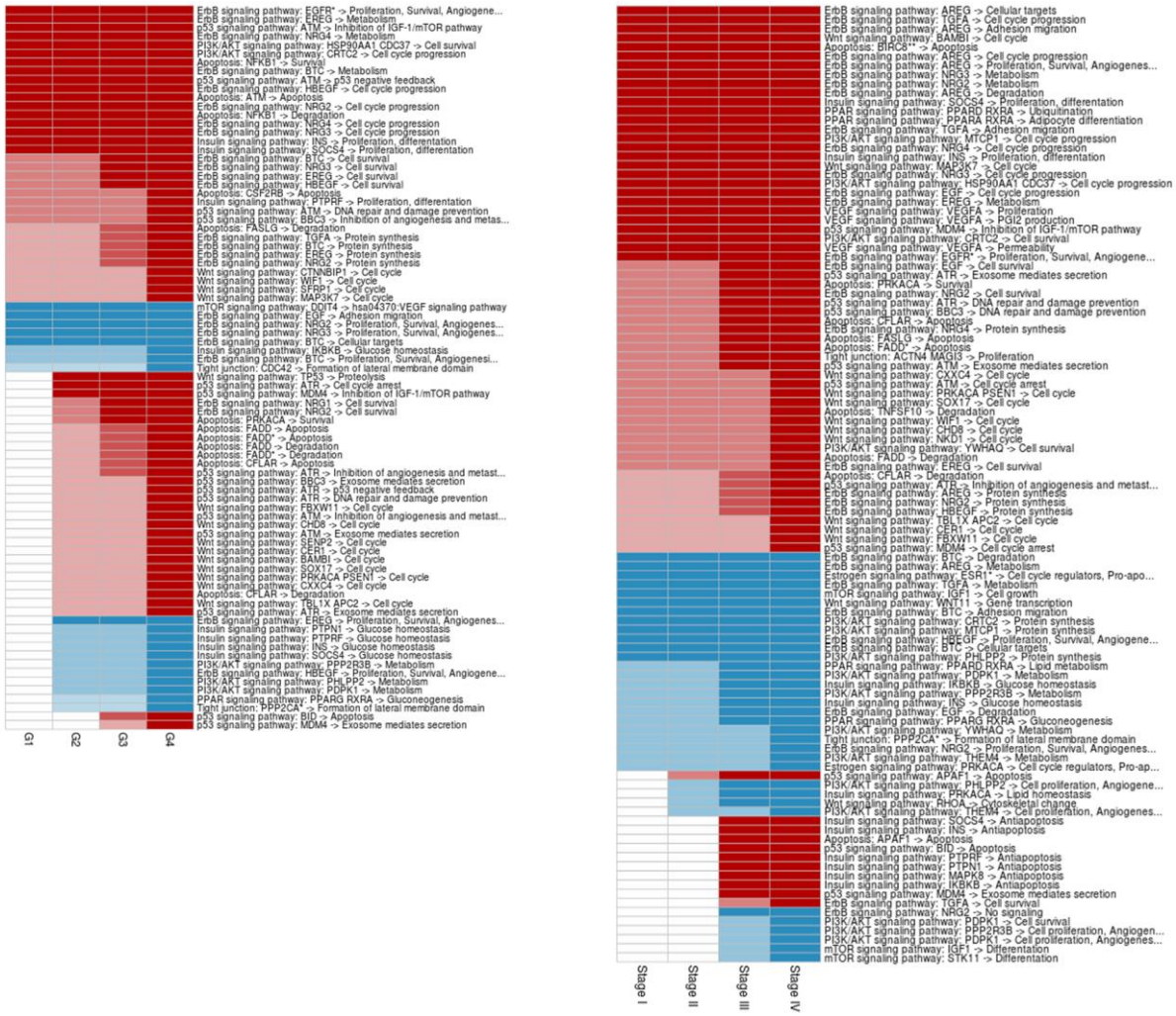

Figure 2*: Evolution of SCA values corresponding to different circuits with progressive behaviour. Upregulated circuit/grades (left) and circuit/stages (right) are coloured in red, and downregulated in blue. The different red/blue intensities describe an increase in up/down regulation in late cancer phases.*

Interestingly, activated and deactivated functions triggered by signalling circuits have a direct relationship to cancer progression. Thus, biological processes such as *cell cycle*, *survival*, *angiogenesis*, *proliferation, antiapoptosis* or *cell survival* are systematically activated as TG and TS progresses. On the other hand, *protein synthesis*, *metabolism*, *glucose homeostasis* and, in general, *differentiation* processes are inhibited, as expected from the indiferentiation process that occurs in cancer. Other functions, like *cell adhesion* are also deactivated, favouring thus invasion and metastasis.

Conclusions

We concluded that gene expression data can be transformed into measurements of SCA values that account for cell functionalities. Such measurements cell functionalities can be related to cancer progression, in particular TG and TS. The cancer hallmarks already described [1] can be considered the consequences of a series of functional hallmark that are elegantly described in the approach proposed here.

We propose that approaches that model cell functionalities will be not only more accurate in predicting phenotypic traits, such as the disease progression, but will also provide insights into the molecular mechanisms that account for such phenotype.

References

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