Genome Medicine

Minireview

Insights into gliomagenesis: systems biology unravels key pathways

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Abstract

Technological advances have enabled a better characterization of all the genetic alterations in tumors. A picture that emerges is that tumor cells are much more genetically heterogeneous than originally expected. Thus, a critical issue in cancer genomics is the identification of the genetic alterations that drive the genesis of a tumor. Recently, a systems biology approach has been used to characterize such alterations and find associations between them and the process of gliomagenesis. Here, we discuss some implications of this strategy for the development of new therapeutic and diagnostic protocols for cancer.

Introduction

One of the most important steps in the genesis of a tumor is the acquisition of both genetic and epigenetic alterations. Although a significant number of cancer-related genes have been identified in the past few decades [1], the emergence of technologies that allow genome-wide screening for alterations in large collections of tumors has affected the field of cancer biology in a dramatic way. The picture that is emerging is that most tumors are genetically heterogeneous and accumulate a large number of genetic and epigenetic alterations. The current level of genetic heterogeneity observed in tumors is, nevertheless, expected to increase in the next few years with the emergence of next-generation sequencing technologies. Collectively, these technologies allow the detection of rare genetic variants present in less than 10% of the tumor cells and that cannot be detected by conventional Sanger sequencing.

Given this, the major challenges in cancer genomics nowadays are: to discriminate alterations that are causally involved and drive tumorigenesis (the drivers) from those that have been accumulated by chance and are neutral to the process (the passengers); to understand the synergistic effects of these alterations on critical cell signaling pathways and on tumor behavior; and to use all this information to improve disease management and patient survival.

Although the driver genetic alterations are important in terms of developing new effective therapeutic strategies, the passengers are also important in the sense that they constitute a supply of genetic alterations that can be used by the tumor to respond to a new set of environmental conditions. For example, passenger genetic alterations do not contribute to tumor growth but can be important in the resistance of a tumor to a chemo- or radiotherapeutic strategy.

How can we identify drivers? One way is to define an expected number of mutations per gene, using the mutation rate, and identify genes with more mutations than an expected threshold. This strategy assumes that genes that are mutated more frequently than expected are more likely to be drivers. Several reports have used this strategy for the identification of cancer-related genes and driver alterations [2-4]. Another possibility is to use a systems biology approach, in which genetic alterations are evaluated in the context of pathways, networks and functional modules [5-7]. Instead of looking at specific genes, the systems biology approach prioritizes higher levels of genetic organization and depends extensively on computational methods that integrate and analyze data from different sources and platforms. For example, data on somatic mutations occurring in breast and colorectal tumors have been integrated with other types of data to provide a network-based view of genetic alterations occurring in these types of tumor [6,7]. In another example, our group has recently integrated different types of data on genes coding for cell surface proteins to identify possible new targets for glioblastoma and colorectal tumors [8].

Gliomagenesis

Gliomas are brain tumors and are among the most devastating of all human tumors. Survival rates are usually measured in months and the most used therapy produces a median survival of only 15 months [9]. Cancer genomics is important for gliomas in the sense that it may help to define classes of patient with distinct prognoses and/or responses to therapeutic strategies. Recent reports from a Johns Hopkins University group [10] and from The Cancer Genome Atlas Research Network [11] have provided a

much broader view of the genetic alterations occurring in gliomas. Although these studies have found single genes that seem to be important in gliomagenesis - such as *IDH1*, encoding isocitrate dehydrogenase 1, which is often mutated in patients with a specific type of glioblastoma, the most lethal type of glioma [10] - the major pattern that emerged from these studies was extremely complex, with many new genetic alterations occurring in dozens of genes in each tumor. Which alterations contribute to the development of cancer is a matter of crucial interest.

Systems biology and gliomagenesis

More recently, a systems biology approach was used by Bredel *et al.* [12] to describe a network model of cooperative genetic changes in gliomas and, most importantly, to evaluate its clinical relevance in terms of patient survival. Bredel *et al.* [12] assumed that different genetic alterations act together to facilitate gliomagenesis in a coordinated and cooperative manner. They carried out genomic profiling on 45 glioma specimens and identified several altered regions spread along different chromosomes showing significant associations. Interestingly, genes within the regions showing a significant association have a more dramatic change in their expression level than genes mapped to random genetic alterations. Furthermore, the authors [12] noted a greater propensity for downregulation in gene expression within the significant regions.

Genes showing a high level of association with gliomagenesis were then mapped into the context of a network of protein-protein or functional interactions. This network was enriched with functional modules related to promotion of tumors and developmental pathways. Using this network, the authors [12] selected a group of genes showing higher connectivity, assuming that alterations in those genes would affect more genes within the network. The association profile of these 'hub' genes and the genes interacting with them was validated by an independent panel of 456 gliomas from several centers in the United States and The Cancer Genome Atlas. This validated set of associations was significantly linked to poor survival rate in different groups of patients with gliomas. Genes with a higher connectivity include *POLD2*, *CYCs*, *MYC*, *AKR1C3*, *YME1L1*, *ANXA7* and *PDCD4*.

Conclusions

The work of Bredel *et al.* [12] and others [5-7] will have a significant impact on the development of diagnostic and therapeutic protocols. If the notion that gliomagenesis is the product of multiple reciprocal genetic alterations stands, this will explain the poor performance of therapeutic interventions that target a single gene product. Bredel and colleagues [12] illustrate this point by showing that even a gene as prominent in gliomagenesis as the epidermal growth factor receptor gene *EGFR* does not act in isolation, but rather in concert with other genetic alterations; this predicts that the targeting of multiple genes will be more effective than monotherapeutic approaches. Recently, the systems biology approach has been used to stratify breast cancer patients for personalized therapies [13], and for breast tumors an expression signature of dozens of genes has been used as a prognostic tool to guide adjuvant treatment decisions [14]. It is reasonable to assume that this scenario is also true for other tumor types.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SJS participated in discussions and wrote a draft of the manuscript. BS and AAC participated in discussions and helped write the manuscript.

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