Complexity of molecular alterations impacts pancreatic cancer prognosis

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INVITED COMMENTARY ON HOT ARTICLES

In a recent seminal study, Breitkreutz et al.\(^1\) compared the complexity of core signaling pathways in a variety of tumor entities including pancreatic ductal adenocarcinoma (PDAC). Specifically, 14 different pathways specific for one type of cancer were extracted from the Kyoto Encyclopedia of Genes and Genomes (KEGG)\(^2,3\). In order to analyze the influence of such a pathway complexity on 5-year survival rates, a metrics for network complexity (node degree entropy) has been used to perform correlation analyses. Prostate cancer was excluded from this analysis due to its highly differentiated phenotype and slow growth. The remaining 13 types of cancer show a high correlation between the 5-year survival rate and the node degree entropy of the corresponding network (R\(^2\) = 0.7), e.g. pancreatic cancer with the shortest 5-year survival rate (5.5%) has a high node degree entropy (H = 2.05) whereas thyroid cancer showing the highest 5-year survival rate (97.2%) has a low entropy (H = 1.48). The authors concluded that complex structured networks generally point to a worse survival rate than simple structured networks. Moreover, they suggest intensifying research on network metrics in the context of survival probabilities and other clinical observations. Indeed, pancreatic cancer is an aggressive cancer entity with a very
complicated cancer signaling network. Although previous genome-wide sequencing efforts have identified a complex network of 12 core signaling pathways influencing the aggressive behavior of pancreatic cancer, it is not known how these 12 core pathways are coordinated or whether there are central players by which the pathways can be interconnected[8]. Assuming that the central players serve as connective ‘linkers’ within complex signaling networks, application of existing knowledge from protein-protein interaction analysis would reduce the complexity of networks, and would therefore help to uncover central players. To this end, Breitkreutz et al[1] analyzed protein-protein interaction networks of the individual specific cancer pathways extracted from KEGG. As many biological networks are scale-free, network analysis would focus on nodes with a high impact. Because node impact is not just given by its network degree, but by its property to connect different nodes or sub-networks, the authors use the betweenness centrality measure for further analysis. The betweenness centrality of a node is the proportion of the shortest paths in the network that include the node. Accordingly, nodes with a high betweenness centrality can be considered as potential therapeutic targets. For each network, the three nodes with the highest betweenness centrality were identified. This analysis yielded three candidate genes for pancreatic cancer consisting of KRAS, JAK1 and RALBP1.

The network analysis suggests that KRAS, JAK1 and RALBP1 play an important role in mediating signal cross talks between different pathways in PDAC. Indeed, nearly all PDAC harbor oncogenic KRAS mutations, and KRAS mutations can also be detected in chronic pancreatitis and various early cancer lesions, such as pancreatic intraepithelial neoplasia, acinar-ductal metaplasia or cystic lesions[9,10]. Therefore, it is not surprising that KRAS has been identified by such analysis. However, KRAS mutations are neither a reliable prognostic marker nor a predictive biomarker for therapy, in as much as clinical trials targeting the KRAS signaling pathway do not show encouraging results[11]. Nevertheless, patients without KRAS mutations show a favorable response to combination treatment with gemcitabine and erlotinib[12].

Mouse models of pancreatic cancer suggest that oncogenic Kras mutation, pancreas-specifically (starting during embryogenesis) expressed from its endogenous locus, initiates alone the development of invasive PDAC albeit at a low efficiency. A ‘second hit’ such as loss of a tumor suppressor or the initiation of inflammation is required to increase the rate of/accelerate malignant transformation[13,14]. These observations underscore the necessity of an interaction between the RAS pathway and other signaling pathways in driving the formation of malignant pancreatic tumors. In addition, they also imply that KRAS effectors are widely ‘connected’ and have a broad biological effect on tumor behavior. A downstream target of the Ras GTPase is RALBP1, the second protein identified by the protein-protein network analysis. The protein is involved in the cellular stress response and is over expressed in several cancers in which it protects transformed cells from apoptosis and mediates resistance to various drugs[15,16]. Indeed, RALBP1 has been considered as a prognostic biomarker in colorectal cancer and high expression of RALBP1 is associated with shortened overall survival and early relapse[17]. In vitro studies of RALBP1 inhibition demonstrate reduced tumor cell proliferation and enhanced apoptosis in non-small cell lung cancer cells[18]. Furthermore, RALBP1 was identified as a possible mediator of metastatic invasion in PDAC[19]. Whether RALBP1 may constitute a potential drug target or a prognostic biomarker in PDAC is unclear.

The third candidate gene is JAK1, which has previously been shown to have pro-tumorigenic effects. JAK1 plays an important role in transmitting inflammatory signals through nuclear factor-κB signaling into epithelial cells. In general, inflammation signaling extensively interacts with oncogenic KRAS signaling and promotes the development of PDAC[16,17]. However, the exact role of JAK1 in this context remains unknown. A clinical trial of a JAK1 inhibitor demonstrated that JAK1 may be a target for myelofibrosis because treatment reduced the level of inflammatory cytokines and improved systemic symptoms[20]. Hence, this data suggest that JAK1 inhibition affects inflammatory processes. Additionally, in vitro studies revealed decreased tumor cell proliferation and activated apoptosis of glioblastoma cells and multiple myeloma cells following JAK1 inhibition[21,22]. However, further investigation is necessary to uncover the potential link between KRAS and JAK1 as well as the potential of JAK1 as a prognostic marker or a drug able target in PDAC.

In conclusion, the study by Breitkreutz et al[1] reveals that KRAS, RALBP1 and JAK1 may constitute a biochemical network which coordinates the malignant behavior of cancer cells. Further analysis of this network may yield novel cancer biomarkers and therapy targets.

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