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Complexity of molecular alterations impacts pancreatic cancer prognosis

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Abstract

Individualized cancer treatment (e.g. targeted therapy) based on molecular alterations has emerged as an important strategy to improve the current standard-of-care chemotherapy. A large number of studies have demonstrated the importance of biomarkers not only in predicting prognosis but more importantly in predicting the response towards therapies. For example, amplification or mutation status of the two biomarkers HER2 (human epidermal growth factor 2) and BRCA (breast cancer) can be used to decide on a specific targeted therapy in breast cancer. However, no biomarkers with a similar clinical impact have been identified in pancreatic ductal adenocarcinoma. Although many genome-wide and proteome-based high-throughput studies have identified candidate genes or proteins as promising biomarkers, none of them were eventually transferred into the clinical setting. Notably, the most reliable markers for predicting prognosis are still the tumor stage and grade and biomarkers for therapy response remain undefined. One reason lies in the lack of systemic approaches to analyze the complexity of dominating cancer pathways and the impact of such signal complexity on prognosis and therapy response.

Key words: Pancreatic cancer; Diagnostic markers; Biomarkers; Targeted therapy; Prognosis; Pathways

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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)[1-3]. 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[4]. 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[5,6]. 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[7]. Nevertheless, patients without *KRAS* mutations show a favorable response to combination treatment with gemcitabine and erlotinib[8].

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[9,10]. 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[11,12]. 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[13]. *In vitro* studies of RALBP1 inhibition demonstrate reduced tumor cell proliferation and enhanced apoptosis in non-small cell lung cancer cells[14]. Furthermore, RALBP1 was identified as a possible mediator of metastatic invasion in PDAC[15]. 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[18]. 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[19,20]. 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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