

STK4: A Potential Novel Biomarker for Pancreas Cancer

November 17, 2014

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Pancreatic ductal adenocarcinoma (PDA) is the most common form of pancreas cancer. Because PDA is notoriously resistant to chemotherapy and often diagnosed after the disease has spread, it carries a very poor prognosis with less than 20 percent of patients surviving past twelve months after diagnosis. A new Fred Hutch study led by former graduate student Dr. Justin Mirus in the labs of Dr. Sunil Hingorani (Clinical Research and Public Health Sciences Divisions) and Dr. Paul Lampe (Human Biology and Public Health Sciences Divisions), addressed some of these challenges by applying a pancreas cancer-tailored, high-density antibody microarray to a mouse model of PDA, to uncover novel candidate biomarkers. "Developing better strategies for early detection of the disease at potentially curable stages is confounded by the difficulties in identifying the appropriate experimental population", explained Dr. Hingorani.

The authors had previously developed a mouse model of PDA that employed conditional, pancreas-specific expression of mutant forms of the *Kras* oncogene and the *Trp53* tumor suppressor (known as the KPC model). This model had been shown to recapitulate many aspects of the human disease (Hingorani et al., 2005). "Interrogating samples from these models at histologically defined stages of preinvasive and invasive disease with a tailored, high-density antibody array platform developed by Dr. Paul Lampe, provided a unique opportunity to identify clinically meaningful biomarkers for this disease", said Dr. Hingorani. As mentioned above, the authors first developed a custom antibody microarray with over 2,500 antibodies that targeted proteins known to be involved in PDA pathogenesis, as well as proteins with a wide range of functions. Next, the investigators interrogated this antibody microarray platform with pancreata from KPC and control mice at 2 and 4 months of age. The 2-month old mice represented early stage disease while the 4-month old mice were characterized by preinvasive as well as invasive PDA. Overall, 71 proteins distinguished KPC pancreatic tissue from normal pancreas. Cross-referencing the 71 proteins with a pancreas cancer biomarker database revealed that 42 of these had been previously implicated in pancreas cancer, whereas the remaining 29 represented novel potential biomarkers. To validate these markers, the authors focused on a set of 16 proteins that were highly upregulated in KPC tissue and found that 7 could be validated by immunoblotting. Importantly, 6 out of the 7 novel biomarkers distinguished KPC mice from mice harboring chronic pancreatitis. For the remainder of the study, the authors

further characterized the spatiotemporal expression of one of the protein markers, the serine/threonine kinase STK4. This immunohistochemical analysis showed that STK4 expression increased from 2-month to 4-month disease and then plateaued, suggesting a potential role for STK4 in the progression from early stage disease to PDA. Finally, the authors queried human tissue microarrays from 25 human PDA and 8 non-disease controls, and found that STK levels indeed increased in human PDA.

In summary, this study combined a faithful model of PDA with a custom antibody microarray, to identify and validate 7 novel PDA candidate biomarkers, and further characterized STK4 as a marker of human PDA. While the function of STK4 in PDA progression is currently unknown, "the kinase identified in this case may also serve as a therapeutic target, an additional avenue that is being explored", added Dr. Hingorani.

[Mirus JE, Zhang Y, Hollingsworth MA, Solan JL, Lampe PD, Hingorani SR](#). 2014. Spatiotemporal proteomic analyses during pancreas cancer progression identifies STK4 as a novel candidate biomarker for early stage disease. *Mol Cell Proteomics*. pii: mcp.M113.036517. [Epub ahead of print]

See also: [Hingorani SR, Wang L, Multani AS, Combs C, Deramaudt TB, Hruban RH, Rustgi AK, Chang S, Tuveson DA](#). 2005. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. *Cancer Cell*. 7(5):469-83.

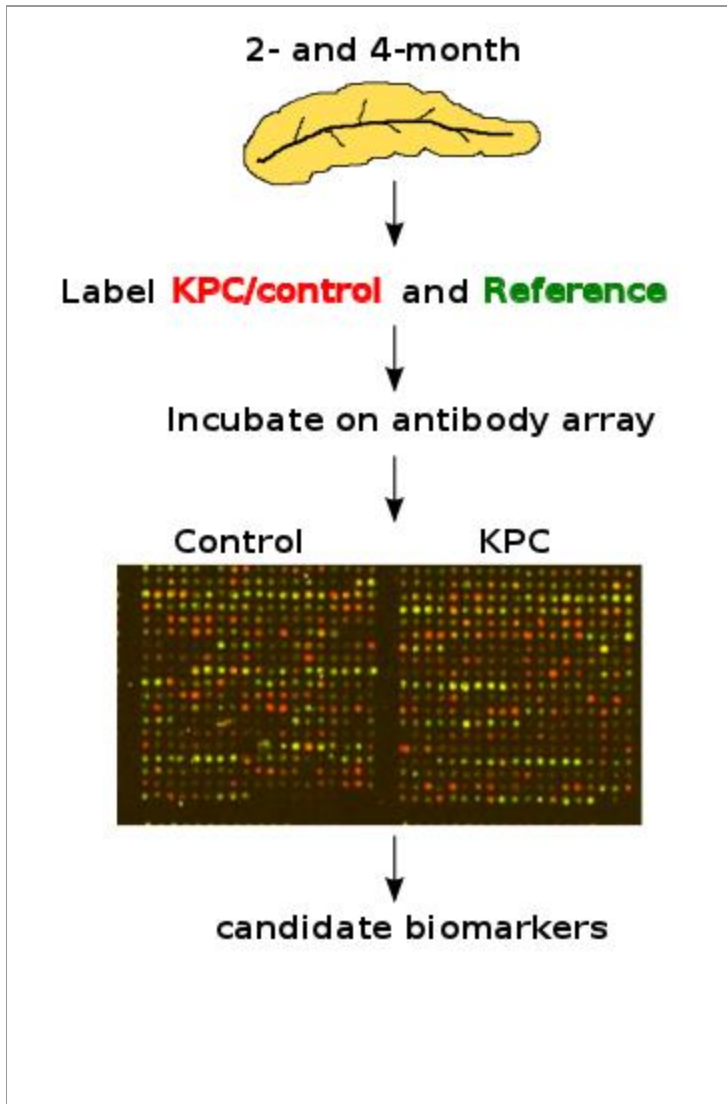


Image by Dr. Alexandre Neves

Schematic of an antibody microarray protocol. Protein lysates from mice with pancreatic cancer (KPC) and from normal pancreata are incubated on a pancreas cancer-tailored antibody microarray. Computational analysis of proteins elevated in KPC relative to controls uncovers candidate biomarkers.