

Commentary: CHIPping away pancreatic tumors?

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In a recent article published in *Oncotarget*, Wang and colleagues report on an interesting observation of a new potentially useful approach in the management of pancreatic cancer (1).

Pancreatic cancer is one of the deadliest with a mortality rate of over 80%. According to the American Cancer Society, in 2014, 46,420 individuals will be diagnosed with pancreatic cancer in the United States alone, and 39,590 will eventually die. Despite advances in research and development of modern therapies, pancreatic cancer remains fatal mainly due to the lack of early diagnosis. Pancreatic cancer is thought to develop over a long period of time with accumulation of successive mutations in various oncogenic proteins. There are four known genetic loci; KRAS, p53, cdkn2a and SMAD4, that are prevalent in pancreatic tumors and are thought to be early events leading to pancreatic cancer (2). KRAS mutations cause constitutive activation and downstream signaling whereas p53 and cdkn2a mutations inactivate the tumor suppressing activity of these proteins. SMAD4 alterations have been correlated with tumor metastasis (2). Alterations in other biomarkers such as epidermal growth factor receptor (EGFR), CXCR4 and hENT1 contribute significantly to the rapid progression of pancreatic tumors; however, they have been found unsuitable for early detection and screening.

Pancreatic tumors are classified into two main types: exocrine and endocrine. The exocrine or ductal pancreatic adenocarcinoma, found in 96% of patients, is very aggressive with an observed 5-year survival rate of 12-14% for patients diagnosed in stage I. The remaining 4% are classified as endocrine tumors, located in the islets of the pancreas and have a better prognosis with a 5-year survival rate of 64% for patients diagnosed at stage I. Current therapeutic interventions employ combination of surgery, radiation, chemotherapy and targeted therapy that, as of today, provide marginal survival benefit but are

clearly insufficient (3). It was thought that known genetic alterations might provide early screening and detection in individuals with a family history of pancreatic cancer, however, in most cases screening for these biomarkers is impractical. Furthermore, accumulation of numerous genetic alterations before any clinical manifestation significantly decreases the effectiveness of the treatment regimen.

The high mortality rate of pancreatic cancer is due to lack of early symptoms and rapid progression upon clinical manifestation. Furthermore, early stage detection of pancreatic cancer is seldom achieved due to lack of appropriate biomarkers, resulting in even higher mortality rates. Therefore, ongoing research has been focused on identifying novel tools and biomarkers for early detection and screening.

In the article by Wang *et al.*, the authors demonstrate that the C-terminal Hsp70-interacting protein (CHIP), a potential biomarker and therapeutic target, acts as a novel tumor suppressor in pancreatic cancer by targeting EGFR stability and downstream signaling (1). EGFR is a transmembrane tyrosine kinase that has been implicated in various human epithelial malignancies, including colon, head and neck, lung and pancreatic cancer (4). Ligand binding to EGFR stimulates tyrosine kinase activity leading to induction of various signaling pathways such as Akt, Src and FAK. Because KRAS is a downstream target of EGFR, EGFR may not play an important role in pancreatic tumors with activating mutations of KRAS. However, tumors with both EGFR overexpression and KRAS mutations are more aggressive and in some cases shorten survival (5). Conversely, EGFR deletion completely prevented pancreatic cancer formation in a KRAS mutant mouse model (6). Therefore, targeting EGFR with the tyrosine kinase inhibitor, erlotinib, in combination with chemotherapy has been used clinically with moderate success.

CHIP, a ubiquitously expressed E3 ubiquitin ligase, is involved in several malignancies, including breast, gastric and prostate cancer (7). It has two functional domains: an N-terminal tetratricopeptide repeat (TPR) domain, involved in protein-protein interactions, and a carboxyl-terminal U-box domain, involved in ubiquitin binding (8). *In vitro* and *in vivo* studies have shown that CHIP acts as a tumor suppressor in breast, gastric and prostate tumors. However, elevated CHIP is also associated with malignant glioma and esophageal squamous cell carcinoma (7). Thus, CHIP seems to function differently in different tumor environments suggesting a complex modulation of downstream targets.

EGFR activation stimulates downstream signaling pathways that regulate cell proliferation, apoptosis, migration and survival (4). Since EGFR is overexpressed in pancreatic tumors, Wang *et al.* studied the functional interaction between CHIP and EGFR. CHIP knockdown increased EGFR levels and increased phosphorylation of downstream targets. CHIP overexpression had the opposite effect, with decreased EGFR levels and reduced phosphorylation of downstream targets. High mortality rates from pancreatic cancer are a result of aggressive tumor growth and metastasis to other organs, such as the liver. CHIP knockdown showed an increase in tumor volume, *in vitro* migration and liver metastasis, whereas CHIP overexpression decreased tumor volume, *in vitro* migration and liver metastasis. This data strongly suggests, as noted by the authors, that CHIP acts as a tumor suppressor in pancreatic cancer by interacting with EGFR and inhibiting EGFR activity and signaling. Furthermore, the authors demonstrated a strong negative correlation between CHIP protein levels and patient survival by performing immunohistological analysis of human pancreatic tumors. It is to be noted that the tumor suppressor role of CHIP is consistent with similar observations in breast, gastric and prostate cancer (7).

The molecular chaperone heat shock protein 90 (Hsp90) interacts with numerous proteins and regulates protein folding and stability (9). In many studies Hsp90 has been found in a complex with heat shock protein 70 (Hsp70), a chaperone involved in ubiquitination and proteasomal degradation of client proteins (10). Essentially, Hsp90 and Hsp70 have opposite roles, in that Hsp90 inhibits, whereas Hsp70 promotes, substrate ubiquitination. The ubiquitin E3 ligase, CHIP interacts with both Hsp90 and Hsp70 via the TPR domain and is responsible for ubiquitin-mediated proteasomal degradation of client proteins (11). The Hsp90-Hsp70-CHIP complex has been implicated in

protein quality control and regulates various client proteins. EGFR, a known Hsp90 client protein, is protected against CHIP-mediated ubiquitination under normal conditions due to Hsp90 chaperone function. Wang *et al.* showed that Hsp90 inhibition accelerated the degradation of EGFR indicating a key role of Hsp90 in regulating stability of EGFR in pancreatic tumors.

Studies have shown that inhibition of EGFR by erlotinib, in combination with the nucleoside analog, gemcitabine, an antimetabolite that targets ribonucleotide reductase, prolongs survival in patients with pancreatic cancer (12). The data shown by Wang *et al.* demonstrate that inhibition of EGFR by the tyrosine kinase inhibitor, erlotinib, alone, did not have a significant impact on pancreatic tumor growth in a mouse model; however, combination of erlotinib and CHIP overexpression significantly reduced tumor growth.

Overall, targeting EGFR activity and signaling seems to be at least partially effective against pancreatic cancer. CHIP levels could be employed as a biomarker for tumor growth and metastasis, however, the role of CHIP in early diagnosis will require further studies.

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