Editorial Commentary

From pancreatic cancer to lung cancer, ZIP4's oncogenic function continues

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Lung cancer is still the leading cause of cancer-related death among both men and women, and accounts for close to one-fourth of all cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) is composed of adenocarcinoma, large cell carcinoma and squamous cell carcinoma and constitutes over 80% of lung cancer cases. NSCLC has an overall 5-year survival rate of around 20% (1), despite great efforts made worldwide over the past decades to combat lung cancer. Pancreatic cancer is projected to be the second leading cause of cancer-related death by 2030 in the United States and likely in most parts of the world due to its rising incidence and minimal improvement in the treatment outcomes. Pancreatic ductal adenocarcinoma, which constitutes more than 90% of pancreatic cancer, has an overall 5-year survival rate of 8–9%. Therefore, thorough understanding of the biology of lung cancer and pancreatic cancer and identification of novel therapeutic targets are still urgently needed and may eventually bring hopes for substantially improving the survival of these two high-mortality malignant diseases.

Zinc, an essential trace element and nutrient in humans, functions as a catalytic cofactor for multiple enzymes and plays an important role in multiple processes including cell growth and boosting of the immune system (2). Zinc is one of the most common trace elements taken by cancer patients (3) and may be useful in the prevention of oral toxicities during irradiation although it does not help in chemotherapy-induced side effects (3). Zinc modulates oxidative stress, inhibits inflammation and thus might help to prevent certain types of cancer (4,5). One meta-analysis of the association between serum zinc levels and lung cancer found that the serum zinc levels in lung cancer patients were significantly lower than in controls in both European and Asian populations (6). In fact, zinc deficiency occurs in cancer patients of many types, such as prostate cancer, which may contribute to increased cancer risks based on some epidemiological studies (2,7). Hence, it has even been recommended that zinc can be added to cancer treatment regimens to alleviate zinc deficiency in cancer patients (2). However, concerns with zinc application in cancer patients come from some controversial biological functions of zinc in cancer. The biological functions of zinc have not been fully elucidated. There was a report on the inconsistent zinc levels between serum and cancer tissues in some cancer types including breast, lung and gastric cancers, in which tissue zinc levels were increased albeit with decreased serum zinc level (7). Overexpression of zinc importers such as ZIP4 in many types of cancer may explain the increase of the intracellular zinc levels in the cancer tissues and have recently been implicated in promoting tumor growth and progression as discussed below.

In mammalian cells, zinc concentrations are controlled by two zinc carrier families: intracellular zinc concentration is increased by ZIP family proteins as zinc importers through promoting extracellular uptake, while reduced by ZnT transporters through efflux (8,9). ZIP4 (encoded by *SLC39A4* gene) is one of the ZIP family and has been suggested to be a prominent cancer-related zinc

importer (10). The oncogenic function of ZIP4 was initially reported by Dr. Li's group (11) in 2007 when studying its expression and function in human pancreatic cancer. Continuous efforts over the past 15 years from this group have convincingly demonstrated that ZIP4 is substantially overexpressed in the majority of clinical pancreatic ductal adenocarcinoma specimens and significantly contributes to human pancreatic cancer pathogenesis and progression (11-15). Its overexpression and involvement in promoting cancer growth and progression were later also demonstrated in other cancer types, including hepatocellular carcinomas (16-18), nasopharyngeal carcinoma (19), oral cancer (20), colon cancer (21), ovarian cancer (22,23) and glioma (24,25) although it was also reported to be downregulated with tumor-suppressor function in prostate cancer (26).

It was previously reported that ZIP4 was overexpressed in some lung cancer cell lines and NSCLC tumor tissues (59%; 26/44), showing consistency with results from lung cancer datasets such as the TCGA database (27). However, the molecular mechanisms underlying ZIP4-mediated NSCLC progression were unclear. In a recently published study from the Li group, Jiang *et al.* (28) confirmed that ZIP4 was overexpressed in NSCLC tumor tissues from multiple cohorts of patients, among which high ZIP4 was detected in 36.4% (32/88) of squamous carcinoma and 60.5% (49/81) of lung adenocarcinoma cancer tissues, respectively, while none of the adjacent tissues showed high ZIP4 expression. Moreover, high ZIP4 expression was associated with more advanced stage and higher grade of NSCLC and, importantly, negatively associated with overall survival and progression-free survival in patients with NSCLC.

To understand the biology of ZIP4 in NSCLC, these investigators found that overexpression of ZIP4 promoted cell migration, invasion and metastasis both *in vitro* and in a mouse lung metastasis model despite having a limited effect on tumor cell survival and growth, while silencing of ZIP4 exerted opposite effects, suggesting that ZIP4 is primarily involved in positive regulation of NSCLC tumor invasion, migration and metastasis. Mechanistically, Jiang *et al.* showed that ZIP4 overexpression increased the expression of Snail, Slug and N-cadherin, while genetic inactivation of ZIP4 downregulated the expression of these genes. Furthermore, Snail, which functions as a transcriptional factor to modulate N-cadherin expression, was shown to be involved in the process of ZIP4-mediated NSCLC migration and invasion. In mouse lung metastatic tumors, ZIP4 expression positively correlated with the levels of Snail, Slug and N-cadherin. Hence, it appears that ZIP4 acts as an important regulator of the Snail/N-cadherin signaling axis in promoting NSCLC progression and metastasis via facilitating the epithelial-mesenchymal transition (EMT) process. As such, ZIP4 was suggested to be a novel predictive marker for poor outcome in NSCLC and a potential therapeutic target in NSCLC (28). This study has clearly provided important insights into the role of ZIP4 in the promotion of NSCLC progression.

It is well known that ZIP4 functions as an important zinc importer to elevate intracellular concentrations of zinc through promoting extracellular zinc uptake (8,9). In a recent study, it was shown that brain metastatic triple-negative breast cancer (TNBC) cells acquire an abnormally high zinc concentration and that the zinc concentration is especially important for the microenvironmental modulation of brain metastatic cells (29). Although ZIP4 overexpression facilitated tumorigenicity in TNBC, it was not sufficient to confer the tested cell line all of the metastatic potential that the brain metastatic TNBC cells had (29). While zinc deficiency occurs commonly in many cancer types including lung cancer (2,5,6) as discussed above, it seems that serum and tissue or intracellular zinc may have a different impact on cancer progression. This notion was supported by a recent study showing that both decreased levels of serum zinc and increased levels of ZIP4 expression in cancer tissue are associated with a poorer prognosis in patients with stages I-III colon cancer (21).

In the study by Jiang *et al.* (28), the connection between ZIP4 and intracellular zinc was not explored. Thus, it remains unknown whether the intracellular level of zinc plays a role in mediating the critical function of ZIP4 as a regulator of Snail/N-cadherin signaling axis in promoting NSCLC progression or whether ZIP4 exerts these biological functions in NSCLC tumor cells and tissues via increasing the concentration of intracellular zinc. It was previously reported that depletion of intracellular zinc induced apoptosis of pancreatic cancer cells, whereas ZIP4 confers a resistance to zinc depletion-induced apoptosis (30). Jiang *et al.* showed that, in NSCLC cells, manipulation of ZIP4 expression (overexpression and knockdown) did not apparently alter tumor cell survival and growth (28). Although such an inconsistency could be explained by the biological difference between pancreatic cancer and NSCLC, it would need to be reconciled in the future. In relation to this issue, other critical questions to be addressed include what the real relationship between serum zinc level and intracellular zinc concentration is and how

this relationship impacts the biology and clinical outcome of lung cancer as well as other cancers whose patients have decreased serum zinc levels (6). Having these critical questions addressed is of particular clinical significance considering that zinc is one of the trace nutritional elements that cancer patients most commonly take (3) and has been recommended to be included in cancer treatment regimens to correct zinc deficiency in cancer patients and potentially to treat cancer (2).

In this study by Jiang *et al.*, it has been shown that ZIP4 induces Snail expression and activity, resulting in activation of N-cadherin to promote EMT and metastasis in NSCLC. How ZIP4 positively regulates Snail expression and activity remains to be examined. Since Snail is a zinc-dependent transcriptional factor (31), it is reasonable to question whether zinc plays a role in the transcriptional regulation. In this study, ZIP4 was also proposed as a potential therapeutic target in NSCLC (28). The challenge is how we can target this protein for the treatment of NSCLC. Hence, further effort in this direction is needed. In summary, the findings from the Li group's prior studies and those from this study by Jiang *et al.* (28) have taken a critical step toward understanding the critical role of ZIP4 in the regulation of pancreatic cancer and NSCLC progression, respectively. Based on these studies, our continuous efforts in this direction are warranted and will eventually enable us to draw a complete picture of the role of ZIP4 including zinc in pancreatic cancer, NSCLC, and many other cancers, which may eventually lead to development of new therapeutic strategies by targeting ZIP4.

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