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Commentary

Proteomic profiling of key signatures from gastric lesions to early gastric cancer

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Gastric cancer (GC) is a leading contributor to global cancer incidence and mortality. It is frequently diagnosed in advanced stages [1,2]. The development of GC is preceded by multi-stage precancerous process. However, molecular signatures underling the dynamic changes of gastric lesions and development of early GC are not well understood. Although recent genomic findings from genomic profiling will facilitate 'next-generation' clinical initiatives in GC precision oncology and prevention [3], the protein sequences/structures are further modulated by post-translational modifications. For a more comprehensive and unbiased proteomic characterization, the Clinical Proteomic Tumor Analysis Consortium has performed mass spectrometry based proteomic and/or phosphoproteomic analyses of tumor tissues from patients with colon, breast, and ovarian cancers [4,5]. These studies have demonstrated that proteomic signatures can offer complementary information for patient stratification to genomic signatures. Several studies investigated proteomic changes between non-cancerous lesions vs GC or GC vs paired normal tissues but were limited by sample size [6–8]. Identifying molecular signatures and biomarkers associated with the progression of precancerous gastric lesions is an important need.

In a recent issue of EBioMedicine, Li and colleagues provide insights into dynamic changes of gastric lesions and development of early gastric cancer by in-depth proteomic profiling of 324 subjects in China [9]. Integrating these proteomic signatures, a risk prediction model significantly improved the ability to predict progression of gastric lesions and GC. Specifically, they identified 6 clusters that possessed similar trajectories, which demonstrated dynamic changes in proteomic profiles from mild gastric lesions, advanced gastric lesions to GC. Among these clusters, cluster-1 enriched in the pathways of biological oxidations and cellular amino acid metabolic process were highly expressed in advanced gastric lesions. Proteins in cluster 2 were enriched in digestion and metabolism of carbohydrates pathways and exhibited decreased expression from subjects with mild to advanced gastric lesions, and then a sharp decrease to GC. Clusters 3 and 4 were increased in GC, which has a diagnostic implication for GC. Additionally, they derived 4 molecular subtypes based on top 100 most-variant proteins. S1 representing proteomic-defined mild gastric lesion and S4 representing the most severe gastric lesion. The distribution of proteomic subtypes appeared independent from H.pylori infection. Logistic regression analyses based on prospective follow-up of Linqu validation subjects found that subtype-S4 had the highest risk of gastric lesion progression. In order to explore biomarkers that associated with gastric lesion progression, 1201 proteins were significantly increased in invasive GC in discovery cohort and further validated that 217 protein were associated the risk of early GC in the Linqu validation set. Among these 217 proteins, the authors demonstrated that four proteins-APOA1BP, PGC, HPX, and DDT were associated with the risk of gastric lesion progression to early GC. The expression of APOA1BP and PGC were significantly decreased among the patients of gastric lesion progression. Although there were no significant differences of the expression of HPX and DDT between baseline and endpoint due to limited sample size, there was a trend towards increased expression of HPX and decreased expression of DDT among progressed subjects at the endpoint. The prediction model significantly improved the ability to prognosticate gastric lesions by integrating risk score of 4 proteins as well as molecular subtypes. Consistent with proteomic results, the authors further confirmed that HPX was increased in HGIN and invasive GC, while APOA1BP, DDT and PGC showed significantly decreased expression in HGIN and invasive GC in 65 patients' samples.

These findings established a model that is associated with progression of gastric lesions to early GC. The current study by Li and colleagues sheds light on dynamic changes of proteomic landscape for gastric lesions and potential predictive biomarkers for the risk stratification on progression of precancerous gastric lesions to early GC. However, many questions remain before drawing conclusions such as the four markers should be validated in independent and larger cohort of GC TMA. In particularly, HPX is a 60-kDa plasma glycoprotein that binds to heme preventing heme-related oxidative stress and toxicity. Interestingly, HPX was increased in GC vs chronic gastric lesions in this study which is consistent with the proteomic profiling in breast cancer from Cine N et al [10]. Since HPX is a secreted protein, ELISA assay is highly recommended in larger cohorts of blood or stomach aspirate samples including normal control, early or late gastric lesions, IM and early or later GC and expect to be an early biomarker for GC. Future functional studies and tissue/blood assay on

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the four makers are required to identify the clinical usefulness of these markers either as diagnostic or therapeutic targets.

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Authors' contributions

Literature search: Y.F., S.Song; Data collection and interpretation: Y. F., S Song, J.A. Ajani; Writing: Y.F., S. Song; Revising: S. Song, J.A.Ajani.

Declaration of Competing Interest

The authors declare no conflict of interest.

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