Helicobacter pylori East Asian type CagA hijacks more SHIP2 by its EPIYA-D motif to potentiate the oncogenicityD.

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Commentator: Dr. Hsiu-Chi, Cheng Location: Room 601, Med College Building

Background: Helicobacter pylori is a major pathogen linked to gastric diseases, with its virulence factor CagA playing a key role in oncogenesis. The East Asian CagA subtype ($CagA^{E}$), featuring the EPIYA-D motif, exhibits greater carcinogenic potential than the Western CagA subtype ($CagA^{W}$) with the EPIYA-C motif, though the underlying mechanisms remain unclear.

Objective/Hypothesis: This study aimed to explore the role of SHIP2 in the heightened oncogenicity of $CagA^{E}$ and elucidate how the EPIYA-D motif contributes to this interaction. It was hypothesized that $CagA^{E}$ binds SHIP2 more effectively than $CagA^{W}$, enhancing oncogenic signaling.

Results: This study found that $CagA^{E}$ binds more SHIP2 than $CagA^{W}$, driven by the EPIYA-D motif's strong affinity for SHIP2's SH2 domain. This interaction enhances Akt signaling, inflammatory responses, and cellular migration and invasion. Structural analysis identified a critical Phe residue in EPIYA-D that drives the higher SHIP2 affinity. Mutating this Phe residue significantly weakened SHIP2 binding and reduced the oncogenic transformations induced by $CagA^{E}$. These results collectively underscore the molecular mechanisms underlying the heightened oncogenic potential of $CagA^{E}$.

Conclusion: $CagA^{E}$'s enhanced oncogenicity is due to its higher affinity for SHIP2, mediated by the EPIYA-D motif. This interaction amplifies Akt signaling and promotes malignant cell behaviors, providing critical insight into H. pylori's pathogenic mechanisms and potential therapeutic targets.