Principal Investigator: Wen Yi
Title: Regulation of Epidermal Growth Factor Receptor Signaling by O-GlcNAcylation

Abstract

Objectives: EGFR signaling plays a critical role in normal physiology such as cell proliferation and cell survival. Aberrant EGFR signaling has been closely associated with various pathologies. In this study, we aim to characterize a previously unknown mechanism for EGFR signaling regulation, and to explore its link with liver cancer development and chemoresistance.

Methods: In the preliminary study, we identified a high level of O-GlcNAcylation on HGS protein, which resides in endosomes and is critically involved in EGFR endosome targeting and degradation. In this study, we first characterized O-GlcNAcylation on HGS, including its modification stoichiometry, dynamics upon stimuli treatment, and sites of modification. Next, we examined how HGS glycosylation affected EGFR intracellular trafficking and degradation using immunofluorescent staining, and electron microscopy. Then we investigated whether HGS glycosylation affected cell proliferation and xenograft tumor growth. Lastly, we performed cellular experiments to probe the effect of HGS glycosylation on liver cancer chemoresistance.

Results: We showed that HGS is modified by O-GlcNAcylation at three sites (Ser297, Ser299 and Ser300). O-GlcNAcylation of HGS inhibits its interaction with STAM, another key protein in the early endosome. Thus, HGS glycosylation impairs the formation of endosomal sorting complex ESCRT-0. Moreover, HGS glycosylation increases HGS ubiquitination and decreases the protein stability in cells. Consequently, HGS glycosylation inhibits EGFR endosomal sorting and lysosomal degradation, leading to accumulation of EGFR and prolonged EGFR signaling in cells. Moreover, HGS glycosylation promotes liver cancer cell proliferation, and xenograft tumor growth in nude mice. Lastly, we demonstrate that HGS glycosylation promotes chemoresistance of liver cancer cells against sorafenib. Collectively, our study reveals a previously uncharacterized role of O-GlcNAcylation in regulating receptor tyrosine kinase endocytic trafficking and signaling, and provides an important insight into the development and progression of diseases with aberrant growth factor signaling, such as cancer, obesity, and diabetes.