Molecular basis of fate-determination of glycoproteins by the sugar-recognizing proteins in cells

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Processing of the *N*-glycans is thought to be coupled with fate-determination of glycoproteins in cells [1]. A series of processing intermediates of glycans, which are generated by the actions of the specific enzymes, express biological signals recognized by the intracellular proteins that operate as molecular chaperones, cargo receptors, and endoplasmic reticulumn (ER)-associated degradation (ERAD) factors. Hence, these sugar-recognizing proteins govern the intracellular processes such as folding, transport, and degradation of glycoproteins. However, the molecular and structural basis of the glycoprotein fate-determination in cell has been poorly understood.

To address this issue, we conducted comprehensive and quantitative analyses of sugar-protein interactions using a sugar library in conjunction with frontal affinity chromatography (FAC)[2,3]. Interestingly, our FAC data revealed that these proteins exhibit the distinct sugar-binding specificities according to their intracellular functions. On the basis of these data, we propose a model in which these proteins play cooperative and complementary roles: Upon deglucosylation, the glycoproteins exit from the chaperone-assisted folding cycle and move on to the anterograde transport, while misfolded glycoprotein that inadvertently escape from the quality control in the ER retrogradely transported to the ER. The mannose trimming in the ER prompts glycoprotein to leave the folding cycle and lead to ERAD. We provide the structural basis for the functional mechanisms of these intracellular proteins using the NMR spectroscopy.

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