Underlying protein shape is a determinant of glycoform diversity

Oliver GRANT [1], Eliza GAZAWAY [1], Robert J. WOODS [1]

[1] Complex Carbohydrate Research Center, University of Georgia, Athens, GA 30602. USA

olgrant@uga.edu

It is frequently observed that a given glycoprotein can contain both predominantly highly-processed and under-processed glycans at different N-linked glycosylation sites. The differences occur despite these sites encountering the same environment while trafficking through the secretory pathways of the endoplastic reticulum and Golgi apparatus. Understanding the structural basis for such differences is important in fundamental processes, including innate and adaptive immune responses(1,2). Our group and others have proposed and demonstrated that accessibility of the glycosylation site correlates with the observed glycoforms at that site(2,3,4). Our molecular modeling efforts combined with experimental work predicted and confirmed that removal of an adjacent subdomain would trigger processing of a naturally under-processed site(4).

In this work we use molecular modeling to demonstrate that correctly combining the 3D structure of ERManI, an enzyme that acts early in the processing pathway, with molecular dynamics simulations of a target glycoprotein can be used to predict whether a given glycosite will be under-processed or not. We outline the subtleties required to successfully employ the technique and demonstrate its usefulness on Pdi1p, a well-characterized model glycoprotein, as well as the more challenging HIV Env SOSIP trimer. The work provides insights into enzymatic recognition of N-glycans and how underlying protein shape is the predominant determinant of glycoform diversity.

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