Deciphering the long distance-glycosylation preferences of GalNAc-Ts

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GalNAc-Ts are a large family of glycosyltransferases that uniquely feature both a catalytic and lectin domain and that are responsible of the mucin-like glycosylation found in higher eukaryotes. To date, the underlying molecular basis of how GalNAc-Ts present distinct long distance-glycosylation preferences remained elusive. Here, through the first crystal structures of complexes of GalNAc-T2 with glycopeptides, we show how the activity profile of GalNAc-T2 is dictated by conformational heterogeneity and relies on a flexible linker located between the catalytic and the lectin domains. Our results also shed light on how GalNAc-Ts generate dense decoration of proteins with O-glycans, and suggest that the flexible linker dictates the lectin domain rotation, which in turn is responsible for the long distance-glycosylation preferences.