Review of: "Genetic regulation of post-translational modification of two distinct proteins"

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The paper by Landini, et al. takes a genomic approach to understanding the understanding the glycosylation of two proteins, transferrin and immunoglobulin G (IgG) [1]. The authors performed GWAS of 35 distinct N-glycan modifications that can be detected on human transferrin (Tf). 6 loci were found to be significantly associated with individual glycans in two distinct genetic cohorts. Those 6 genes were glycosylation enzymes MGAT5, ST3GAL4, B3GAT1, FUT6 and FUT8 plus the transferrin gene itself. A similar analysis was then performed with IgG. This revealed two separate glycosylation enzymes, ST6GAL1 and MGAT3, as well as FUT6 and FUT8.

Colocalization analysis was performed to assess whether the same variants in FUT6 and FUT8 could be controlling glycosylation of both substrate proteins. While two individual glycan traits of Tf co-localized with the same variants within FUT6, they did not co-localize with FUT8 variants. This discrepancy can be understood by the mapping of the variants to putative transcription factor binding sites at FUT6 and FUT8. Since Tf is expressed strongly in hepatocytes and IgG expression is limited to B cells, it is reasonable that distinct regulatory proteins would be present. Regulatory sequence analysis pointed to the factors HNF1A as potentially regulating Tf with IKZF1 regulating IgG heavy chain expression.

The ability of the FUT8 locus to modulate the glycosylation of both TF and IgG is not surprising. FUT8 is the only enzyme capable of adding a-1,6 linked core fucose to N-glycans and both Tf and IgG have been reported to undergo core fucosylation [2]. The ability of the FUT6 locus to affect both Tf and IgG is less expected. FUT6 is involved in antennary a-1,3 fucosylation [3]. As Landini et al state, IgG is not typical for IgG; they postulate that the enzyme might be required to modify another protein or enzyme involved in IgG post-translational modification. This is an interesting possibility to consider. However there are other possibilities as well.

Although the Landini, et al. paper focused on IgG, which is highly abundant, the IGH heavy chain locus contains sequences that encode the heavy chains for other Ig species, including IgE. IgE has multiple site of N-linked glycosylation [4]. Perhaps the genetic linkage between FUT6 and IgG is a consequence of class switching from IgG to IgE. A recent report has implicated FUT6 as being important for basophil function [5]. Defects in FUT6 function leads to a loss of surface Sialyl-Lewis x on the surface of the cells and lower IgE titers. The linkage between these observations may be worth exploring in the future.

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