

Alzheimer and sugars

From: <http://www.functionalglycomics.org/fg/update/2008/080710/full/fg.2008.30.shtml>

**Note that GlcNAc is glucose (“Glc”) with the functional groups we discussed: an amino group (“N”) and another one called the acetyl group (“Ac”)**

## **Alzheimer disease and protein turnover: A GlcNAc trick** *Functional Glycomics* (10 July 2008) | doi:10.1038/fg.2008.30 . viewed: July 28, 2008

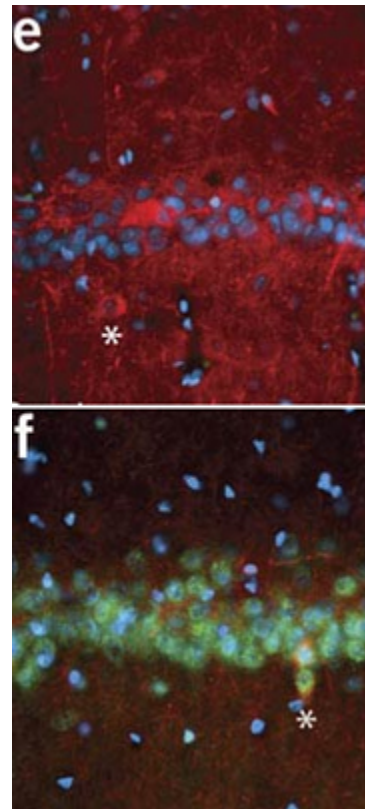
Protein turnover may be regulated by O-glycosylation with *N*-acetylglucosamine (GlcNAc), and an O-GlcNAcase-inhibitor complex and an O-GlcNAc transferase homolog reveal surprising new structural features.

**Figure Legend:** O-GlcNAcylation (green) increases and phosphorylation (red) decreases in the rat hippocampus after (bottom image) thiamet-G treatment. From Yuzwa *et al.*; click [here](#) for a full size image.

O-GlcNAcylation of nucleocytoplasmic proteins is ubiquitous, reversible and has been shown to regulate the life span of proteins such as [p53](#). O-GlcNAc transferase (OGT) attaches and O-GlcNAcase (OGA) removes GlcNAc from serines and threonines, and both enzymes have a broad substrate specificity. O-GlcNAcylation has been shown to play a role in dynamic processes such as [neuronal activity](#), and increasing evidence shows that it [interacts](#) with phosphorylation in many signaling pathways. Three publications now provide new insight into the biological role of O-GlcNAcylation and the enzymatic mechanisms of OGT and OGA.

Reporting in *FASEB*, Guinez *et al.* noted a ubiquitination peak followed by maximum O-GlcNAcylation after the application of heat stress to liver HepG2 cells. Furthermore, cells grown in the presence of glucosamine had more O-GlcNAcylation and ubiquitinated proteins, whereas OGT knockdown by RNA interference reduced these amounts and diminished the viability of HepG2 cells towards heat. Thus, O-GlcNAcylation and ubiquitination appear to be linked, with O-GlcNAcylation being a novel player in cellular stress reactions.

Proteasome subunits and components of the deubiquitination pathway have been [shown](#) to be dynamically O-GlcNAcylation. When HepG2 cells were incubated with glucosamine, Guinez *et al.* observed increased O-GlcNAcylation of the [E1 enzyme](#) — which activates ubiquitin and initiates ubiquitination — and decreased O-GlcNAcylation



when OGT was silenced. Taken together, these results add further evidence for a general role of O-GlcNAcylation in protein turnover.

In *Nature Structural and Molecular Biology*, Martinez-Fleitez *et al.* highlight the structural features of an OGT homolog that contribute to its broad specificity. The tetratricopeptide repeat (TPR) domain, which is known to bind the OGT substrates, forms a superhelical structure. The length and shape of the superhelical groove, which may direct the polypeptide towards the C-terminal glycosyltransferase domain, confers only minimal structural requirements onto the substrate. Martinez-Fleitez *et al.* hypothesize that the differences in O-GlcNAcylation efficiency may derive from the orientation of substrates in OGT's active center, which is also dependent upon the affinities of substrates and other interacting molecules to the TPR domain. Furthermore, the structure of the superhelical TPR domain harbors more putative binding sites for proteins that can alter OGT's enzymatic activity.

Published in *Nature Chemical Biology*, Yuzwa *et al.* use the earlier [observation](#) that microtubule-associated protein tau ([MAPT](#)) is overphosphorylated and under-O-GlcNAcylated in Alzheimer disease (AD) as a motivation for developing an OGA inhibitor that has the potential to change the ratio of these modifications on MAPT. With the structural features of known OGA inhibitors in mind, the authors synthesized a highly potent inhibitor named thiamet-G that interacts electrostatically with the catalytic residue Asp 242 in OGA rather than through weak hydrogen bonds. The inhibitor is also highly selective as it has a 37,000-fold stronger affinity to OGA than to the structurally related lysosomal beta-hexosaminidases.

The authors went on to test the effectiveness of thiamet-G for increasing O-GlcNAcylation in both rats and the neuronal cell line PC12. After administering thiamet-G, there was a strong decrease in MAPT phosphorylation on Ser 396 — a marker for AD disease status. These results offer remarkable insight into the mechanisms of OGA and open up the possibility for developing brain-specific inhibitors of OGA.

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### **Original paper:**

1. Guinez, C. *et al.* Protein ubiquitination is modulated by O-GlcNAc glycosylation. *FASEB Journal* 23 April 2008 (doi: 10.1096/fj.07-102509) | [Article](#) |
2. Martinez-Fleitez, C. *et al.* Structure of an O-GlcNAc transferase homolog provides insight into intracellular glycosylation. *Nature Structural & Molecular Biology* 15, 764–765 (2008). doi:10.1038/nsmb.1443 | [Article](#) |
3. Yuzwa, S. A. *et al.* A potent mechanism-inspired O-GlcNAcase inhibitor that blocks phosphorylation of tau *in vivo*. *Nature Chemical Biology* 29 June 2008 (doi: 10.1038/nchembio.96) | [Article](#) |