CELL CYCLE NEWS & VIEWS

O-GlcNAcylation: A sweet thorn in the spindle!

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Cell cycle is finely orchestrated by a multitude of actors rigorously organized spatially and temporally, and dysregulation of this process is one of the hallmarks of cancer. During the last half century, many efforts have been made to describe and understand the regulation of cell cycle by post-translational modifications such as phosphorylation, acetylation, methylation, ubiquitination or SUMOylation. In the early 1990's, the recently discovered modification O-GlcNAcylation attracted attention: in response to mitogens, T-lymphocytes' cytosolic and nuclear O-GlcNAcylated proteins were respectively down and upregulated.¹ Since then, many studies showed that interfering with cell cycle progression destabilizes O-GlcNAcylation dynamics and *vice versa*.

In 2005, the last author of this report, Chad Slawson, and Gerald W. Hart, who is considered to be the “O-GlcNAc's father,” observed that modifying the expression of the O-GlcNAc cycling enzymes greatly affected mitotic progression.² They provided evidence that OGT (O-GlcNAc transferase), the enzyme that adds the GlcNAc residue onto the target proteins, localized to the mitotic spindle during mitosis and that its overexpression resulted in aneuploidy (in an independent report, our group found that the metaphase II meiotic spindle was O-GlcNAc modified and interacted with OGT in *Xenopus laevis* oocytes.³). Latter, Slawson and Hart showed that OGT and OGA (O-GlcNAcase) that removes the modification, interacted with the mitotic kinase Aurora B and PP1 (Protein Phosphatase 1) to control midbody stability and vimentin phosphorylation during M phase.⁴ In this Cell Cycle volume,⁵ Lanza et al pointed out cell cycle aberrations in OGA knockdown HeLa cells. Consequently to blockade of O-GlcNAc removal, they observed a disturbance in cyclins expression, an abnormal RB (Retinoblastoma) phosphorylation, an increased inhibitory phosphorylation at tyrosine 15 of CDK1 (Cyclin dependent kinase 1 that binds cyclin B to form the M-phase promoting factor in eukaryotes) and, in accordance with their previous report,⁶ a tighter chromatid packing at the spindle midzone. More interestingly again, EWS (Ewing Sarcoma Breakpoint Region 1) is O-GlcNAcylated and its

modification was increased in OGA knockdown cells explaining all or part the aberrant spindles and aneuploidy. While the authors did not dismiss the possibility that an unknown O-GlcNAcylated protein impairs the correct localization of Aurora B to the spindle midzone, it appears that EWS, known to localize and to recruit the mitotic kinase to the spindle during metaphase,⁷ is the designed culprit that under the wrong influence of sugars pushes the thorn into the well-oiled spindle machine!

The work by Lanza et al provides once again proof that a misbalance in O-GlcNAcylation dynamics leads to cell cycle defects. This glycosylation has been shown to interfere at many levels of the cell cycle and to fluctuate all along this complex process. UDP-GlcNAc, the nucleotide-sugar that supplies the GlcNAc moiety for O-GlcNAcylation processes is at the crossroad of many metabolic pathways and is therefore considered a nutritional sensor: it can be assumed that O-GlcNAcylation of cell cycle key-regulatory factors depends upon nutritional status and is modified in patients suffering metabolic diseases. In light of the paper from Lanza et al, a deregulation of spindle formation could arise from a default of the O-GlcNAcylation machinery and may be associated to cancer development. Unfortunately, it should not be evident to set upright the correct O-GlcNAcylation levels since, as underlined by the authors, a precise homeostatic level of O-GlcNAc cycling is necessary for the spindle and for all other crucial components or regulators of cell cycle.

Potent and selective OGT and OGA inhibitors were synthesized and showed high efficiency in cultured cells and animal models. But, because in mammals O-GlcNAcylation is found in all cell types and because it interferes with most of the crucial biological processes, it is unlikely that inhibitors of the O-GlcNAcylation enzymes is conceivable. On the other hand, designing small-molecules inhibiting proteins interactions, e.g. OGT-cell cycle regulators, seems wiser and more selective for a precise molecular process. While less evident to conceive, these inhibitors may appear as promising tools to remove the thorn off the spindle.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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