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Ubiquitylation is one of the most common protein modifications and arguably the most versatile. How this post-translational modification shapes the intracellular signaling networks that dictate specific cellular states and behaviors is a central focus of **the Oh laboratory**. We recently identified a novel ubiquitin-dependent mechanism that integrates gene expression with cellular division to preserve the identity of proliferating cell types. Our current focus is to elucidate how various cancer cell types hijack this system to confer specific proliferative and survival advantages. The goals of this exploration are to target the ubiquitin system for drug discovery and to find new strategies to rewire the gene expression landscape of cancer cells.

How cells process information and make decisions is essential for their survival. The intracellular signaling events that ultimately evoke specific cellular responses make frequent use of ubiquitylation. Failure to properly do so can cause abnormal cell growth and uncontrolled proliferation, both hallmarks of tumorigenesis. Our lab is broadly interested in understanding the ways in which ubiquitylation gates key decision-making processes and how misregulation of this modification contributes to various malignancies.

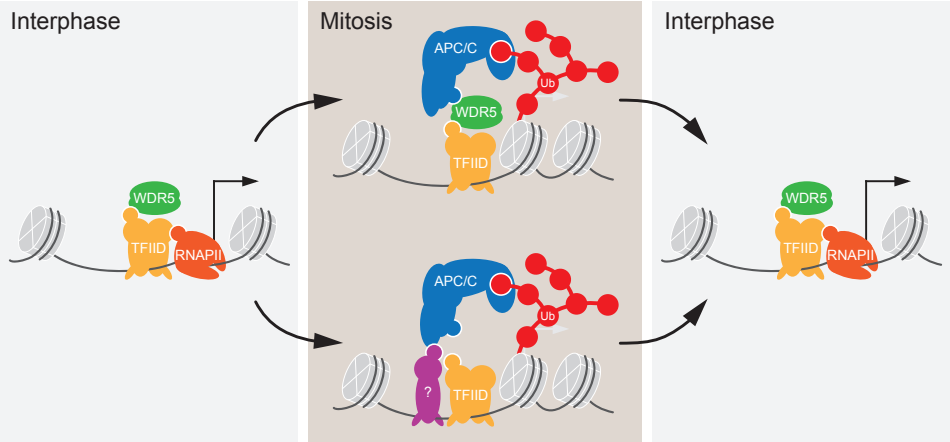
Ubiquitin-dependent control of gene expression

The identity of every cell is governed by the coordinated expression of specific gene networks. Yet dividing cells temporarily halt their transcriptional output during mitosis, thus how these cells preserve a transcriptional memory that defines their cellular state is not completely understood. Using modern genetic discovery platforms, we found that the ubiquitin ligase APC/C (anaphase-promoting complex) is required for controlling the pluripotent identity of human embryonic stem cells. Our studies revealed that the APC/C is recruited to a subset of gene promoters by the chromatin recruitment factor WDR5, which enables the APC/C to decorate nearby histone proteins with ubiquitin chains assembled through specific linkages. These ubiquitin polymers serve as potent extraction signals for the ATP-dependent segregase p97/VCP. The displacement of histone proteins removes a critical barrier to transcription, ensuring the rapid re-expression of pluripotency genes upon entry into the next cell cycle. Altogether, our work highlights an unexpected role for ubiquitylation in gene expression control.

A key implication of this mechanism is that the APC/C can direct the identity of any dividing cell type, including abnormally proliferating cancer cells. Our ongoing research focuses on identifying which cancer types are dependent on the APC/C for their identity and characterizing the molecular basis for this control. Interestingly, the APC/C binds to a number of cancer-linked transcription factors, with many of these interactions only observed in specific cancer lines, suggesting that a single enzyme can elicit a multi-faceted response by tailoring a custom gene expression program for each cancer type.

Decoding the chromatin-bound ubiquitin code

Ubiquitin can also form polymeric chains that adopt unique structures. This



A model for how APC/C controls gene activity in dividing cell types. The expression of self-renewal genes is dependent on WDR5, while the expression of cancer-specific genes requires factors that are yet to be identified.

topological diversity translates into a diversity of functional outcomes, making this modification exceptionally versatile as a regulatory system. Our lab found that the APC/C deposits defined ubiquitin polymers – linked via residues Lys11 and Lys48 – on chromatin-bound substrates. Yet whether and how other ubiquitin chain types control gene expression is unknown. Ongoing efforts in our lab include developing new strategies to probe for the various linkage types that regulate gene activity and understanding the molecular basis for these linkages. Our ultimate goal is to untangle the complexity of the chromatin-bound ubiquitin code and to decipher how this code is controlled. Major questions include understanding how specificity of this modification is achieved and whether ubiquitylation might crosstalk with other post-translational modifications.

Selected Publications:

Oh E†. Monitoring bacterial translation rates genome-wide. *Methods Mol Biol*. 2021 Mar 26; 2252:3–26.

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*Equal contributions