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Elia Laboratory

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In response to DNA damage from environmental or endogenous sources, cells evoke an elaborate signaling network known as the DNA damage response (DDR). This response functions to preserve genomic integrity, which is necessary for normal development and the prevention of cancer. **The Elia laboratory** studies the DNA damage response, focusing on pathways regulated by ubiquitin-dependent signaling and pathways that promote the stabilization and repair of stalled replication forks. We utilize innovative proteomic and genetic approaches to investigate these processes. Our ultimate goal is to understand how DDR disruption influences cancer progression and can be exploited to target tumors with specific DNA repair defects.

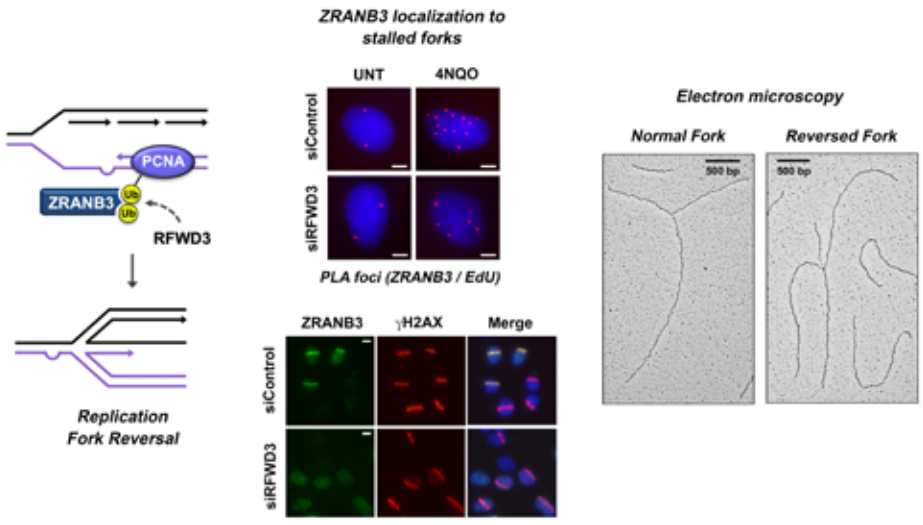
Ubiquitin signaling in the DNA damage response

DNA within cells is under continual assault from metabolic and environmental sources. In response to the ensuing damage, cells activate a signaling network called the DNA damage response (DDR). Defects in this response can lead to hereditary cancer syndromes and can underlie the genomic instability which is a hallmark of sporadic cancers. The DDR promotes genomic integrity by targeting hundreds of factors in diverse pathways ranging from DNA replication and repair to cell-cycle arrest, senescence, and immune regulation. Execution of the DDR relies upon a dynamic array of protein modifications, with ubiquitination playing a central role. Our lab elucidates ubiquitin-dependent signaling pathways that regulate and integrate diverse DDR factors.

Replication-coupled repair and cancer

Replication fork collapse can induce chromosome instability and mutagenic events that cause cancer. Organisms have therefore evolved pathways to stabilize stalled replication forks and to repair collapsed forks through processes such as homologous recombination (HR). Multiple factors involved in HR and replication fork stabilization, such as BRCA1 and BRCA2, are mutated in hereditary cancer syndromes, highlighting the importance of these pathways. We have demonstrated that the ubiquitin ligase RFWD3, which is mutated in the cancer predisposition syndrome Fanconi anemia, ubiquitinates the single-stranded DNA binding factor RPA to promote homologous recombination at stalled replication forks and replication fork restart (*Mol Cell* 2015b).

Replication fork reversal is an important mechanism to protect the stability of stalled forks. While multiple enzymes have been identified that can remodel forks, their regulation remains poorly understood. We have recently discovered a new function for RFWD3 in the regulation of fork remodeling (*J Cell Biol* 2023). We have found that RFWD3 promotes PCNA polyubiquitination to recruit the DNA translocase ZRANB3 to stalled replication forks. Through the analysis of replication intermediates by electron microscopy, we found that RFWD3 promotes replication fork reversal in a ZRANB3-epistatic manner. We are continuing to elucidate novel mechanisms of replication-coupled repair and fork stabilization regulated by ubiquitin signaling.



RFWD3 promotes PCNA polyubiquitination to recruit the DNA translocase ZRANB3 to remodel stalled replication forks (J Cell Biol 2023).

Quantitative proteomics

Numerous ubiquitin ligases have been implicated in the DNA damage response, yet finding their substrates by simple binding techniques can be difficult due to weak substrate interactions. To circumvent this problem, we have pioneered a quantitative proteomic approach to globally profile ubiquitination. Initially, we used this approach to identify substrates of Cullin-RING ubiquitin ligases (*Cell* 2011), which are involved in numerous DNA repair processes. Subsequently, we used it to uncover novel ubiquitination events directly stimulated by DNA damage (*Mol Cell* 2015a), demonstrating the vast breadth of ubiquitin signaling in the DDR. We are continuing to use innovative proteomic approaches to characterize novel and poorly understood ubiquitin ligases in DNA damage signaling pathways.

Targeted cancer therapy

Defects in the DNA damage response can render tumors dependent upon specific DNA repair pathways for survival. Moreover, targeted modulation of the DDR can affect tumor sensitivity to genotoxic treatments and immunotherapy. Increased understanding of DNA repair pathways will lead to enhanced opportunities for developing therapies that target cancers with DNA repair defects, and for improving the efficacy of genotoxic and immunotherapy agents. We are employing methods to translate our work to the development of such therapies.

Selected Publications:

Moore CE, Yalcindag SE, Czeladko H, Ravindranathan R, Wijesekara Hanthi Y, Levy JC, Sannino V, Schindler D, Ciccia A, Costanzo V, **Elia AE**. RFWD3 Promotes ZRANB3 Recruitment to Regulate the Remodeling of Stalled Replication Forks. *J Cell Biol*, 2023; 222(5): e202106022

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