分子細胞生物学セミナー

Ubiquitin-mediated recruitment of genome caretakers to DNA double-strand breaks

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A striking feature of the cellular response to DNA double strand breaks (DSBs) is the accumulation of proteins into large and microscopically discernible structures in the vicinity of the lesions – the so-called ionizing radiation induced foci (IRIF). This accumulation process is orchestrated by post-translational histone modifications, which serve as affinity platforms for DNA damage response (DDR) proteins. The most proximal of these modifications is phosphorylation of the histone variant H2AX by the ATM kinase (γ-H2AX), which leads to the recruitment of MDC1 and its associated protein partners. One of these is the ubiquitin ligase RNF8, the activity of which initiates a complicated cascade of chromatin ubiquitylation events, which ultimately facilitate the recruitment of downstream DDR factors such as 53BP1, BRCA1 and RAD18.

DDR-associated chromatin ubiquitylation is an exquisitely complicated and highly regulated process that requires the action of three ubiquitin ligases, RNF8, HERC2 and RNF168. The latter targets histone H2A for ubiquitylation at K13 and K15, providing affinity sites for the downstream factors. The role of RNF8, however, is less clear. Together with HERC2 and UBC13, RNF8 forms a ubiquitin ligase complex, the activity of which is required to target RNF168 to sites of DNA damage through local ubiquitin recognition. While initially it was thought that RNF8 and RNF168 both targeted H2A-type core histones, recent advances strongly suggests that RNF8 modifies a unique and unknown substrate to provide a recruitment platform for RNF168 at sites of DNA damage.

In my talk, I will review the status of our ongoing efforts to understand the DDR-associated chromatin pathway. I will describe the elaborate regulation of this pathway by activating SUMOylation, deubiquitylating enzymes and other mechanisms that restrain the extent of local ubiquitylation. Finally, I will share our recent findings regarding the identity of RNF8’s elusive substrate.

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