Regulation of histone H2A ubiquitination in the maintenance of genome stability
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Outline
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As outlined in the preceding introductory chapters, histone H2A ubiquitination plays important roles in a variety of DNA-based processes. In Chapter 1, we introduced negative regulation of H2A ubiquitination by deubiquitinating enzymes (DUBs) in regulation of transcription, the DNA damage response (DDR) and cell cycle progression. In chapter 2, we gave an extensive introduction of the relative contributions of the H2A ubiquitination pathways associated with the DDR. The experimental work described in this thesis is aimed at increasing our understanding of the mechanisms by which enzymes involved in the regulation of H2A ubiquitination levels promote genome stability.

In chapter 3, we identify the DUB USP3 as an enzyme that deubiquitinates H2A and is required for regulation of basal levels of mono-ubiquitinated H2A. We show that DNA damage induces H2A ubiquitination and present evidence that USP3 is required for restoration of H2A ubiquitination levels in late stages of the DDR. Moreover, we show that USP3 is required to avoid spontaneous genome instability.

In Chapter 4, we examine the latter phenotype in more detail using cells isolated from a new mouse model of Usp3 deficiency. We show that these cells harbor spontaneous DNA breaks and present results of experiments aimed at identification of the mechanism by which USP3 prevents DNA breaks.

It has been shown that DNA damage induced H2A ubiquitination is promoted by two ubiquitin E3 ligases, RNF8 and RNF168. Recruitment of RNF8 is followed by that of RNF168 and it has been postulated that RNF8 ubiquitinates H2A first, followed by RNF168-mediated ubiquitin chain extension. In Chapter 5, we describe a significant modification of this model, by showing that RNF168 rather than RNF8 is the primary E3 ligase that catalyzes DSB-induced H2A ubiquitination.

Finally, in chapter 6, a general discussion of the findings presented in chapters 3-5 is provided. We formulate new questions that arise from these findings and discuss their implications for development and treatment of cancer.