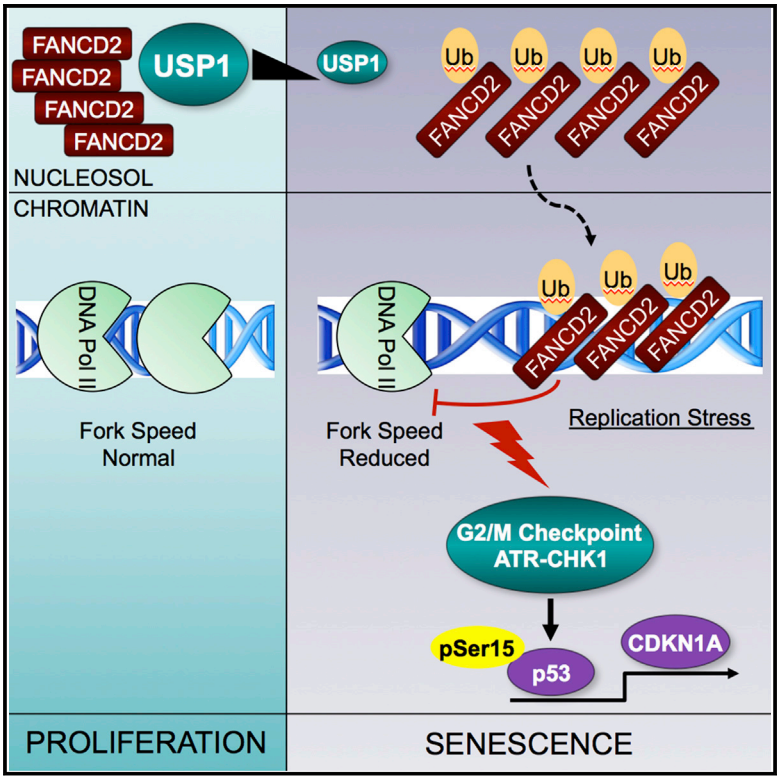
Cell Reports

USP1 Regulates Cellular Senescence by Controlling Genomic Integrity

Graphical Abstract



Highlights

- USP1 repression is a hallmark of oncogene-induced senescence
- USP1 repression induces aberrant FANCD2 chromatin aggregation and replication stress
- USP1 repression induces replication arrest via p53, CDKN1A, ATR, FANCD2, and FANCI
- USP1 repression induces sensitivity to DNA interstrand crosslinker reagents

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In Brief

Ogrunc et al. identify the deubiquitinating enzyme USP1 as an active contributor to oncogene-induced senescence. They show that USP1 controls replisome dynamics and genome stability and that USP1 dysfunction induces aberrant aggregation of mono-ubiquitinated FANCD2 concomitant with a chronic DNA damage response and senescence induction.

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Report

USP1 Regulates Cellular Senescence by Controlling Genomic Integrity

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SUMMARY

Oncogene-induced senescence (OIS) is a potent barrier for the transformation of pre-cancerous cells. The molecular pathways involved in the execution of OIS are still incompletely understood, but they include chronic DNA damage signaling and post-translational modifications of key factors. Here, we show that OIS-associated transcriptional downregulation of deubiquitinating enzyme USP1 triggers and maintains a DNA damage checkpoint response with atypical DNA lesions that is dependent on functional FANCD2-FI-ATR-CHK1-p53-CDKN1A signaling. We find that a reduced USP1 level causes aberrant aggregation of its target FANCD2 concomitant with replication stress, accumulation, and colocalization of γ-H2Ax and p53-binding protein 1 (53BP1) in large and unusual sparse DNA damage foci and an increased number of polyploid cells and cells arrested in G2/M, as well as a sensitization of senescence-bypassing cells to DNA interstrand crosslinking-mediated cell death. Our study identifies USP1 as a key senescence regulator controlling genomic integrity and a promising target for anti-cancer therapy.

INTRODUCTION

Cellular senescence is a tumor suppressor mechanism that stably arrests cell proliferation of pre-cancerous cells. The arrest is accompanied by a senescence-associated secretory phenotype (SASP), the expression of many inflammatory cytokines and growth factors, that reinforces the senescence arrest. The most prominent senescence-inducing stimuli are activated oncogenes (e.g., oncogenic RAS and oncogene-induced senescence [OIS]). Irrespective of the stimulus, two major tumor suppressor pathways are activated: p53/CDKN1A (alias $p21^{CIP}$) and Rb/CDKN2A (alias p16) (Campisi, 2013). OIS is triggered, at least in part, by DNA replication stress and a concomitant activation of a persistent DNA damage response (DDR), resulting in SASP activation and G1, intra-S, and G2/M cell-cycle checkpoint arrests. OIS also is characterized by an increase in γ-H2Ax and phospho-53BP1 DNA damage foci and mediated by ATM:CHK2/ATR:CHK1 kinases as well as p53 and its downstream target CDKN1A (Bartek et al., 2007; d'Adda di Fagagna, 2008). OIS-associated replication stress is affiliated with an increased replication origin firing and reduced replication fork progression (Hills and Diffley, 2014). However, our knowledge concerning the factors and underlying mechanisms involved in this process is still incomplete.

Ubiquitin conjugation is dynamically controlled by deubiquitinating enzymes (DUBs) and regulates many cellular functions including replication (Chen and Sun, 2009; Reyes-Turcu et al., 2009). For example, DUB USP1 regulates the function of inhibitors of DNA binding (IDs1–4), proliferating cell nuclear antigen (PCNA), as well as Fanconia Anemia (FA) pathway proteins FANCD2 (FD2) and FANCI (FI) by counteracting their mono-ubiquitination (Nijman et al., 2005; Williams et al., 2011; Huang et al., 2006). IDs are HLH transcription factors that inhibit differentiation and senescence (Zebedee and Hara, 2001). USP1 promotes ID protein stability and antagonizes differentiation and also enhances stem cell maintenance by regulating CKN1A expression (Williams et al., 2011). USP1-mediated deubiquitination of the DNA replication processivity factor, PCNA, acts as a safeguard against error-prone translesion synthesis (TLS) of DNA (Huang et al., 2006). Mono-ubiquitination of FD2 (FD2-Ub) and FI (FI-Ub) is a key event in the activation of the FA pathway that contributes to the resolution of endogenous replication-coupled DNA inter-strand crosslinks (ICLs). In line with this, FD2-Ub