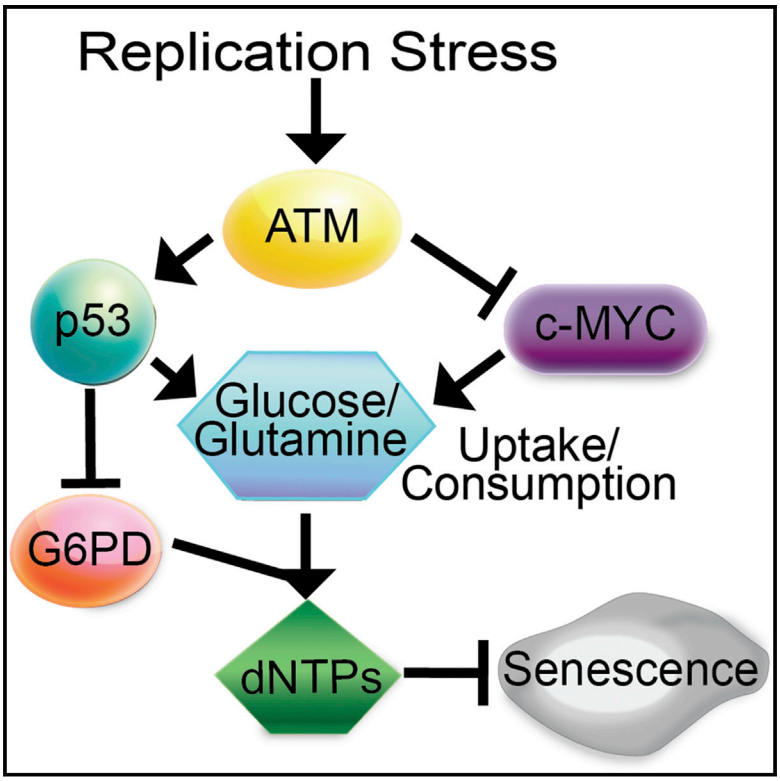
Report

Cell Reports

ATM Couples Replication Stress and Metabolic Reprogramming during Cellular Senescence

Graphical Abstract



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In Brief

Replication stress and metabolic reprogramming are hallmarks of cancer. Aird et al. demonstrate that ATM couples replication stress and metabolic reprogramming during senescence. ATM thus inhibits the cancer-associated metabolic program to promote senescence in response to replication stress.

Highlights

- ATM knockdown rescues dNTP levels to bypass replication-stress-induced senescence
- ATM knockdown enhances glucose and glutamine consumption for dNTP biosynthesis
- Rescue of dNTP levels correlates with an increase in G6PD activity by ATM knockdown
- ATM knockdown coordinately suppresses p53 and upregulates c-MYC to shift metabolism

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ATM Couples Replication Stress and Metabolic Reprogramming during Cellular Senescence

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SUMMARY

Replication stress induced by nucleotide deficiency plays an important role in cancer initiation. Replication stress in primary cells typically activates the cellular senescence tumor-suppression mechanism. Senescence bypass correlates with development of cancer, a disease characterized by metabolic reprogramming. However, the role of metabolic reprogramming in the cellular response to replication stress has been little explored. Here, we report that ataxia telangiectasia mutated (ATM) plays a central role in regulating the cellular response to replication stress by shifting cellular metabolism. ATM inactivation bypasses senescence induced by replication stress triggered by nucleotide deficiency. This was due to restoration of deoxyribonucleotide triphosphate (dNTP) levels through both upregulation of the pentose phosphate pathway via increased glucose-6-phosphate dehydrogenase (G6PD) activity and enhanced glucose and glutamine consumption. These phenotypes were mediated by a coordinated suppression of p53 and upregulation of c-MYC downstream of ATM inactivation. Our data indicate that ATM status couples replication stress and metabolic reprogramming during senescence.

INTRODUCTION

Replication stress induced by deficiency in cellular deoxyribonucleotide triphosphate (dNTP) levels is an important early event during cancer initiation (Bester et al., 2011), while its bypass correlates with cancer progression (Bester et al., 2011; Zeman and Cimprich, 2014). Replication stress causes DNA damage accumulation and genomic instability (Bester et al., 2011; Burhans and Weinberger, 2007; Zeman and Cimprich, 2014), which is a hallmark of cancer (Negrini et al., 2010). Notably, activation of oncogenes is known to decrease dNTP levels and consequently triggers replication stress (Aird et al., 2013; Bartkova et al., 2006; Di Micco et al., 2006; Mannava et al., 2013). In normal diploid cells, activation of oncogenes, and the subsequent replication stress, causes a tumor-suppressive, stable cell-growth arrest termed cellular senescence (Yaswen and Campisi, 2007). Indeed, oncogene-induced suppression of nucleotide metabolism via suppression of ribonucleotide reductase M2 (RRM2) underlies the observed replication stress and the associated DNA damage response (DDR) during senescence (Aird et al., 2013). Therefore, senescence suppresses tumors initiated by replication stress (Bester et al., 2011; Zeman and Cimprich, 2014). dNTP biosynthesis relies on glucose and glutamine consumption, which are at the heart of cancer metabolism (Ward and Thompson, 2012). However, the role of metabolic reprogramming in response to replication stress is unknown. Here, we report that ataxia telangiectasia mutated (ATM) status couples replication stress and metabolic reprogramming during senescence.

RESULTS

Knockdown of ATM Bypasses Replication-Stress-Induced Senescence

Suppression of RRM2, which depletes the levels of all four dNTPs, underlies replication stress observed during oncogene-induced senescence (Aird et al., 2013). This induces a robust DDR and ultimately a stable senescence-associated cell growth arrest. The replication stress sensors ataxia telangiectasia and Rad3-related protein (ATR) and ATM are activated by oncogenes during senescence (Di Micco et al., 2006). We sought to determine whether ATM and/or ATR are regulated during senescence induced by short-hairpin-mediated RRM2 knockdown (shRRM2). shRRM2 significantly activated both ATM and ATR, as demonstrated by immunofluorescence using phospho-specific antibodies (Figures 1A, 1B, and S1A). Next, we examined whether these proteins are necessary for the observed senescence. We knocked down ATM or ATR in combination with RRM2 knockdown with two independent short hairpin RNAs (shRNAs) for ATM (shATM) or ATR (shATR). shATM in combination with shRRM2 suppressed senescence markers such as p21 expression (Figure 1C) and senescence-associated β-galactosidase (SA-β-gal) activity (Figures 1D and 1E). This correlated with