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Sommario	Oncogene Induced Senescence (OIS) is a tumor suppressive barrier that blocks cell cycle permanently. OIS results from a robust DNA damage response (DDR) activation due to oncogene-induced hyper-proliferation. By performing a whole genome analysis of DNA replication dynamics occurring upon oncogene activation, I discovered that oncogene activation alters DNA replication by increasing replication fork speed and fork stalling, while decreasing the frequency of replication initiation. This is accompanied by a prompt DDR activation. As cells approach senescence the frequency of initiation increases, the level of fork stalling and fork speed decreases. Oncogene activation leads to DNA replication stress mainly at fragile sites and since telomeres resemble fragile sites, I then demonstrated that oncogene activation impairs telomere replication, by increasing fork stalling at telomeres. This is accompanied by increased fragile telomeres, stochastic telomeric attrition and persistent telomeric DDR. These results revealed a novel link between oncogene activation and telomere dysfunction, refining the model underlying OIS establishment. Oncogene activation increases Reactive Oxygen Species (ROS). Beyond their toxicity, ROS are essential second messengers mediating mitogenic signalling. We discovered that oncogene-induced ROS is mediated by the NADPH oxidase NOX4. Upon oncogene activation, NOX4 pharmacological inhibition blocks ROS production, resulting in fork

	speed reduction and differential regulation of local replication origin initiation. These results revealed a fundamental role of NOX4 and ROS in mediating oncogene-induced hyperproliferation. Polycomb repressive complexes (PRCs) repress genes involved in development, proliferation and differentiation by EZH2-mediated H3K27 trimethylation. Recent independent studies revealed a more direct PRCs role on S phase progression and DNA replication. We show that EZH2 KO leads to impairment of cell cycle progression, with cells blocked at G1/S transition. Furthermore EZH2 KO impairs DNA replication, by reducing fork speed, increasing the frequency of initiation and fork stalling, demonstrating that PRCs deficiency leads to replication stress.
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