Review

Redox control of cell proliferation

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Cell proliferation is regulated by multiple signaling pathways and stress surveillance systems to ensure cell division takes place with fidelity. In response to oxidative stress, cells arrest in the cell-cycle and aberrant redox control of proliferation underlies the pathogenesis of many diseases including cancer and neurodegenerative disorders. Redox sensing of cell-cycle regulation has recently been shown to involve reactive cysteine thiols that function as redox sensors in cell-cycle regulators. By modulating cell-cycle regulators these redox-active thiols ensure cell division is executed at the right redox environment. This review summarizes recent findings on regulation of cell division by the oxidation of cysteines in cell division regulators and the potential of targeting these critical cysteine residues for cancer therapy.

Redox signaling is critical to cell proliferation

In eukaryotes, cells divide when they attain a certain size or when triggered by extracellular stimuli such as growth factors or hormones. Proliferative signals flow through intracellular signaling pathways to activate the cell-cycle (Figure 1). Stress signals from within or outside a cell oppose proliferation. Therefore, cells rely on proliferative signaling pathways, as well as stress surveillance systems (or checkpoints), to regulate entry into the cell-cycle [1,2].

Stress signaling, particularly in response to DNA damage and infection, is vital for survival to ensure cells elicit appropriate defense or repair mechanisms [3]. The signaling cascades triggered by DNA damage and inflammatory responses have been well studied [1,4]. In addition to the primary damage, many stress situations induce reactive oxygen species (ROS). ROS are highly reactive radicals or molecules produced intracellularly from several compartments (mitochondria, endoplasmic reticulum, peroxisomes) [5]. However, they are also induced by external sources such as ionizing agents, vitamins, or herbicides [6]. ROS can interact with biomolecules resulting in oxidation of amino acyl residues in proteins, mutations in DNA, and lipid peroxidation producing more free radicals. Excess production of ROS in cells overwhelms cellular detoxifying systems, resulting in oxidative stress [6].

ROS are not always deleterious; they can act as a messenger in signaling cascades involved in cell proliferation and differentiation [7]. In mammalian cells, interactions between growth factors and receptors are known to generate ROS, which at low concentrations are required to activate proliferative signaling for cell division [8,9]. In yeast, proliferation is synchronized with a metabolic cycle so that cell division occurs late in the oxidative phase of respiratory metabolism and DNA synthesis, and mitosis occurs in the reductive phase during glycolytic or fermentative metabolism [10]. In embryonic development, a programmed fluctuation of oxidative state is important to determine cell fate – an hypoxic environment is important for proliferation, whereas mild oxidative conditions leads to differentiation [11]. At higher ROS levels, cell division is stalled, and after prolonged arrest, cells die from apoptosis [12,13]. Loss of redox control in cell division can result in quiescent cells re-entering cell division leading to cancer, aberrant fetus development, and neurodegenerative disorders [14]. Hence, cell division is highly regulated by the cellular redox environment, and the concentration of ROS determines whether cell division is positively or negatively regulated. Moreover, ROS sensing is also important in redox signaling. ROS production is usually localized; ROS act rapidly and damage biological molecules in close proximity. Unlike most DNA damaging agents, ROS are relatively short-lived and the nature of ROS raises the question of how cells sense and mediate cell-cycle control in response to ROS. Here, we provide evidence of a new paradigm for oxidative stress signaling that does not always depend on a defined cascade of signal transduction mediated by phosphorylation and triggered by specific recognition of a molecule based on parameters such as shape, charge, or hydrophobicity [15], but instead on direct oxidation of regulatory molecules or transcription factors. A surprising number of cell-cycle regulators can be modified by cysteine oxidation – a signal that could be almost as important as phosphorylation (Figure 1).

Recently, an increasing body of work has indicated that redox signaling is mediated by switching the redox state of certain cysteine residues in proteins to elicit an oxidative stress response in cells (Box 1) [16]. Although reactive cysteine residues have been identified in many cell-cycle regulators, their function in controlling cell division has only recently been elucidated in yeast [17,18]. Redox regulation by specific cysteine residues opens up the possibility of manipulating cell division by designing redox-active molecules to block the activity of cell-cycle regulators. This review focuses on the sensing mechanism in cells for redox control of cell division to ensure proliferation is executed in the right redox environment. The advantages of such a system will be highlighted, and how these cysteine residues in cell-cycle regulators may be targeted for development of therapeutics will also be discussed.

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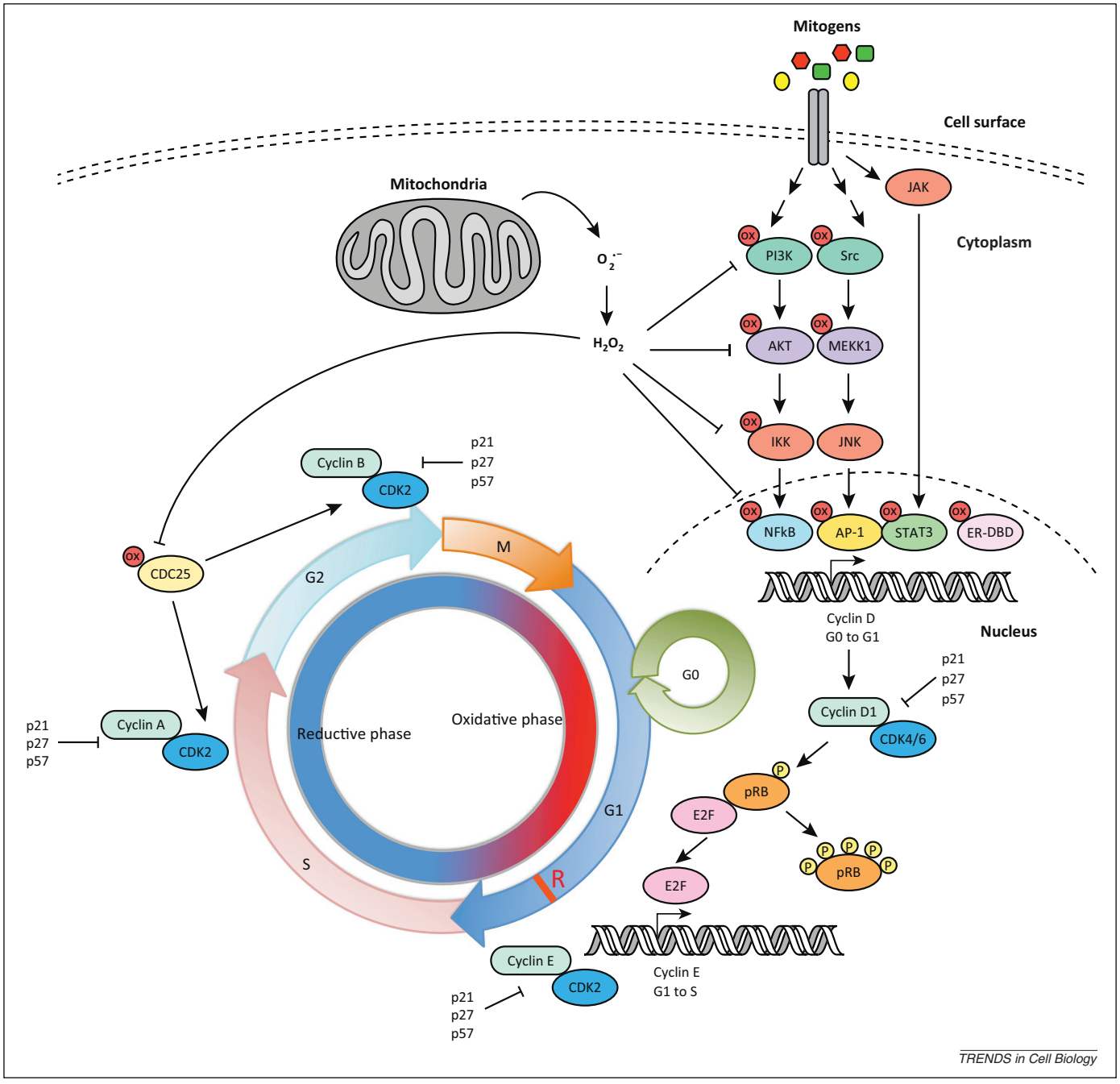

Figure 1. Overview of redox control of the eukaryotic cell-cycle. ROS (such as superoxide and H_2O_2) are produced as a result of oxidative phosphorylation in the mitochondria. Cell-cycle regulators (abbreviations are given in the text) with reactive cysteine residues are highlighted by a red circle labeled with 'ox'. In response to mitogens, signaling pathway kinases convey proliferative signals to activate expression of cyclin D. Cyclin D complexes with Cdk4 or Cdk6 and phosphorylates pRB to release its inhibitory effects on E2F driving cells to re-enter the cell-cycle from quiescence to G1. Once the restrictive point at late G1 (labeled as R) is passed, cells are committed to cell division. Activation of E2F leads to the transcription of cyclin E for transition from G1 to S phase. Subsequent expression of cyclin A and cyclin B leads to transition of S to G2 and G2 to M phases, respectively. The phosphatase Cdc25 activates cyclin A–Cdk1, cyclin B–Cdk1, cyclin E–Cdk2 for entry into M phase by removing the inhibitory phosphorylation on Cdk1 and Cdk2. Opposing the activity of CDKs (cyclin A–Cdk1, cyclin B–Cdk1, cyclin E–Cdk2, cyclin D–Cdk4/6) are CKIs (p21, p27, p57), which sequester CDKs and block their kinase activity. The cell-cycle is synchronized with the metabolic cycle of the cells with S phase and M phase occurring only during the reductive phase of metabolism (blue) and G1 in the oxidative phase (red).

Cell arrest in response to oxidative stress

G1/S and G2/M phase

In the eukaryotic cell-cycle, the transition of different phases is driven by the activities of various phase-specific cyclin–CDK (cyclin-dependent kinase) complexes (Box 2). Their activities are subjected to inhibition by CDK inhibitors, which block cell-cycle progression. Depending on the type of ROS, cells can arrest at G1 or G2 in the cell-cycle. Superoxide-generating compounds and linoleic acid hydroperoxide (LoaOOH) induce G1 arrest in eukaryotic cells [13,19,20], whereas in yeast H_2O_2 induces DNA damage and affects the transcription complex Mcm1p–Fkh2p–Ndd1p leading to cell-cycle arrest at G2 [20,21]. In mammalian cells, in response to oxidative stress the expression of the CKI p27 is activated to sequester the cyclin E–Cdk2 and cyclin D–Cdk4 complexes, arresting cells at G1.

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