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Cell cycle regulation of mitochondrial function

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Specific cellular functions, such as proliferation, survival, growth, or senescence, require a particular adaptive metabolic response, which is fine tuned by members of the cell cycle regulators families. Currently, proteins such as cyclins, CDKs, or E2Fs are being studied in the context of cell proliferation and survival, cell signaling, cell cycle regulation, and cancer. We show in this review that cellular, animal and molecular studies provided enough evidence to prove that these factors play, in addition, crucial roles in the control of mitochondrial function; finally resulting in a dual proliferative and metabolic response.

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Introduction

Mitochondria, which are believed to have evolved from the endosymbiosis of an alpha-proteobacterium [1], are cellular organelles that act as the engines of eukaryotic cells. Because of the energy and intermediate metabolite-producing functions of mitochondria, their activity needs to be tightly regulated in response to cellular and organismal needs. Cells activate/trigger different cellular signaling pathways to fulfill their needs, and very often, these responses couple gene regulation to the dynamic regulation of organelle function.

Numerous cellular signaling pathways drive cell cycle progression in response to specific stimuli. The regulation of the cell cycle has been a very productive area of research since the 1970s, after the discovery of the cdc2 gene by Paul Nurse [2]. In this review, we will focus on the regulation of the function of a specific organelle, the mitochondrion, by cell cycle regulators and on the reciprocal, subsequent regulation of the cell cycle by mitochondria.

Cell cycle regulators control progression through the eukaryotic cell cycle, and major components of this group of proteins are the family of cyclin-dependent kinases (CDKs) and their regulatory subunits, the cyclin proteins. The activity of CDKs is mainly regulated by the cyclic expression of their binding cyclins or by control of their interactions with these cyclins or the CDK inhibitory proteins (CDK inhibitors (CKIs) or Ink4 family members). Cyclin–CDK complexes catalyze the phosphorylation of members of the retinoblastoma (pRB) protein family (pRB, p107, and p130). Phosphorylation of pRB by cyclin–CDK releases the E2F-DP transcription factors, thereby ensuring the expression of genes required for cell cycle progression [3]. Conversely, the family of CDK inhibitors (INK and CIP/KIP) block CDK activity in response to quiescence stimuli.

Numerous cellular signaling pathways, including those that drive cell division, interact tightly with the mechanisms that regulate mitochondrial function, namely mechanisms that regulate mitochondrial fission and fusion, mitochondrial biogenesis, mitochondrial activity, and finally, mitochondrial apoptosis (intrinsic pathway).

In addition to archetypal cell cycle regulators, key transcription factors that also play roles in proliferation and cell cycle arrest, are also essential players in the regulation of mitochondrial function. This is the case of the tumor suppressor p53, which serves not only as a regulator of apoptosis but also as a direct regulator of mitochondrial DNA replication and integrity, and of autophagy. This has been recently reviewed in [4,5].

The role of cell cycle regulators in controlling the biogenesis and metabolic activity of mitochondria

Mitochondrial biogenesis is controlled through coordinated transcriptional regulation of nuclear and mitochondrial genes. The key transcription factors ruling mitochondrial biogenesis are peroxisome proliferator-activated receptors (PPARs), PGC1 coactivators (PGC1α and PGC1β), and nuclear respiratory factors 1 and 2 (NRF1 and NRF2). The activity of these transcription factors is controlled by the energetic demands of the cells (recently reviewed in [6]). Regulation of mitochondrial biogenesis sustains mitochondrial activity, which can be dependent on the tricarboxylic acid cycle (Krebs or TCA cycle) or electron transport chain (ETC).

Cell cycle regulators have been recently linked to mitochondrial biogenesis. Indeed, cyclin D1−/− hepatocytes exhibit increased mitochondrial size, increased mitochondrial activity, and increased expression of NRF1 [7]. On the other hand, the overexpression of cyclin D1 led to a

twofold decrease in mitochondrial activity that was mediated by CDK4 kinase activity but was independent of RB. Interestingly, the addition of serum to starved cells induced cyclin D1 expression and reduced NRF1 activity; more precisely, the NRF1 and cyclin D1 expression patterns were inversely correlated during cell cycle progression [7].

Furthermore, the deletion of pRB resulted in failure to induce the mitochondrial biogenesis transcription program in erythroid progenitors as a result of decreased PGC1β expression, thus decreasing the transcription of the PGC-1 regulated genes. Surprisingly, pRB−/− erythroid progenitors do not exhibit increased proliferation but fail to downregulate cell cycle genes and induce the mitochondrial biogenesis program [8]. The importance of the crosstalk of cell cycle regulators and mitochondrial function in red cell development was also highlighted in a recent study demonstrating that proper regulation of cyclin E levels is essential for limiting ROS accumulation, mitochondrial biogenesis and oxidative metabolism during erythrocyte maturation [9]. Insufficient mitochondrial content upon pRB deletion was also observed in a model of mouse muscle cells [10] and in mouse embryonic fibroblasts (MEFs) that also lacked the other two pocket protein family members, p107 and p130 [11•]. In contrast, the loss of RBF1, the Drosophila pRB homolog, was recently shown to be associated with the opposite phenotype, that is, increased cellular oxidation by altered glutamine catabolism, using fly larvae and imaginal discs as models [12,13•]. Consistent with this observation was the finding that increased CycD–Cdk4 in Drosophila led to increased mitochondrial biogenesis [14], which correlated with increased levels of mitochondrial DNA and elevated ATP synthase and cytochrome C expression. Interestingly, adult flies overexpressing CycD–Cdk4 were two times more active than control flies. On the other hand, flies deficient for CycD or Cdk4 exhibited mitochondrial biogenesis defects and were less active. The effects of CycD–Cdk4 on mitochondrial biogenesis were mediated by EWG (erect wing gene), the Drosophila NRF1 ortholog, TFAM and the Drosophila homolog of NRF2, Delg (Drosophila Ets-like gene) [15,16]. Because CDK4 and its partners, the type D cyclins, are negative regulators of pRB, the findings on the regulation of mitochondrial biogenesis in Drosophila contradict those using pRB-deficient and cyclin D1-deficient mouse-derived models. Distinct functions of the cyclin and CDK families in Drosophila and mammalian cells could underlie these differences.

Our laboratory recently demonstrated that the cell cycle regulator E2F1, as a part of the CDK4-RB-E2F1 axis, acts upstream of the regulation of the expression of key oxidative metabolism genes that control energy expenditure in response to exercise or thermogenesic stimulation. E2f1, in association with pRB, represses mitochondrial genes under basal conditions, and this negative regulation of gene expression was abrogated upon CDK4 activation. Indeed E2f1−/− mice showed increased expression of mitochondrial ETC, fatty acid oxidation and uncoupling genes as well as of genes involved in mitochondrial biogenesis in muscle and brown adipose tissue. Increased mitochondrial gene expression resulted in an increased number of mitochondria and in a markedly oxidative phenotype. Mechanistic studies revealed that the E2f1–pRB complex bound to the promoters of numerous oxidative genes. Upon appropriate stimulation, pRB was phosphorylated, thus facilitating gene transcription [17••]. These results are in agreement with those of previous studies by other laboratories, which demonstrated that siRNAs against E2F1 in human cells prompted the induction of the TOP1MT (mitochondrial DNA Topoisomerase 1) mRNA as well as increased the transcription and replication of the mitochondrial genome [18].

Surprisingly, again in the Drosophila model, dDP mutants exhibited decreased ETC and OXPHOS gene expression, resulting in diminished ATP levels, decreased mitochondrial activity, and fragmented mitochondria. Moreover, using transmission electron microscopy (TEM), mitochondria from dDP mutant eye discs exhibited a more round morphology. Moreover, dDP, dE2f1, dE2f2 and RBF1 were detected at the promoters of the downregulated genes [19•]. The same group confirmed their observations in a human osteosarcoma cell line in which E2F activity was blunted using DP1 and DP2 siRNAs, a dominant-negative form of DP1, or a mutant E2F that does not bind DNA. They observed similar ChIP occupancy, a punctuate mitochondrial pattern, reduced Mitotracker staining (thus reduced mitochondrial activity) and altered mitochondrial morphology at the ultrastructural level [19•]. It is difficult to explain these paradoxical results other than that they are a result of differences in cell types or possibly due to the formation of distinct E2F complexes with specific activities.

Other CDK family members have been linked to mitochondrial activity. CDK1, along with B1 cyclin, was demonstrated to couple the G2 > M transition with mitochondrial respiration by extensive phosphorylation of electron transport chain complex I subunits. Phosphorylation by CDK1 is necessary to activate the complex and the production of sufficient ATP for rapid cell cycle progression [20••].

Overall, regulation of mitochondrial function by the CDK–RB–E2F pathway is conserved from flies to mammals, but this mechanism of control has most likely gained complexity due to the emergence of several paralogs of each of the genes (Table 1). Taken together, the current knowledge from both Drosophila and mouse models suggest that E2F1, similar to the regulation of cell cycle genes, can either repress or stimulate the expression of OXPHOS target genes in a pRB-dependent