Cell cycle-regulated manganese superoxide dismutase activity via reversible phosphorylation

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The constant stress environment that the cells live in required the development of defense systems against free radical and radiation insults. One of the major antioxidant enzymes responsible for detoxifying free radical species is manganese superoxide dismutase (MnSOD, Sod2), which is specifically localized into the mitochondria of cells. MnSOD catalyzes the conversion of two molecules of superoxide anion into water and hydrogen peroxide, the latter of which is then further oxidized to water. The significance of the role of MnSOD activity was shown by the studies showing that the loss or deficiency of MnSOD sensitize cells to ionizing radiation[1-3]. Likewise, reinstating MnSOD into the MnSOD-deficient cells restored the radioresistant phenotype, indicating that MnSOD is important in protecting cells against radiation via the reduction of mitochondrial damages caused by free radicals created by radiation, which may lead to cellular apoptosis. The regulation of MnSOD activity, especially via phosphorylation, has been indicated in both plants and bacteria; however, the kinases/phosphatases involved in the regulatory phosphorylation events and their potential effects on MnSOD activity remained largely unknown in mammalian cells.

Cyclin B1 and its catalytic partner Cdk1 play several important roles in physiological response of cells, particularly during cell division and mitosis. We have previously reported that the cell cycle kinase, Cdk1, localize in the mitochondria under both normal and stress conditions[4]. The presence of the minimal Cdk1 phosphorylation consensus sequence (S/T P) in MnSOD protein sequence encouraged us to hypothesize that the cell cycle regulator Cdk1 is a potential upstream kinase of MnSOD in the mitochondria under stress conditions. Cdk1-mediated phosphorylation of MnSOD may increase the function of MnSOD, resulting in reduced free radical concentration within the mitochondria. Thus, the current study attempts to determine whether cyclin B1/Cdk1 complex is able to phosphorylate MnSOD and and regulate its activity as well as the overall mitochondrial functions.

One of the major phosphatases which nullify the function of cyclinB1/Cdk1 is Cdc14. Despite the well-known functions of Cdc14 in budding yeast, little is known regarding its function in mammalian cells. The antagonizing relationship between Cdc14 and the cell cycle regulator cyclinB1/Cdk1 complex leads to the hypothesis that Cdc14 may as well antagonize mitochondrial cyclin B1/Cdk1 by directly dephosphorylating MnSOD similar to dephosphorylating CyclinB1/Cdk1 complex and indirectly resulting in decreased phosphorylation of MnSOD. Taken together, this study aims to elucidate the balance between mitochondrial cyclin B1/Cdk1- and Cdc14-regulated MnSOD activity and the anti-oxidation of mitochondrial superoxide species.

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