Stony Brook University
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Doctoral Defense Announcement

Abstract

Base Excision DNA Repair in the Mitochondria of Differentiated Neuronal Cells

By

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Healthy mitochondria are vital for maintaining neuronal function over the lifespan of an organism. Since mitochondria contain their own DNA, functional DNA repair pathways in the organelle are necessary for mitochondrial maintenance. Mitochondria do not have the complete complement of DNA repair pathways found in the nucleus. Thus far, base excision repair (BER), mismatch repair, and double-strand break repair have been detected in mitochondria, although these pathways have fewer proteins compared to nucleus. Of these, BER acts on small, non-distorting base lesions, the main type of damage expected to arise from oxidative reactions.

This dissertation focuses on BER after cellular differentiation. There is mounting evidence that BER occurs more slowly in differentiated cells compared to proliferating cells. In terminally differentiated cells, the nuclear genome is no longer being replicated; therefore, proteins involved in these pathways are correspondingly downregulated in the nucleus. However, mitochondria continue to replicate and divide even in a non-dividing cell, which necessitates efficient DNA repair. It may be that proteins shared between the nucleus and mitochondria are continually localized to the mitochondria after differentiation. Alternatively, mitochondria-specific proteins may compensate for the loss of shared proteins. Of particular interest are four proteins implicated in "long-patch" base excision DNA repair in mitochondria: Fen1, DNA2, MGME1 and EXOG. Investigating the regulation and function of these proteins should give insight into the modulation of BER during cellular differentiation.

Using CAD cells, a neuroblastoma cell line that differentiates to neurons in vitro, proliferating progenitors and terminally differentiated neurons were compared. Upon CAD cell differentiation, Fen1 and DNA2 were downregulated, while MGME1 and ExoG were expressed at about the same level. However, mitochondria isolated from differentiated CAD cells performed slower flap excision than the mitochondria extracted from proliferating cells. Despite slower flap excision, differentiated cell mitochondria accumulated less damage than did proliferating cell mitochondria. Taken together, these data imply that long-patch BER flap excision occurs more slowly in differentiated cells, both in the nucleus and mitochondria, but that general mitochondrial DNA repair capacity of differentiated cells is improved over that of proliferating cells.

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