ISAKOS

International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine

9th Biennial ISAKOS Congress • May 12-16, 2013 • Toronto, Canada

Paper #252

The Role of Mitochondrial Reactive Oxygen Species in Matrix Metalloproteinase Expression

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Summary:
These current data indicate that mitochondria DNA integrity plays an important role in the regulation of MMP levels. These data are important help understand the mechanisms involved in the progression of OA and identifying a potential therapeutic approach for treating this disease.

Abstract:
Introduction:
Upregulation of matrix metalloproteinases (MMPs) is a hallmark of osteoarthritis progression. It has been demonstrated that reactive oxygen species (ROS) may play a role in this process. Moreover, mitochondrial DNA (mtDNA) damage and dysfunction also are present in osteoarthritic chondrocytes. However, there are no published studies investigating the relationship between mitochondrial ROS, mitochondrial dysfunction and MMP expression. The purpose of the present study was to evaluate whether enhancing MtROS production utilizing the redox cycler menadione would change MMP expression and whether the DNA repair enzyme hOGG1 would play a role in repairing the effects of mitochondrial ROS.

Materials & Methods:
We hypothesized the presence of hOGG1 will result in subsequent reduction of reactive oxygen species, mitochondrial dysfunction and matrix metalloproteinase expression. Ten 3-5 day old rats were used for primary culture for each experiment. Fifteen mice that over express the DNA repair enzyme hOGG1 and OGG1 knockout mice were utilized. Knees were isolated from 4-7 day old pups and primary chondrocytes were isolated and seated to confluency. Chondrocytes then were exposed to menadione and MMP levels were determined. MitoSox red was used to observe for mitochondrial ROS production, while Southern blot technique was utilized to analyze mtDNA damage. Western blot and zymography were used to view MMP expression and activity respectively.

Results:
Menadione induced mtDNA damage and dysfunction in chondrocytes. There was a dose-dependent relationship between MMP levels and menadione dose. The results show that there is less MMP expression in mice that over express hOGG1 than in wild-type mice. Additionally, OGG knockout mice had higher MMP levels than wild-type mice. To explore whether modulating mtDNA integrity to regulate MMP production as a therapeutic strategy for treating OA, a novel protein was used to transiently target the DNA repair enzyme hOGG1 to chondrocyte mitochondria. Results showed a significant reduction in MMP levels.

Conclusions:
MtDNA integrity plays an important role in the regulation of MMP levels. These data are important for understanding the mechanisms involved in the progression of OA, and identifying a potential therapeutic approach for treating this disease.