

cisplatin으로 유도된 신장손상에서 NQO1 결핍으로 인한 MRN 복합체 발현 변화

충남대학교 수의과대학

김영중, 김태원, 박세라, 김현태, 류시윤, 정주영

NQO1 Deletion Leads to Reduced MRN Complex Expression in Cisplatin Nephrotoxicity

Young Jung Kim, Tae-Won Kim, Se-Ra Park, Hyun-Tae Kim, Si-Yun Ryu, Ju Young Jung

Department of Veterinary Medicine, Chungnam National University, Daejeon, Republic of Korea

Introduction: Mre11, Rad50, and Nbs1 (MRN) complex are known to participate in the early phase of the cellular response to the DNA damage. NAD(P)H:quinone oxidoreductase 1 (NQO1) protects against various pathogenesis and disruption of NQO1 enhances susceptibility to the stimuli and aggravates disease conditions. The aim of this study was to explore whether NQO1 could regulate the MRN complex expression under DNA damage caused by cisplatin.

Material & Methods: In vitro study was performed to assess NQO1 and MRN complex expressions after cisplatin treatment using ACHN cells. After confirm the increment of NQO1 and MRN complex expression after cisplatin treatment, NQO1 knockdown C57BL/6N mice were hired for further in vivo study. Three days after cisplatin (18 mg/kg) injection, all mice were sacrificed under carbon dioxide anesthesia and the kidneys were subjected to the immunohistochemistry and immunoblot analysis. Additional in vitro study was performed to support the effect of NQO1 on MRN complex expression using siNQO1 treated ACHN cells with time and dose-dependent cisplatin treatment.

Results: In the ACHN cells, increased MRN complex were accompanied by enhanced NQO1 expression after cisplatin treatment. These was consistent in the in vivo study. After cisplatin injection, NQO1 knockout mice showed severely damaged renal tubules with apoptotic renal cells compared with the NQO1 intact mice. In contrast, the level of MRN complex in the immunoblot assay were relatively reduced compared to NQO1 intact wild type mice after cisplatin injection. Moreover, MRN complex were weakly expressed in the nuclei of s3 segment of the proximal tubules in NQO1 knockout mice compared with NQO1 wild type mice, which was confirmed in the immunohistochemistry study. Depletion of NQO1 reduced the SIRT1 and PARP1 expression, known to participate in the stress response by regulating DNA damage response factor.

Conclusion: These finding suggested that the NQO1 might regulate MRN complex expression through enhances SIRT1 and PARP-1 in cisplatin-induced acute nephropathy.

Key Words: MRN 복합체, 시스플라틴, NQO1
MRN complex, Cisplatin, NQO1