9 - Molecular Cell Biology

OC-025 - (23981) - THERAPEUTIC POTENTIAL OF MPMBP AGAINST IRON-MEDIATED OXIDATIVE STRESS IN DOXORUBICIN-INDUCED TESTICULAR TOXICITY

H. Ikema (Japan)[1]; J. Shibata (Japan)[1]; Y. Fujino (Japan)[2]; T. Inaida (Japan)[3]; H. Nagai (Japan)[3]; S. Sugimura (Japan)[3]; H. Shinoda (Japan)[4]; Y. Shimizu (Japan)[4]; T. Ushiki (Japan)[5]; H. Yamashiro (Japan)[2]

1 - Graduate School of Science and Technology, Niigata University; 2 - Faculty of Agriculture, Niigata University; 3 - Department of Biological Production, Tokyo University of Agriculture and Technology; 4 - Graduate School of Dentistry, Tohoku University; 5 - School of Medicine, Niigata University

Hikari Ikema
Niigata

Jin Shibata
Niigata

Yuta Fujino
Niigata

Tomoya Inaida
Tokyo

Hiroki Nagai
Tokyo

Satoshi Sugimura
Tokyo

Hisashi Shinoda
Miyagi

Yoshinaka Shimizu
Miyagi

Tatsuo Ushiki
Niigata

Hideaki Yamashiro
Niigata

Doxorubicin (DOX) is an anthracycline chemotherapeutic agent commonly used in cancer treatment; however, it induces testicular toxicity that compromises male fertility. Although the exact mechanism remains unclear, iron-mediated oxidative stress is increasingly recognized as a key contributor. This study aimed to elucidate the role of iron-dependent oxidative stress in DOX-induced testicular damage and to evaluate the therapeutic efficacy of a novel bisphosphonate, [4-(methylthio)phenylthio] methane bisphosphonate (MPMBP), in mitigating such toxicity.
Male mice received a single intraperitoneal injection of DOX (5 mg/kg), and testicular samples were collected weekly for up to five weeks. MPMBP was administered concurrently with DOX and then every five days. Testicular histopathology was assessed using HE staining. Gene expression analysis focused on iron metabolism, the Nrf2, xCT, GPX4 antioxidant pathway by qPCR, and apoptosis-related markers. Elemental iron distribution in testicular tissue was visualized using electron probe microanalysis (EPMA).
DOX treatment resulted in a significant reduction in testicular weight, depletion of spermatocytes, vacuolation of seminiferous tubules, and iron accumulation. A marked downregulation of Gpx4 and upregulation of apoptosis-related

genes were observed, particularly at four weeks. These changes were partially reversed by MPMBP treatment, despite persistent suppression of Gpx4 expression.
This study is the first to demonstrate that DOX-induced testicular injury involves ferroptosis-like mechanisms mediated by iron overload and oxidative stress. MPMBP administration alleviated testicular damage, suggesting its potential as a novel therapeutic agent for preserving spermatogenesis function during chemotherapy.

Palavras-chave : testicular toxicity, oxidative stress, apoptosis