Project title: Comprehensive Cancer Center of Taipei Medical University Program title: Prostate Cancer Research
Project title: Comprehensive Cancer Center of Taipei Medical University Program title: Prostate Cancer Research

Reactive Oxygen Species-Mediated Switching Expression of MMP-3 in Stromal Fibroblasts and Cancer Cells during Prostate Cancer Progression

Chia-Ling Hsieh[1], Che-Ming Liu[1, 2], Katsumi Shigemura[3], Wei-Hua Lee[4], Kuan-Chou Chen[5], Leland W. K. Chung[6], Shian-Ying Sung[1, 7]

謝嘉玲，劉哲銘，重村克己，李偉華，陳冠州，鍾維國，宋賢穎

[1.]The Ph.D. Program for Translational Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan, [2.]The Ph.D. Program for Cancer Biology and Drug Discovery, China Medical University and Academia Sinica, Taichung, Taiwan, [3.]Department of Urology, Kobe University Hospital, Kobe, Japan, [4.]Department of Pathology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan [5.]Department of Urology, Shuang Ho Hospital, Taiwan Medical University, New Taipei City, Taiwan, [6.]Uro-Oncology Research Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA USA [7.]Joint Clinical Research Center, Office of Human Research, Taipei Medical University, Taipei, Taiwan

Study on the aberrant control of extracellular matrices (ECMs) have mainly focused on the role of malignant cells but less on that of stromal fibroblasts during cancer development. Herein, by using paired normal and prostate cancer-associated stromal fibroblasts (CAFs) derived from a co-culture cell model and clinical patient samples, we demonstrated that although CAFs promoted prostate cancer growth, matrix metalloproteinase-3 (MMP-3) was lower in CAFs but elevated in prostate cancer cells relative to their normal counterparts. Furthermore, hydrogen peroxide was characterized as the central modulator for altered MMP-3 expression in prostate cancer cells and CAFs, but through different regulatory mechanisms. Treatment of CAFs but not prostate cancer cells with hydrogen peroxide directly inhibited mmp-3 promoter activity with concomitant nuclear translocation of nuclear factor-κB (NF-κB), indicating that NF-κB is the downstream pathway for the transcriptional repression of MMP-3 in CAFs. Hydrogen peroxide reduced thrombospondin-2 (an MMP-3 suppressor) expression in prostate cancer cells by upregulating microRNA-128. To the best of our knowledge, this is the first study to demonstrate the crucial role of reactive oxygen species in the switching expression of MMP-3 in stromal fibroblasts and prostate cancer cells during tumor progression, clarifying how the tumor microenvironment modulates ECM homeostasis control.