Expression of SIRT1 and DBC1 is Associated with Poor Prognosis of Soft Tissue Sarcomas

Jung Ryul Kim¹, Kyu Yun Jang².
¹Chonbuk National University, Medical School, Jeonju, Korea, Republic of; ²Chonbuk National University, Medical School, Jeonju, Korea, Republic of.

Disclosures:
J. Kim: None. K. Jang: None.

Introduction: SIRT1 (silent mating type information regulation 2 homolog 1) is a type III histone deacetylase, but, also deacetylates non-histone proteins, especially proteins involved in tumorigenesis. A role of SIRT1 as a non-histone deacetylase tumor promoter which is centrally mediated by functional inhibition of P53 has been proposed. The expression of SIRT1 increases resistance to anticancer agents and is associated with progression of cancers and poor prognosis of cancer patients. Recently, the roles of SIRT1 and deleted in breast cancer 1 (DBC1) in human cancer have been extensively studied and it has been demonstrated that they are involved in many human carcinomas. However, their clinical significance for soft-tissue sarcomas has not been examined. In this study, we evaluated the expression and prognostic significance of the expression of SIRT1, DBC1, P53, β-catenin, cyclin D1, and Ki67 in soft-tissue sarcomas.

Methods: One hundred four cases of soft-tissue sarcoma patients who underwent curative surgical resection in Chonbuk National University Hospital between July 1998 and December 2011 were included in the present study. All of histological types of tumor and histologic grading were retrospectively reviewed according to the 2013 World Health Organization classification of tumors of soft tissue and bone. The sarcomas included in this study according to the histological types were 20 leiomyosarcoma, 16 synovial sarcoma, 11 undifferentiated sarcoma, 10 myxoid liposarcoma, 4 well differentiated liposarcoma, 3 dedifferentiated liposarcoma, 6 Ewing sarcoma, 6 malignant peripheral nerve sheath tumor, 5 adult fibrosarcoma, 5 angiosarcoma, 4 myxofibrosarcoma, 4 epithelioid sarcoma, 3 alveolar rhabdomyosarcoma, 2 embryonal rhabdomyosarcoma, 2 pleomorphic rhabdomyosarcoma, 2 low grade myofibroblastic sarcoma, and one clear cell sarcoma. Tissue microarray was established from the most representative solid area of tumor from the paraffin-embedded tissue blocks after review of original H&E slides. Immunostaining for SIRT1, DBC1, P53, β-catenin, and cyclin D1 were evaluated to estimate the nuclear positivity of tumor cells according to the Allred scoring system.

Results: Immunohistochemical expression of SIRT1, DBC1, P53, β-catenin, and cyclin D1 were seen in 71% (74 of 104), 74% (77 of 104), 53% (55 of 104), 48% (50 of 104), and 73% (76 of 104) of sarcomas, respectively. Expression of SIRT1 significantly correlated with tumor stage (P = 0.013), distant metastasis (P = 0.001), histological grade (P = 0.008), mitotic count (P = 0.002), Ki67 index (P = 0.014), cyclin D1 expression (P < 0.001), β-catenin expression (P < 0.001), P53 expression (P = 0.003), and DBC1 expression (P < 0.001). DBC1 expression was also significantly correlated with tumor stage (P = 0.019), distant metastasis (P = 0.003), histological grade (P = 0.013), mitotic count (P = 0.032), cyclin D1 expression (P < 0.001), β-catenin expression (P < 0.001), and P53 expression (P = 0.005). P53 expression significantly correlated with patient age, tumor stage, distant metastasis, histological grade, tumor differentiation, mitotic count, Ki67 index, cyclin D1 expression, and β-catenin expression. The expression of β-catenin was significantly associated with histological grade, tumor differentiation, mitotic count, and cyclin D1 expression. The expression of cyclin D1 was significantly associated with tumor stage, histological grade, tumor differentiation, and mitotic count. Ki67 index was significantly associated with tumor stage, distant metastasis, histological grade, tumor necrosis, and mitotic count. Expression of SIRT1 was significantly associated with shorter overall survival (OS) (P < 0.001, hazard ratio (HR): 7.357, 95% confidence interval (95% CI): 2.871-18.855) and event-free survival (EFS) (P < 0.001, HR: 4.186, 95% CI: 2.055-8.525) by univariate analysis. DBC1 expression was also significantly associated with shorter OS (P = 0.029, HR: 2.338, 95% CI: 1.090-5.185) and EFS (P = 0.005, HR: 2.761, 95% CI: 1.361-5.601) by univariate analysis. The expression of P53, β-catenin, and cyclin D1 were significantly associated with shorter OS (P < 0.001, P = 0.002, and P = 0.006, respectively) and EFS (P < 0.001, P = 0.026, and P = 0.007, respectively) by univariate analysis. The Ki67 index also predicted shorter OS (P = 0.002) and EFS (P = 0.007). From the multivariate analysis, the expression of SIRT1 was an independent prognostic indicator significantly associated with both OS and EFS. The patients with SIRT1 expression had a 10.062-fold (95% CI, 2.851-35.509) greater risk of death (P < 0.001) and a 2.459-fold (95% CI, 1.166-5.185) greater risk of EFS (P = 0.018). In addition, tumor stage (P = 0.002), tumor depth (P = 0.007), tumor necrosis (P = 0.007), P53 expression (P = 0.033), DBC1 expression (P < 0.001), and β-catenin expression (P = 0.020) were independent prognostic indicators of shorter OS by multivariate analysis. Tumor depth (P = 0.017), distant metastasis (P < 0.001), tumor necrosis (P = 0.035), and P53 expression (P = 0.004) were independent prognostic indicators of EFS.

Discussion: In this study, the expression of SIRT1, DBC1, P53, β-catenin, cyclin D1, and Ki67 were significantly correlated with each other, and their expression predicted shorter survival by univariate analysis. Especially, the expression of SIRT1 was an
independent prognostic indicator of OS and EFS by multivariate analysis. These findings suggest that the expression of SIRT1 and DBC1 can be used as clinically significant prognostic indicators for sarcoma patients. Moreover, SIRT1- and DBC1-related pathways may be involved in the progression of soft-tissue sarcomas and SIRT1- and DBC1-related pathways may provide targets for novel therapeutic approaches for soft-tissue sarcomas. Our result showed that the expression of SIRT1 is common in soft-tissue sarcomas regardless of histological type. In this report, we are the first to demonstrate that DBC1 expression in soft-tissue sarcoma significantly correlated with higher tumor stage, higher histological grade, presence of distant metastasis, and increased mitotic count. Moreover, DBC1 expression predicted shorter OS and EFS. In line with our results, DBC1 expression significantly correlated with the progression and survival of human carcinomas, such as gastric carcinoma, breast carcinoma, esophageal carcinoma. However, the soft-tissue sarcomas included in this study were heterogeneous. Therefore, further study focused on specific types of soft-tissue sarcoma is needed to understand the exact role of SIRT1- and DBC1-related pathways in sarcomas and determine the best use of them as therapeutic targets for the treatment of specific types of soft-tissue sarcoma.

Significance: This study is the first to demonstrate that the expression of SIRT1 and DBC1 could be used as novel prognostic indicators of soft-tissue sarcoma. In addition, SIRT1, β-catenin, and DBC1-related pathways may be involved in the progression of sarcomas and could be new therapeutic targets for the treatment of soft-tissue sarcomas.

Acknowledgments: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2011-0028928).

References: 1

ORS 2014 Annual Meeting
Poster No: 1986