

medical history was significant for osteoporosis, but there was no history of anti-resorptive drug use. Upon examination, a gingival alveolar swelling was noted. Biopsy revealed high-grade adenocarcinoma, with immunohistochemical features most consistent with a breast primary. Subsequently, it was learned that the patient had a history of breast cancer, treated by total mastectomy of the left breast over three years previously with no previous evidence of metastases. The rarity of metastatic lesions to the jaw makes diagnosis particularly challenging. This case emphasizes the importance of assembling a thorough medical history as part of a complete patient work-up, especially in the presence of atypical symptoms or radiographic findings

**THE TRANSITION OF TISSUE INHIBITOR OF METALLOPROTEINASE-4 TO -1 EXPRESSION MODULATES YAP/TAZ MEDIATED AGGRESSIVE PHENOTYPE IN LIPOSARCOMA.** DR. MADHU SHRESTHA, DR. TOSHINORI ANDO, DR. CHEA CHAN-BORA, DR. IKUKO OGAWA, DR. MUTSUMI MIYAU-CHI, PROF. TAKASHI TAKATA. HIROSHIMA UNIVERSITY

**Objectives:** Liposarcoma(LS) is the most common soft-tissue sarcoma. The histological spectrum has a well-differentiated-liposarcoma(WDLS) and a more aggressive dedifferentiated-liposarcoma(DDLs). Advanced therapeutic strategies based on molecular mechanism are urgently needed, especially for DDLs. Previously, we reported that TIMP-1 (a member of tissue-inhibitor-of-metalloproteinase), with its receptor CD63 activates yes-associated protein (YAP) and transcriptional co-activator with PDZ binding motif (TAZ) to promote cancer cell proliferation. Aberrant YAP/TAZ activation in LS is reported, however, contribution of TIMP-1-YAP/TAZ axis in LS remains unclear. Intriguingly, TIMP-4 is known to share CD63 as TIMP-1, but its role in LS is unknown. Here we clarified the expression and function of TIMP-1 and -4 through YAP/TAZ regulation in LS.

**Materials & Methods:** Cell lines of WDLS(94T778) and DDLs(SW872) were used for in vitro experiments such as Western blotting, RT-PCR, cell-proliferation, migration and apoptosis assay.

**Results:** Database analysis showed high TIMP-1 expression in DDLs patients correlating with poor prognosis, while high TIMP-4 expression in WDLS patients with better prognosis. TIMP-1 knockdown in DDLs cells inactivated YAP/TAZ and suppressed cell-growth, migration, which was rescued by constitutively active form of YAP5SA. On the other hand, cell-growth and migration were significantly increased in TIMP-1 over expressing WDLS cells, which was suppressed by verteporfin (a YAP/TAZ inhibitor). TIMP-4 knockdown in WDLS activated YAP/TAZ, promoted cell-proliferation and migration, which was inhibited by verteporfin treatment or YAP/TAZ knockdown. Recombinant TIMP-4 showed opposite results in DDLs cells significantly. TIMP-4 CD63 binding inactivated YAP/TAZ in WDLS.

**Conclusion:** The switching of TIMP-4 to -1 expression during transition from a WDLS to a DDLs led to activation of YAP/TAZ and promoted cell-proliferation, migration, inducing poor prognosis. TIMP-1 and -4 as novel YAP/TAZ regulators may warrant future possibilities of targeting key molecules in development of diagnostic and therapeutic novelties in treating LS.

**ARECA NUT EXTRACT ENHANCED M2-LIKE MACROPHAGE POLARIZATION AND FIBROBLAST ACTIVATION.** DR. LIEN-YU CHANG<sup>A</sup>, MR. PO-JU HSIAO<sup>B</sup>, MS. CHIH-YUN LU<sup>B</sup>, DR. YI-CHUN LIN<sup>C</sup>, PROF. SHAN-LING HUNG<sup>B</sup>, PROF. YU-LIN LAI<sup>C</sup>. <sup>A</sup> NATIONAL YANG-MING UNIVERSITY, INSTITUTE OF ORAL BIOLOGY, DEPARTMENT OF DENTISTRY; <sup>B</sup> TAIPEI VETERANS GENERAL HOSPITAL, DEPARTMENT OF STOMATOLOGY; <sup>C</sup> NATIONAL YANG-MING UNIVERSITY, INSTITUTE OF ORAL BIOLOGY, DEPARTMENT OF STOMATOLOGY; NATIONAL YANG-MING UNIVERSITY, DEPARTMENT OF DENTISTRY

**Objectives:** Areca nut chewing habit is popular in Taiwan and is closely related to oral squamous cell carcinoma (OSCC). Both activated fibroblasts expressing alpha-smooth muscle actin ( $\alpha$ -SMA) and tumor-associated macrophages showing M2 polarization in stroma are supposed to be crucial in tumor progression. The purpose of the study was to examine the profile of stromal fibroblasts and macrophages in areca-associated oral cancer tissues, their *in vitro* effects of areca nut extract (ANE) and two common oral insults, nicotine (NT) and lipopolysaccharides (LPS), on primary oral fibroblasts and human macrophages were also investigated. The study was approved by institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan. Oral tissues were obtained with informed consent from patients undergoing routine surgical treatment.

**Findings:** Tissue sections showed that compared to the tumor-adjacent normal tissues (ANT), OSCC revealed a higher expression of pan-macrophage marker CD68, M2 markers CD163 and arginase-1 and activated fibroblast marker  $\alpha$ -SMA, but not M1 marker CD86. In *in vitro* cell experiments, all of ANE, NT and/or LPS treatments could increase  $\alpha$ -SMA expression and collagen production by oral fibroblasts. But only ANE treatment group, not NT or LPS group, enhanced the expression of M2 marker arginase-1 by macrophages. Furthermore, conditioned media acquired from macrophages (CM-Mac) of ANE treatment group increased the collagen production and IL-6 secretion by fibroblasts. CM-Mac of LPS treatment group also increased IL-6 secretion. Taken together, fibroblasts could be activated by ANE, NT and LPS, but only ANE could enhance macrophage M2-like polarization which in turn further increased fibroblast protein production.

**Conclusions:** Areca nut might compromise oral health by the setup of tumor-promoting microenvironment with local immune dysregulation via the enrichment of activated fibroblasts and M2-like macrophages.

**INCREASED SOX2-POSITIVE CELLS IN BRAF (V600E) MUTATED AMELOBLASTOMAS.** DR. JULIA YU FONG CHANG<sup>A</sup>, DR. CHIH-HUANG TSENG<sup>B</sup>, DR. PEI HSUAN LU<sup>A</sup>, DR. YI-PING WANG<sup>A</sup>. <sup>A</sup> NATIONAL TAIWAN UNIVERSITY HOSPITAL, <sup>B</sup> KAOHSIUNG MEDICAL UNIVERSITY HOSPITAL

**Objective:** SRY related HMG box gene 2 (SOX2) is a transcription factor expressed in embryonic and adult stem cells. SOX2 positive dental epithelial stem cells have been shown to give rise to all dental epithelial cell lineages. Increased SOX2 expressing cells has been reported in ameloblastic carcinomas than ameloblastomas, which might indicate SOX2 contributes to the pathogenesis of ameloblastic neoplasms. Recent and our