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その他

座長：遠藤 眞美（日本大学松戸　歯学部障害者歯科学講座）
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[P70]Signaling of myeloid CD11c^{+}-dendritic cell-derived osteoclast precursor (mDDOCp) for osteoclastogenesis via the environment milieu onto arthritic bone loss vs. remodeling

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Objectives: Arthritic bone loss vs. remodeling in our skeleton involves the pivotal pathways, where the RANKL-RANK/OPG-triad signals via TRAF6/transducer-complexes in the osteoclast/OC, OC-precursors/OCp and immune-cells via environmental milieu at the osteo-immune interface. Our lab pioneered the characteristic OCp from myeloid-CD11c^{+}-dendritic-cell-precursors (mDDOCp) in response to RANKL and osteotropic cytokines stimuli (i.e., TNF-a, TGF-β, *etc.*), from which we proposed to study how signal-interactions between TGF_b-vs.-IL-17 in mDDOCp lacking TRAF6-signaling on osteoclastogenesis and bone loss.
Methods: We employed established protocols to generate CD11c^{+}DDOC-cells lacking TRAF6-signaling in BM/ splenic-cells of ³6-wk-C57BL/6-chimeric mice post-lethal-irradiation and reconstituted with BM/fetal-liver cells of TRAF6$^{(-/-)}$-mice, then-subjected to co-cultures with/without naï ve-CD4^{+}T-cells (or mRANKL:50-100ng/ ml) and *Aggregatibactor Actinomycetemcomitans*/JP2-strain sonicate-Ag (*Aa*-Ag), where exogenous $rmTGF_b$ or mIL-17 vs. anti-TGF_b-neutralizing-Mab was individually added *in-vitro*, followed by enumerating surface- areas of TRAP^{+}-CD11c^{+}DC/mm^2 in bone/dentine resorptive-pits. In parallel, CD11c^{+}-DDOC from WT-TRAF6$^{(+/+)}$- mice-BM/splenic-cells (w/wt rmM-CSF-&-rmRANKL) were set as controls for the statistics (i.e., student-t-test or ANOVA).
Results &Conclusion: The resulting data showed that: **i)** TRAF6/transducer-signaling was essential for RANKL/RANK- associated (WT)-DDOC-mediated osteoclastogensis/bone resorption; **ii)** rmTGF-b added into TRAF6$^{(-/-)}$- derived-DDOC co-cultured with RANKL-&-*Aa*-Ag significantly rescued the reduced TRAP$^{(+)}$-DDOC/OC activity detected in resorptive-pits (p=0.006); whereas, adding rmIL-17 unexpectedly further enhanced such rescued TRAP$^{(+)}$-DDOC/OC activity measured (p=0.041), higher than that detected above, suggesting that TGF-b individually or with-IL-17 synergistically, mediated TRAF6-independent rescue-signaling onto the effector, DDOC; **iii)** conversely, addition of anti-TGF-b-neutralizing-Mab in co-cultures of **ii)** depicted, or replacing rmRANKL with naï ve-CD4^{+}T-cells &*Aa*-Ag, significantly reduced TRAP$^{(+)}$-DDOC/OC activity on resorptive-pits (p=0.008) as shown in **ii)**, indicating that IL-17-signaling for the functional activity of mDDOCp/OCp, required TGF-b in the environmental milieu, regardless RANKL-RANK/TRAF6-signaling or other inter-players expressed *in-situ* and nearby. These novel findings may suggest that such non-discriminative signaling via TGF_b-vs.-IL-17 for rescue-effector functions in CD11c^{+}mDDOCp/OCp may underpin new insight for the alternative pathway of osteoclastogenesis or bone loss, which will require further study for its *in-vivo* significance through animal models and human conditions; including the arthritic/articular-joint disorders and/or periodontitis. (The project was supported by National Health Research Institute of Taiwan: Grant # NHRI-EX101-9946SI)（ COI: The authors declare no conflict of interest

regarding the contents of this abstract for scientific presentation）（IRB: The present project was conducted according to the guidelines of Institution Animal Care &Use Committee (IACUC), which was approved for the IACUC-protocol #98017 &#98183, as the IRB-supported equivalent for all animal experiments and study, at the Kaohsiung Medical University (KMU), Kaohsiung, Taiwan.）