Effects of exosomes released by NSCLC cells on osteoclasts differentiation

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Non-small cell lung cancer (NSCLC) has a poorly 5-year survival rate, as a consequence of the delay in the detection of the disease. The majority of patients are diagnosed in an advanced disease stage. Bone metastasis is the most frequent complication in NSCLC resulting in osteolytic lesions. The perfect balance between bone-resorbing osteoclasts (OCs) and bone-forming osteoblasts (OBs) activity is lost in bone metastasis, inducing osteoclastogenesis. Most of the patients with lung cancer are treated with EGFR inhibitors (TKIs). Numerous studies show in patients with NSCLC the presence of somatic mutations at the level of the exons coding for tyrosine kinase domain of the EGFR. The cell line CRL 2868 presents the "activating" mutation of exon 19, that confers sensitivity to treatment with TKIs.

Recent studies demonstrated that exosomes, nano-size vesicles that shuttle proteins, lipids and nucleic acids, have a key role in tumor progression and premetastatic niche formation. Exosomes are involved in modulation of metastasis formation; we investigated the role of NSCLC cell-derived exosomes in OCs differentiation. We show that CRL 2868 cells release exosomes which are actively internalized by RAW 264.7 cell line, a cellular model of preosteoclasts. CRL 2868 cell-derived exosomes positively modulate pre-osteoclast migration and play a significant pro-differentiative role of RAW 264.7 cells, inducing the expression of osteoclast markers such as Cathepsin K (CTSK), Matrix Metalloproteinases 9 (MMP9) and Tartrate-resistant Acid Phosphatase (TRAP). Our data indicate that CRL2868-exosomes modulate OCs function and differentiation. Further studies will be carried out to investigate the role of TKI in OCs differentiation.