Epigenetic regulation of bone metastasis and osteoclast differentiation

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Osteoclasts are multinucleated bone-resorbing cells and generated by the fusion of mononuclear precursor cells of the monocyte-macrophage lineage. A group of genes regulating osteoclast differentiation positively or negatively have been identified and the deregulated expression of these genes has been documented to cause various skeletal diseases. MMP-9 is a member of MMP family that has been studied mainly with respect to its role in extracellular matrix remodeling. Unexpectedly, however, we found that MMP-9 moves into the nucleus and mediates histone H3 N-terminal tail proteolysis at osteoclastogenic genes in RANKL-induced osteoclast precursor (OCP) cells. Our observation that MMP-9 knockdown abrogates H3 N-terminal tail proteolysis and osteoclastogenic gene expression is supportive of the idea that MMP-9 is the major protease responsible for H3 N-terminal tail proteolysis-mediated gene activation occurring in OCP-induced cells. Furthermore, our follow-up studies indicate that specific patterns of histone posttranslational modification are key regulators of MMP-9 protease activity toward target chromatin domains in OCP-induced cells. Cancer cells frequently spread to bone and secrete soluble signaling factors to accelerate osteoclast differentiation and bone resorption. Since chromatin signaling and regulatory factors have been implicated in epigenetic control of cancer metastasis, we also investigated their possible roles as modulators of metastatic potential of cancer cells to bone. We show that specific histone modification and histone variant tightly regulate cancer bone metastasis and osteoclast differentiation. The observed effects require epigenetic control of genes encoding secreted factors that influence cancer cell metastasis and osteoclast differentiation. Consistent with these data, osteoclastogenesis and osteoporosis are significantly affected following the administration of recombinant forms of secreted factors into mice. More interestingly, our mechanistic studies reveal that histone modification functionally interacts with histone variant to alter the expression and functional properties of metastasis-associated genes in cancer cells in the bone microenvironment.

Speaker Biography

Woojin An investigates the biological role of chromatin modification and its basic concept and mechanism of action in gene regulation and cell differentiation. By using multiple new technologies, his recent studies are mainly directed toward understanding chromatin reorganization and histone modification-mediated recruitment of novel regulatory factors to specific target genes.

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