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Global Congress on

Nucleic Acids: Biology, Health & Diseases

August 04-05, 2016 New Orleans, USA

MacroH2A acts as a key regulator of osteolytic bone metastasis of cancer cells

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Breast cancer tends to metastasize to bone, and more than half of all patients dying of breast cancer have evidence of osteolytic bone metastasis. Breast cancer-derived factors facilitate this bone metastatic process by generating a permissive microenvironment in the target organs for the engraftment of cancer cells as well as the establishment of metastatic foci. Histone modifications and variants play a crucial role in remodeling chromatin organization and modulating gene expression in various cancer cells including breast cancer cells. Altered expression of metastasis- associated genes by distinct combinations of histone modifications and variants is linked to multiple stages of breast cancer metastasis to bone. Yet, how this epigenetic resetting of gene expression in breast cancer cells contributes to osteolytic metastasis and bone lesions remains unclear. We show that histone variant macroH2A is capable of governing the early events of osteolytic lesion formation by inhibiting the expression of lysyl oxidase (LOX), which is a key factor for osteoclastogenesis. We demonstrate that macroH2A, in complex with EZH2 histone methyltransferase and Mybbp1a transcription repressor, occupies the promoter and coding regions of LOX gene, elevates the levels of histone H3 lysine 27 trimethylation, and thereby keeps the gene in a repressed state. Our data unravel an unexpected role for macroH2A in regulating the pathogenesis and progression of breast cancer bone metastasis and illustrate the power of combined biochemical and cellular approaches for mechanistic analyses.

Biography

Woojin An has completed his PhD from Oregion State University and Post-doctoral studies from the Rockefeller University. He is an Associate Professor of University of Southern California Keck School of Medicine. He has published more than 50 research papers in reputed journals and has been serving as a reviewer for multiple journals and grant study sections.

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