UNC ORTHOPAEDICS

OrthoRaMS SEMINAR SERIES

Orthopaedic Research and Musculoskeletal Science

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Location: Dickson Conference Room, 3200 Thurston Bldg.

ApoE: A new target to improve aged bone fracture healing

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Gurpreet Baht, Ph.D. is an Associate Professor in the Department of Orthopaedic Surgery and a faculty member of the Duke Institute of Molecular Physiology (DMPI) at Duke University. Dr. Baht's research focus is on understanding age-associated deficits in bone healing. Using models such as parabiosis and bone marrow transplantation in conjunction with proteomics and single-cell RNA sequencing, Dr. Baht has been able to identify signaling pathways and molecules important in robust bone healing. The Baht Lab is now focusing on using this knowledge to identify novel therapeutic interventions to improve bone healing. https://www.thebahtlab.com/home

ABSTRACT

Bone fracture healing is impaired with advanced age however the underlying mechanism is unknown. Our previous work indicated circulating apolipoprotein E (ApoE) as an aging factor, increasing with age and impairing bone regeneration. Since the liver is the primary source of circulating ApoE, we deleted hepatic expression of ApoE using Albumin-Cre;ApoEfl/fl (ΔApoE) mice and investigated tibial fracture healing in aged (24-month-old) mice. ΔApoE mice displayed 95% reduction in circulating ApoE; micro-CT and histological analysis demonstrated increased bone deposition in 21-day fracture calluses. ApoE-treatment of aged BMSCs in tissue culture models inhibited osteoblast differentiation. Subsequent RNA sequencing of these cultures indicated that the Wnt/β-catenin was the primary target of this ApoE-based inhibition. Indeed, ApoE treatment had no inhibitory effect on cultures in which β-catenin levels were stabilized. We determined Lrp4, whose expression was required in ApoE-based inhibition of Wnt/β-catenin signaling and osteoblast differentiation, to be the osteoblast cell surface receptor to ApoE. Importantly, we validated this ApoE-Lrp4-Wnt/β-catenin molecular mechanism in human osteoblast differentiation. Finally, we identified an ApoE-neutralizing antibody (NAb) able to lower levels of circulating ApoE when delivered systemically. Aged, wildtype mice underwent fracture surgery and were treated with NAb 3 days post injury. Their fracture calluses contained 35% more bone tissue, evidencing improved aged fracture healing. Our work here identifies novel cross-organ communication, liver-to-bone cross-talk via hepatic ApoE expression. Using this information, we have developed a noninvasive, translatable therapeutic intervention for bone regeneration and provides a translatable therapeutic intervention.