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C1q-induced activation of Wnt signaling in aging and aging-related disorders

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Abstract

Wnt signaling is an evolutionarily conserved signaling pathway that plays critical roles during embryonic development. Proper regulation of Wnt signaling is also important during postnatal period and aberrant activation of Wnt signaling is known to play a causative role during cancer formation. Recently, increased activity of canonical Wnt signaling is also implicated in mammalian aging and aging-related phenotypes. Here we show that complement C1q is a novel activator of canonical Wnt signaling and is deeply involved in pathophysiology of aging-associated disorders. Mass-spectrometric analysis revealed that complement C1q is one of the protein that binds to Wnt receptor Frizzled and activates canonical Wnt signaling. Serum C1q concentration is increased with aging, and Wnt activity is augmented during aging in the serum and multiple tissues of wild type mice but not of C1qa-deficient mice. Skeletal muscle regeneration in young mice is inhibited by exogenous C1q treatment, whereas aging-associated impairment of muscle regeneration is restored by inhibition of C1s or deletion of *C1qa* gene. Prevalence of various diseases, such as heart failure, diabetes, and arteriosclerosis, is increased with aging and those diseases are often linked with chronic inflammation observed in the elderly. Either systemic or local C1q level is increased in those pathologies and inhibition of C1s or deletion of *C1qa* gene ameliorate the severity of those diseases. These findings collectively suggest the unexpected role of complement C1q in Wnt signal transduction and in mammalian aging and imply the role of C1q-induced activation of Wnt signaling in the pathophysiology of certain diseases which is associated with aging and chronic inflammation.