Seung Chung et al., J Clin Cell Immunol 2017, 8:5 (Suppl)
DOI: 10.4172/2155-9899-C1-039

Complement C5a in nerve regeneration under inflammatory injury

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Tooth nerve damage from bacterial invasion (decay) or trauma is very common. Proper nerve regeneration is crucial for maintaining tooth viability as shown by previous studies of nerve denervation using rodent models that resulted in severe defects on tooth structure and function. These defects include significantly reduced survival and regeneration rate of exposed dental pulp tissue and severe morphological defects such as dento-alveolar ankyloses. Although dental nerve appears to have a critical importance in maintaining tooth morphology and viability, very little is known about initial mechanisms that regulate dental nerve regeneration especially beneath a caries injury site. To date, no investigation has systematically explored the effect of the complement system, which is one of the first components of innate immunity and inflammation, on dental nerve regeneration and its interaction with pulp fibroblasts under caries. Complement activation on human pulp fibroblasts has been suggested to provide a link between pulp inflammation and its regeneration capacity. Of central interest, we demonstrated for the first time that nerve outgrowth is controlled by local elevated expression of discrete nerve growth factors (neurotrophins) released from nearby pulp fibroblasts upon carious injury through interaction with the complement system. Our results demonstrate that complement component C5a receptors (C5aR) are ectopically expressed in human pulp fibroblasts both *in vitro* and *in vivo* shortly after carious injury. We provide direct evidence of C5aR`s critical role in the expression and secretion of brain-derived neurotropic factor (BDNF) by pulp fibroblasts leading to a significant neurite outgrowth enhancement toward the injured site. Surprisingly, we further confirmed the negative regulation of BDNF-secretion by C5L2, a previously defined 'non-functional C5a receptor', in biological regulation of C5a signaling. p38a mitogen activated protein kinase (MAPK) is well established as a mediator of inflammatory responses and previously suggested in downstream regulation by C5aR in other systems. Indeed, our initial assays demonstrate that p38 MAPK plays a key role in the modulation of neurotrophin secretions and this is C5a signalling dependent linking this key molecule to the mechanisms of action of C5a. Our study provdes molecular understanding of initial steps of dentin-pulp regeneration by linking neurite outgrowth to pulp fibroblast function through complement system activation. These studies will provide the basis for potential therapeutic interventions of dentin repair and vital tooth preservation.

Biography

Seung Chung received his PhD in Neuroscience in 2008 from University of Calgary Cummings School of Medicine, Canada and currently is an Assistant Professor at the University of Illinois at Chicago College of Dentistry. His lab focuses on determining the role of the complement system in nerve regeneration of human carious teeth and investigating the molecular mechanisms of the p38 mitogen activated protein kinase and chromatin-remodelling factor Brg1 in nerve myelination and remyelination.

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