

# 大学院特別講義のご案内

日時：平成27年8月28日(金) 17:00～18:30 場所：医学部基礎研究棟4階セミナー室 (B40-13)

講師：Dr. Matthew P Hoffman, Chief, Matrix and Morphogenesis Section, LCDB, NIDCR, NIH, DHHS

演題：3-O-sulfated Heparan Sulfate and FGFR2b Signaling Control Progenitor Expansion During Salivary Gland Development

**要旨：** Stem/progenitor cell therapy has been proposed to repair the permanent radiation damage to salivary glands that occurs during therapy for head and neck cancer. A biopsy would be used to expand the resident stem/progenitor cells in vitro for autologous transplantation. Expanding salivary stem/progenitors in culture for transplantation is an important step. Fibroblast growth factor (FGFR) signaling is critical for salivary stem/progenitor cell expansion during embryonic organogenesis and heparan sulfate proteoglycan co-receptors are required for FGFR signaling. The exquisite control of growth factor function by heparan sulfate (HS) is dictated by the tremendous structural heterogeneity of sulfated modifications. It is not known how specific HS structures control growth factor-dependent progenitor expansion during organogenesis. Epithelial KIT<sup>+</sup> progenitors are important for development and regeneration of salivary glands but the mechanisms by which KIT<sup>+</sup> progenitors generate these branching tissues are not well understood. Using fetal salivary gland development, we show that signals from the mesenchyme stimulate both FGFR2b and KIT signaling to expand distal KIT<sup>+</sup> progenitors. We also isolated KIT<sup>+</sup> progenitors and profiled expression of HS biosynthetic enzymes. Enzymes generating a specific type of 3-O-sulfated-HS (3-O-HS) are enriched, and FGF10/FGFR2b signaling directly regulates their expression. Bioengineered 3-O-HS binds FGFR2b and stabilizes FGF10/FGFR2b complexes in a receptor- and growth factor-specific manner. Rapid autocrine feedback increases 3-O-HS, KIT and progenitor expansion. Knockdown of multiple Hs3st isoforms limits fetal progenitor expansion, but is rescued with bioengineered 3-O-HS. Rapidly altering a specific 3-O-sulfated epitope provides a cellular mechanism to modulate the response to FGFR2b signaling and control progenitor expansion. 3-O-HS may expand KIT<sup>+</sup> progenitors in vitro for regenerative therapy.

Dr. Hoffmanは米国NIHのNational Institute of Dental and Craniofacial Researchの細胞外マトリックス、器官形成部門の若手主任として、世界的に活躍中です。唾液腺をモデルにして、上皮形態形成の分子機構を幹細胞レベルから器官レベルまで多岐にわたり解析をされており、再生医療にとっても重要なヒントを提案されています。今回、上皮管腔分岐形成に対するヘパラン硫酸とFGFの作用について解説して頂く予定です。2011年は歯学研究科にお越し頂きましたが、今回は医学系研究科で最新の研究データを紹介して頂きます。

【参考文献：Dev Cell 32(6):667-77, 2015, Dev Cell 8;31(5):519-20.2014, Dev Cell 30(4):449-62, 2014, Dev Cell 29(6):662-73, 2014, Nat Commun. 4:1494, 2013】

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歯学研究科 顎口腔機能治療学 阪井 丘芳 (内 2275)

\*大学院生以外の先生方にも多数ご参加頂きますようお願い申し上げます。  
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