The 702nd Kitasato Medical Society Invitational Academic Lecture Series Abstract

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Role of EFA6, Exchange Factor for Arf6, in epithelial cell polarity and breast cancer development

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The formation of multicellular organs occurs through the concerted organization of the four primary tissues. Among these, the epithelia, which line the inner cavity of all organs forms a permeability and exchange barrier with the luminal outside world. During embryonic development, there is a conversion of well-polarized primitive epithelial sheets into mesenchymal cells through a process called epithelial-mesenchymal transition (EMT). After migration, these cells re-polarize to form a secondary epithelia through mesenchymal-epithelial transition (MET). In adults, these two morphogenetic events are diverted by cancer cells to promote their progression toward metastasis and dormancy.

In the past, we have demonstrated that EFA6 contributes to apico-basal polarity by facilitating the assembly of the tight junction (TJ), responsible for the barrier function, as well as the formation of the luminal compartment in in vitro cell models. In addition, we showed that exogenous expression of EFA6 can restore functional TJ and luminogenesis in the weakly tumoral mammary cell line MCF7. Further, transcriptomic analyses of human breast tumor samples indicated that loss of EFA6 expression is correlated with the breast cancer Claudin-low subtype defined by the loss of expression of the TJ molecules and an EMT gene expression signature.

I will present unpublished data that extend our molecular understanding as to how EFA6 promotes luminogenesis. I will also discuss preliminary experiments that indicate that EFA6 loss of expression stimulates breast cancer development in vivo generating tumors with characteristics of the Claudin-low subtype. Altogether, our data demonstrate that EFA6 is an important regulator of epithelial homeostasis and acts as an antagonist to breast cancer.

The 704th Kitasato Medical Society Invitational Academic Lecture Series Abstract

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Building the lymphatic vasculature: From progenitor cells to functional vessels and how things go wrong in human lymphatic vascular disorders

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We and others recently demonstrated that heterozygous germline mutations in the zinc finger transcription factor GATA2 underlie Emberger syndrome, a disorder characterised by lymphedema and predisposition to myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) (Kazenwadel et al., *Blood* 2012, Ostergaard et al., *Nat Gen* 2011). This discovery was the first to demonstrate an important role for GATA2 in the lymphatic vasculature. We subsequently determined that Gata2 is crucial for lymphatic vascular development by orchestrating the construction and maintenance of lymphovenous and lymphatic vessel valves (Kazenwadel et al., *J Clin Invest* 2015). Our current work aims to define the mechanisms by which GATA2 controls valve morphogenesis in the lymphatic vasculature. We have identified a novel enhancer element upstream of the key lymphatic transcriptional regulator PROX1 that is bound by GATA2, FOXC2 and NFATc1 and is differentially epigenetically regulated in blood vascular endothelial cells compared to lymphatic endothelial cells. Moreover, we have shown that this element has the capacity to drive reporter gene expression to the lymphatic vasculature and in particular, at high levels in valve endothelial cells. Current work aims to investigate the requirement of this enhancer for lymphovenous and lymphatic vessel valve development, together with the upstream mechanisms that regulate enhancer activity. We have also identified additional key target genes of GATA2 in the lymphatic vasculature, at least two of which are also mutated in human lymphoedema syndromes. These genes and their roles in lymphatic vessel morphogenesis will also be discussed. Ultimately, understanding the genetic basis of lymphoedema will inform our knowledge of the cellular events and signalling pathways important for building functional lymphatic vessels, information that will underpin the design of novel, targeted therapeutics able to promote lymphatic vessel function and thereby treat lymphoedema.