CDB SEMINAR

Date:	Thursday, August 12
Time:	15:00 P.M.～ 17:00 P.M.
Place:	1F Auditorium of Building C, CDB

15:00-16:00

Speaker1: **Frank R. Schubert**

< Institute of Biomedical and Biomolecular Science University of Portsmouth>

Title: **"Transcriptional control of early neuronal specification in the embryonic midbrain"**

Summary:

The complex array of neuronal connections in the vertebrate brain derives from a simple, conserved scaffold of axon tracts in the early embryonic brain. The mechanisms governing the formation of these tracts are largely unknown. We are interested in the molecular cues responsible for the formation of the early axon tracts, in particular in linking transcription factors that are expressed in a spatially restricted manner with the specification of neuronal fates.

To this aim, we have first characterised the expression patterns of several homeodomain transcription factors like *Pax6*, *Six3*, *Emx2* and *Sax1* in the ventral midbrain-forebrain border. From this area, two prominent early axon tracts are derived: the caudad extending medial longitudinal fascicle (mlf) and the dorsad, contralaterally projecting posterior commissure (pc). We could demonstrate that Sax1 is expressed in the nucleus of the mlf, and subsequently used electroporation in the chick to analyse the role of *Sax1* in the development of this tract. Ectopic expression of a *Sax1* expression construct leads to an enlargement of the mlf, while conversely *VP16-Sax1*, in which the eh1-like transrepression domain of *Sax1* has been replaced with the transactivation domain of *Herpes simplex VP16*, results in a reduction of the mlf. The morphological phenotype is mirrored by changes in gene expression, as *Sax1* can ectopically activate *Emx2* transcription, while *VP16-Sax1* represses the expression of *Emx2* and *Six3*.

Our results show a critical role for *Sax1* in the formation of the mlf, and point towards the positional coding of neuronal fate by combinations of homeobox genes, analogous to recent finding in hindbrain and spinal cord.

16:00-17:00

Speaker2: **Susanne Dietrich**

< Department of Craniofacial Development, King's College London>

Title: **"Casting a smile and wagging the tail. . . how to make skeletal muscle in different areas of the vertebrate embryo"**

Summary:

Skeletal muscles are the basis for any coordinate movement, be it locomotion, food uptake, respiration or speech. Thus, skeletal muscles are a prerequisite for life. However, loss of muscle function and muscle wasting are common phenomena. It occurs when aging, it is associated with HIV/AIDS or with cancer burden, and it cuts short the life of patients suffering from muscular dystrophies such as Duchenne's.

Current approaches to muscle wasting focus on the use of muscle stem cells. These cells seem to use the embryonic molecular tool kit when they differentiate. However, the embryo employs distinct programmes to form muscle at different sites of the body. These programmes are not well characterized. Therefore, it remains unclear, which of the embryonic programmes, if any, are used by muscle stem cells or could be exploited in tissue engineering.

It is established that in the trunk one programme accounts for the formation of epaxial muscles (deep muscles of the back), and a second for the development of the hypaxial muscles (all lateral, ventral and superficial muscles). Hypaxial muscles however develop by two distinct mechanisms, as muscles for the diaphragm and limbs are made from migratory muscle precursors, while intercostal and abdominal muscles stem from non-migratory cells. Finally, none of the trunk programmes seem at work in the head.

In this talk I will present our work aimed at unraveling of the various myogenic programmes.

(1) Out on a limb: formation of migratory muscle precursors

Trunk muscles form from the segmental paraxial mesoderm, the somites. We previously showed that signals from surface ectoderm and lateral plate mesoderm induce hypaxial muscle formation, antagonizing the signals from neural tube and notochord that stimulate epaxial myogenesis. However, these signals act at all axial levels, and thus do not discriminate between migratory and non-migratory muscle precursor formation. Our recent findings suggest that the signals from lateral mesoderm and ectoderm are permissive for hypaxial muscle formation. In addition, localized cues within the somite decide, whether muscle precursors are specified as migratory or non-migratory. These cues are *Hox/Hom* genes, which control positional information in the body.

(2) Border dispute: How to segregate epaxial and hypaxial programmes

In the adult, epaxial-hypaxial muscles are separated by the lateral myoseptum. In the embryo however, epaxial-hypaxial muscle precursors reside in adjacent territories of the somite, without any morphological boundary between them. Thus, a molecular mechanism must be in place to segregate the two myogenic programmes and to subsequently physically separate the epaxial-hypaxial muscle anlagen. Our data indicate that *En1* and *Sim1* expression demarcate the epaxial-hypaxial boundary within the somite. Employing cell aggregation assays, we demonstrate that this expression boundary is a true compartment boundary. Misexpression studies revealed that *En1* is not simply a marker: the factor actively promotes epaxial and suppresses hypaxial programmes, and may play a role in the establishment of the correct innervation patterns of muscle.

(3) What makes us smile

In the head, skeletal muscles develop from two sources, the non-somitic head mesoderm anterior to the otic vesicle (provides the eye, jaw and facial muscles) and the occipital somites posterior to it, (provide some pharyngeal and laryngeal muscle, and all muscles of the tongue). The occipital somites have been secondarily incorporated into the head during vertebrate evolution.

It was know for some time that important upstream regulators of trunk myogenesis are absent from non-somitic head mesoderm. Our data established that the genuine, non-somitic head mesoderm is unable to activate these trunk muscle markers. Moreover, it requires head-specific cues for its myogenic differentiation, which is suppressed by myogenic signals from the trunk.

(4) Ticket to ride: formation of tongue muscles

Tongue muscles stem from the occipital somites, and are thought to develop like migratory muscle precursors for the limb. However, when key regulators for migratory muscle precursor formation are mutated, limb muscles perish while tongue muscles prevail. We show that indeed, these regulators are dispensable for tongue muscle development as the tongue muscle precuror cells are swept to their target site by powerful morphogenetic movements.

Host ： Shigeru Kuratani <Evolutionary Morphology Biology , CDB>

E-mail: saizo@cdb.riken.jp Tel: 078-306-3064(ext. 4501) RIKEN Center for developmental Biology http://www.cdb.riken.go.jp/