DEPARTMENT OF ONCOLOGY-PATHOLOGY,
CANCER CENTRUM KAROLINSKA
Karolinska Institutet, Stockholm, Sweden

IMAGING VASCULAR DEVELOPMENT IN ZEBRAFISH (DANIO RERIO)

AKADEMISK AVHANDLING
Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i CCK lecture hall R8:00

Thursday the 5th of June, 2014, at 9.00 am

Av **Staffan Nyström**

Huvudhandledare:
Prof. Lars Holmgren, Ph.D.
Karolinska Institutet
Dept. of Oncology-Pathology

Bihandledare:
Assoc. Prof. Per Uhlén, Ph. D.
Karolinska Institutet
Dept. of Medical Biochemistry and Biophysics

Arindam Majumdar, Ph. D.
Uppsala Universitet
Dept. of Immunology

Opponent
Prof. Stefan Schulte-Merker, Ph. D.
Hubrecht Institute
Utrecht, NL

Examination Board
Prof. Laszlo Szekely, M.D., Ph. D.
Karolinska Institutet
Dept of Microbiology, Tumor and Cell Biology

Assoc. Prof. Johan Kreuger, Ph. D.
Uppsala Universitet
Dept. of Medical Biochemistry and Microbiology

Monica Andersson Lendahl, Ph. D.
Karolinska Institutet
Dept .of Cell and Molecular Biology

Stockholm 2014

ABSTRACT

Formation of a functional vascular network is a prerequisite for physiological organ function in vertebrates. Pathological vascularization furthermore plays a role in several human diseases, such as diabetic retinopathy, cardiovascular disease and cancer. Understanding the mechanisms governing embryonic vascular development may give more insight into pathological vascularization. Vascular development has classically been subdivided into two subcategories: (1) vasculogenesis - the *de novo* creation of vessels from angioblast precursors and (2) angiogenesis - the creation of blood vessels from preexisting vessels. Although a large number of studies have been performed on vascular development, several biological mechanisms behind both angio- and vasculogenesis remain unresolved.

The aim of Paper I was to analyze the role of Angiomotin-like protein 1 (AmotL1) in developmental angiogenesis. We showed that AmotL1 is an important mediator of endothelial cell junction formation *in vivo*.

In Paper II, we show (*in vivo*, *ex vivo* and *in vitro)* that Shingosine-1-phosphate receptor 1 (S1PR1) is a critical negative regulator of angiogenic sprouting. S1PR1 loss of function causes endothelial hypersprouting both in mouse and zebrafish, whereas activation inhibits sprouting and enhances cellular adhesion. This article shows how a blood borne signal (S1P) induces vascular stabilization via S1PR1, junctional VE-cadherin and inhibition of VEGFR2 signaling.

In Paper III, individual cell tracking of precursors originating in the LPM confirmed that precursors migrate to the midline in two waves in accordance with cell identity. Arterial-venous specification appears to occur in the lateral plate mesoderm (LPM), whereupon sprinting (fast migrating) precursors migrate to dorsal positions at the midline – forming the dorsal aorta (DA). Although the bulk of asymmetrical divisions presumably occurs in the LPM, some hemangioblasts continue to divide asymmetrically at least once during axial vessel formation.