Eldad Tzahor

Tovi Harel
Shlomi Lazar
Libbat Finkel
Ariel Rinon

Molecular crosstalk between embryonic progenitor cells: Effects on cell fate and lineage determination

Department of Biological Regulation

Tel. 972 8 934 **3715** **Fax.** 972 8 934 **4116**
E-mail: eldad.tzahor@weizmann.ac.il
Web page: www.weizmann.ac.il/Biological_Regulation/NewFiles/tzahor.html

The progeny of the fertilized egg must diversify into hundreds of cell types that eventually give rise to an intricate series of muscles, bones and cartilage that form the embryo. In my laboratory, our main goal is to elucidate how embryonic cells determine what fates to adopt, and differentiate accordingly. Determination of cell fate requires a molecular "dialogue" between adjacent cell populations to ensure that the complex processes underlying embryonic development proceed accurately; yet, the details of these molecular interactions remain elusive. Using both an avian embryo model as well as a mouse genetic approach, we aim to unravel the molecular underpinnings of the crosstalk between naïve embryonic cells (Figure 1A). We focus on the following topics: the molecular differences between various embryonic progenitor cells such as skeletal muscle cells, cardiac myocytes and neural crest cells; the signals and molecules that govern decisions of cell fate; and the molecular and cellular mechanisms that enable signaling pathways such as Wnt to influence cellular outcomes in varying ways.

In the past, we focused on the signaling molecules that regulate heart formation during early vertebrate embryogenesis. More recently, we have been studying the signals that induce skeletal muscle formation in the head. These studies, performed in the chick embryo, have shown that the Wnt signaling pathway blocks the differentiation of mesoderm into skeletal and cardiac muscle (Tzahor et al., 2003; Tzahor and Lassar, 2001).

The heart is the first definitive organ to form during embryonic development (Olson and Schneider, 2003). Recent studies in vertebrates have clarified that there are two fields of cardiac progenitors, the primary and secondary heart fields. In contrast to our understanding of how cardiac formation arises from the anterior lateral mesoderm (the primary heart field), the nature of the signals and progenitor cells that contribute to the formation of the outflow (arterial) region of the heart (the secondary heart field) have not as yet been elucidated.

One of our objectives is to study secondary heart field formation in the chick embryo, utilizing both *in vitro* and *in vivo* experimental systems. First, we systematically analyze gene expression in the outflow tract region and surrounding tissues, to

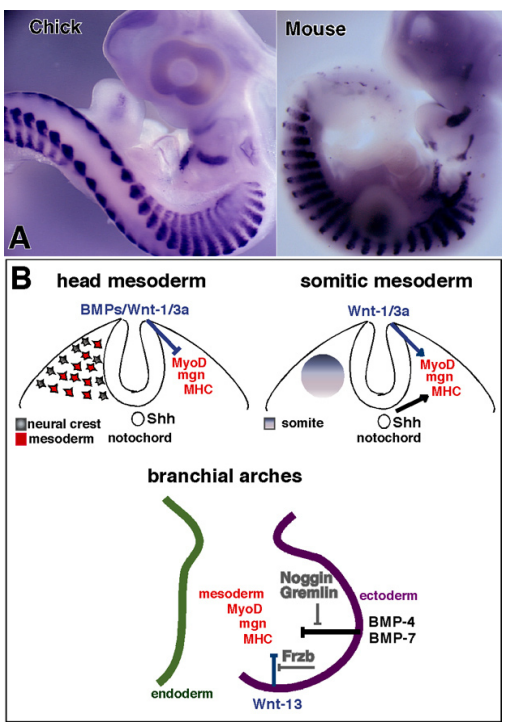

Fig. 1 *(A) In situ hybridization analysis of the skeletal muscle regulator MyoD in both chick and mouse embryos. (B) A schematic drawing of the signals that controls cranial muscle formation. In the head, the Wnt signaling pathway acts to repress skeletal muscle differentiation, while in the trunk, this signaling pathway stimulates myogenesis (Tzahor et al., 2003).*

identify molecular markers characteristic of this region. RT-PCR and fate-mapping techniques are used to identify cardiac progenitors in the outflow tract. Once we have identified molecular markers for the outflow tract progenitors, we will then focus on the signaling molecules that are believed to influence formation of the secondary heart field.

In order to determine the molecular differences between cardiac and skeletal muscle precursors, we further plan to establish a "combinatorial transcription factor profile" of these mesodermal progenitors that will enable us to predict the various cell fates.

During the past decade, the tissues and signaling molecules that induce the formation of skeletal muscle from somites have been intensively studied (Christ and Ordahl, 1995). Recently, it has been postulated that distinct regulatory cascades control myogenic differentiation in the head and the trunk. However, while the tissues and signaling molecules that induce skeletal myogenesis in the trunk (somites) have been identified, the source of the signals that trigger skeletal muscle formation in the head remain obscure. Though it was previously shown that Wnt molecules are required to stimulate myogenesis in the trunk, we recently demonstrated (Tzahor et al., 2003), that these same Wnt molecules block skeletal muscle formation in the head (Figure 1B).

We seek to resolve this apparent paradox by searching for candidate genes that are differentially expressed in the trunk and in the cranial paraxial mesoderm. Among our candidate genes are the transcription factors Paraxis and Pax-3 that promote myogenesis in the trunk. Another signaling mechanism that has been shown to influence trunk myogenesis is the Notch pathway. The effects of these genes on the Wnt signaling pathway will be determined, following ectopic expression of Paraxis, Pax-3 or members of the Notch signaling pathway in the cranial paraxial mesoderm of the chick embryo.

The crosstalk between cranial neural crest cells (Abzhanov et al., 2003) and skeletal muscle progenitors of mesodermal origin in the head (Noden, 1986), is an additional research interest in our lab. Cranial paraxial mesodermal cells provide most of the precursors that form the facial muscles, whereas cranial neural crest progenitors give rise to the majority of the skeletal elements within the head (among other cell types). Currently, we combine mouse genetic models with our avian experimental system to explore the signals and tissues governing the patterning and development of both muscles and skeletal elements in the embryonic head. Such studies involve the analysis of skeletal muscle markers in various mouse mutants that are defective in CNC migration and differentiation patterns.

Abnormalities in heart or craniofacial development constitute a major proportion of birth defects. Chronic heart failure and other muscle-related diseases caused by the loss or dysfunction of muscle cells are also serious health concerns. A deeper understanding of the mechanisms that govern normal developmental processes is essential, if we are to effectively diagnose, treat and even prevent these disorders. Moreover, various embryonic cell types such as those we are investigating are currently being tested for tissue repair in animal models, to enable the development of stem cell therapies for treatment of various degenerative diseases.

Selected Publications

Abzhanov, A., Tzahor, E., Lassar, A. B., and Tabin, C. J. (2003). Dissimilar regulation of cell differentiation in mesencephalic (cranial) and sacral (trunk) neural crest cells *in vitro*. Development 130, 4567-4579.

Christ, B., and Ordahl, C. P. (1995). Early stages of chick somite development. Anat Embryol (Berl) 191, 381-396.

Noden, D. M. (1986). Patterning of avian craniofacial muscles. Dev Biol 116, 347-356.

Olson, E. N., and Schneider, M. D. (2003). Sizing up the heart: development redux in disease. Genes Dev 17, 1937-1956.

Tzahor, E., Kempf, H., Mootoosamy, R. C., Poon, A. C., Abzhanov, A., Tabin, C. J., Dietrich, S., and Lassar, A. B. (2003). Antagonists of Wnt and BMP signaling promote the formation of vertebrate head muscle. Genes Dev 17, 3087-3099.

Tzahor, E., and Lassar, A. B. (2001). Wnt signals from the neural tube block ectopic cardiogenesis. Genes Dev 15, 255-260.

Acknowledgements:

Supported by grant from the Estelle Funk Foundation for Biomedical Research