

DEVELOPMENT AT A GLANCE

The lateral plate mesoderm

Karin D. Prummel^{1,2,*}, Susan Nieuwenhuize^{1,2,*} and Christian Mosimann^{1,2,‡}

ABSTRACT

The lateral plate mesoderm (LPM) forms the progenitor cells that constitute the heart and cardiovascular system, blood, kidneys, smooth muscle lineage and limb skeleton in the developing vertebrate embryo. Despite this central role in development and evolution, the LPM remains challenging to study and to delineate, owing to its lineage complexity and lack of a concise genetic definition. Here, we outline the processes that govern LPM specification, organization, its cell fates and the inferred evolutionary trajectories of LPM-derived tissues.

¹University of Colorado School of Medicine, Anschutz Medical Campus, Department of Pediatrics, Section of Developmental Biology, 12801 E 17th Avenue, Aurora, CO 80045, USA. ²Department of Molecular Life Sciences, University of Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland. *These authors contributed equally to this work

‡Author for correspondence (christian.mosimann@cuanchutz.edu)

id K.D.P., 0000-0001-6077-6407; C.M., 0000-0002-0749-2576

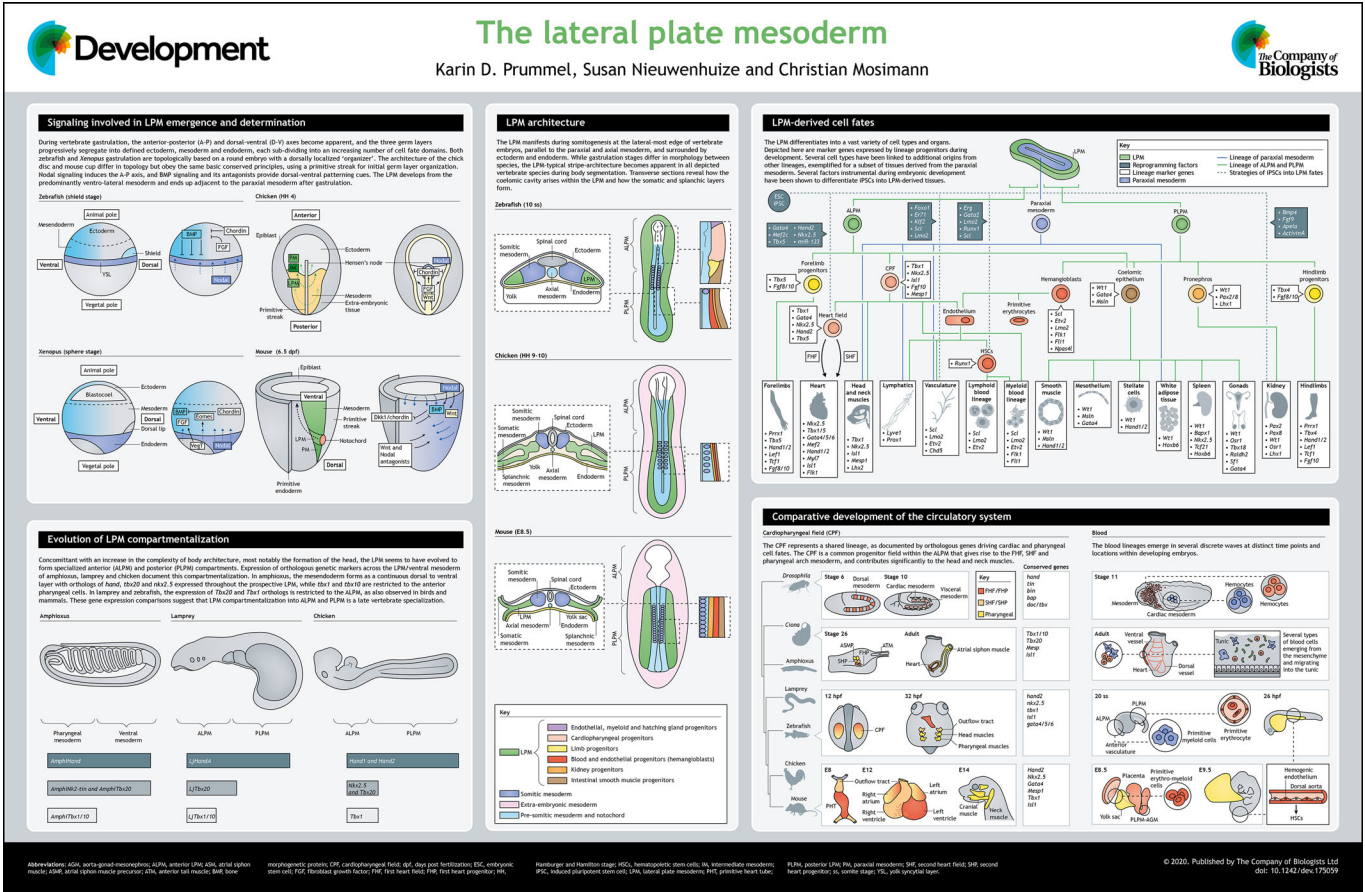
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution and reproduction in any medium provided that the original work is properly attributed.

Finally, we discuss the development of seemingly disparate organ systems that share a common LPM origin.

KEY WORDS: Lateral plate mesoderm, Cardiovascular system, Cell fate, Development, Evolution, Gene regulation

Introduction

During gastrulation in vertebrates, the mesoderm forms axial, paraxial and lateral domains that harbor precursor cells for distinct organ systems. The lateral plate mesoderm (LPM) condenses into bilateral sheets of cells at the lateral edge of the developing vertebrate embryo, classically referred to as the lateral plate. While clearly discernible after gastrulation, the dynamic nature of the LPM is challenging to visualize and track during earlier development. Moreover, fate maps derived from various model organisms provide seemingly conflicting data, in part due to differences in lineage-tracing techniques and readouts (Lane and Smith, 1999), as well as uneven nomenclature to describe the LPM as ventral mesoderm, leading-edge mesoderm, visceral mesoderm, ventrolateral mesoderm or lateral mesoderm.



The LPM also develops into a bewildering array of downstream cell fates. Lineage maps derived from transplantation and cell labeling experiments have linked the LPM to the origin of cardiovascular, hematopoietic, kidney, smooth muscle, craniofacial (head/neck) muscle, mesothelial and limb connective tissue progenitors (Lane and Smith, 1999; Selleck and Stern, 1991; Warga and Nüsslein-Volhard, 1999). While these cell fates contribute essential structures to the adult vertebrate body, their earlier developmental connection is not immediately apparent from the final functional organs.

Recent breakthroughs in genetic lineage tracing, reporter assays, live imaging and single-cell RNA-sequencing continue to uncover new details of the LPM and its derivatives, detailing its substantial contribution to the evolution of the vertebrate body plan. Here, we outline how the LPM emerges within the embryo and summarize the latest insights into how the LPM generates its diverse interconnected cell fates.

LPM specification and organization

Although the characteristic stripe architecture of the LPM becomes apparent during the segmentation stages, the LPM originates during gastrulation together with the axial and paraxial mesoderm between ectoderm and endoderm (Davidson and Zon, 2004; Lawson et al., 1991; Rosenquist, 1970; Tam and Beddington, 1987). Prominent signaling cascades influencing early LPM formation include the bone morphogenetic protein (BMP) and Nodal pathways that coordinate the patterning of anterior-posterior (A-P) and dorso-ventral axes (Arnold and Robertson, 2009; Hill, 2018; Martinez-Arias and Steventon, 2018). High levels of BMP signaling in the ventral domain of the embryo chiefly specifies the mesoderm territory that forms the LPM in all vertebrates (Ferretti and Hadjantonakis, 2019; Nishimatsu and Thomsen, 1998). Nonetheless, coinciding with Nodal activity, LPM-assigned cell fates also emerge along the marginal zone of *Xenopus* and zebrafish embryos that contribute the cells at the circumference of the forming embryo (Lane and Smith, 1999; Prummel et al., 2019; Schier and Talbot, 2005; Warga and Nüsslein-Volhard, 1999). Prominently shown in zebrafish embryos, an increasing range or activity of BMP signaling in ventralized mutants results in larger domains of LPM-expressed genes for erythrocyte, pronephros and vascular lineages (Hammerschmidt et al., 1996; Mullins et al., 1996; Sidi et al., 2003). Conversely, dorsalizing mutations that affect BMP ligands, BMP regulators or the loss of ventro-posterior transcription factors, such as *Cdx4*, cause the loss of posterior LPM structures (Davidson et al., 2003; Hild et al., 1999; Kishimoto et al., 1997; Mullins et al., 1996; Nguyen et al., 1998; Ro and Dawid, 2009; Schier and Talbot, 2001). Nonetheless, BMP and Nodal are not instructive to trigger LPM formation per se (Xu et al., 2014), hinting at a more-complex signaling interplay leading to LPM induction. Fibroblast growth factor (FGF), canonical Wnt and retinoic acid (RA) signaling also influence the emerging LPM domains (Furthauer et al., 2004; Holley and Ferguson, 1997; Rossant and Tam, 2009; Schier and Talbot, 2005), including the specification of the heart field (Deimling and Drysdale, 2011; Gessert et al., 2010; Itoh et al., 2016; Lengerke et al., 2011; Wang et al., 2019a) or of kidney and blood progenitors (Duester, 2008; Lasagni et al., 2015; Naylor et al., 2016; Niederreither and Dollé, 2008).

Following gastrulation, the LPM takes on its characteristic architecture: bilateral stripes ('plates') of LPM progenitors form laterally in the embryo and subsequently partition along the A-P and medial-to-lateral axes into dedicated cell fate domains (Gurdon, 1995; Kessler and Melton, 1994; McDole et al., 2018; Prummel et al., 2019). Convergent extension of the embryo axis involving planar cell polarity (PCP) signaling also affects the final position of

the LPM adjacent to the forming somites (paraxial mesoderm) and in relation to the ectoderm and the endoderm (Erter et al., 2001; Heisenberg and Solnica-Krezel, 2008; Saykali et al., 2019); however, LPM-specific mechanisms of cell arrangement have yet to be described in detail. In amniotes, the post-gastrulation LPM splits into a dorsal somatic layer and a ventral splanchnopleuric layer. During body segmentation, the LPM further separates into distinct anterior (ALPM) and posterior (PLPM) domains, while the bilateral cell fields gradually differentiate into descendant cell fates with distinct gene expression patterns.

Lineage markers in the LPM

The diverse temporal, spatial and combinatorial activities of the signaling pathways involved in LPM specification make their exact influence challenging to dissect. Furthermore, the lack of a concise genetic or molecular definition of the LPM has limited its description. The bulk of our understanding of LPM fates derives from the regionalized, post-gastrulation expression patterns of individual transcription factor genes. Most prominently, the expression of (and transgenes based on) *Foxf1*, *Bmp4*, *Hoxb6*, *Hand1*, *Hand2*, *Gata4* and *Prrx1* have been harnessed in mouse and chick embryos to track various aspects of LPM patterning (Becker et al., 1996; Firulli et al., 1998; Martin and Olson, 2000; Ormestad et al., 2004; Rojas et al., 2005). However, these gene expression domains are either broader than, or delineate only parts of, the entire LPM. While expression of the T-box factor brachyury is commonly used as reference for mesodermal lineages in mammals (Huber et al., 2004; Loh et al., 2016; Technau and Scholz, 2003), expression and activity of brachyury is dispensable for LPM formation in a variety of animal models, mainly contributing to tail formation and its ancestral role in notochord development (Clements et al., 1996; Gurdon, 1995; Halpern et al., 1993; José-Edwards et al., 2015; Schulte-Merker et al., 1994; Wilkinson et al., 1990).

Conversely, the +2.0 kb enhancer in the zebrafish *draculin* (*drl*) locus (+2.0*drl*) is specifically active in LPM-primed mesendoderm during zebrafish development by responding to the mesendoderm regulators eomesodermin A, FoxH1 and Mix11, together with BMP- and Nodal-controlled Smads (Prummel et al., 2019). Although *drl* seems to be a zebrafish-specific zinc-finger gene, +2.0*drl* enhancer-based reporter transgenes also label the emerging LPM in chick, axolotl and lamprey, and in the nonvertebrate chordates *Ciona* and amphioxus, suggesting that LPM emergence is instructed by a conserved molecular program (Prummel et al., 2019). It remains to be determined whether LPM formation is universally controlled by eomesodermin A, FoxH1 and Mix11 orthologs across chordates, which mechanisms induce expression of the genes that pattern the LPM post-gastrulation, and whether any of these conserved genes are LPM specific.

Evolution of the LPM

The seemingly complex developmental relationship of the final organs of the LPM becomes more accessible in the light of their evolutionary connections. In amphioxus, the mesendoderm forms as a continuous dorsal to ventral layer, and a LPM-resembling domain can be recognized in between the dorsal somites and the ventral endoderm (Bailey and Miller, 1921; Bertrand et al., 2011b; Holland, 2018; Onimaru et al., 2011). This seemingly simple setup could hint at the original mesendoderm architecture in the last common chordate ancestor (Kozmik et al., 2001), which is set up by the conserved LPM-instructing program (Prummel et al., 2019). Amphioxus orthologs of genes expressed in the LPM in vertebrates,

such as *Foxf1*, Hand genes, *Tbx20* and *Nkx2.5*, are active throughout the whole ventrolaterally located mesoderm, indicating that the LPM in amphioxus does not segregate into ALPM and PLPM, whereas ALPM and PLPM are clear features in lampreys (Onimaru et al., 2011; Tanaka, 2016a). These observations suggest that LPM compartmentalization along the embryonic axes is a vertebrate adaptation. Curiously, in *Drosophila*, visceral mesoderm formation depends on Bap and the *Foxf1* ortholog Bin, whereas heart formation relies on GATA factors together with Hand and Tin, the orthologs of the vertebrate heart regulators Hand1, Hand2 and *Nkx2.5* (Azpiazu and Frasch, 1993; Bodmer, 1993; Zaffran et al., 2001). This conservation of LPM-associated gene expression hints at a deeply rooted molecular LPM program dating back to early bilaterians.

From stripes to organs: development of LPM-derived structures

Cardiovascular system

The formation of the circulatory system provides an illustrative example for LPM-derived organ development. During early somitogenesis, the heart forming in the ALPM and the endothelial and hematopoietic lineages forming in both ALPM and PLPM become detectable by both shared and specialized gene expression patterns. In the ALPM, endocardial and myocardial progenitor populations become detectable adjacent to cranial endothelial progenitors by expression of *Nkx2.5*, *Etv2*, *Lmo2* and *Scf/Tal1*, whereas the PLPM harbors the trunk endothelial and primitive erythrocyte progenitors also expressing *Etv2*, *Lmo2*, *Scf/Tal1* and *Gata1*, but not *Nkx2.5* (Bussmann et al., 2007; Davidson and Zon, 2004; Loh et al., 2016; Scialdone et al., 2016; Tremblay et al., 2018; Vincent and Buckingham, 2010).

Heart

In the emerging mouse mesendoderm, *Mesp1* expression downstream of *Eomes* demarcates the earliest cardiac progenitors (Costello et al., 2011; Kitajima et al., 2000; Saga et al., 2000) that upregulate *Gata4*, *Nkx2.5* and *Hand2* (Bondue et al., 2008; Kelly et al., 2014). This initial requirement for *Mesp* factors holds true for cardiac progenitor formation in *Ciona* (Satou et al., 2004). In contrast, *Mesp1* orthologs in *Drosophila* and in zebrafish seem dispensable for cardiogenesis (Deshwar et al., 2016; Moore et al., 2000; Yabe et al., 2016). These peculiar findings suggest a degree of flexibility in cardiac progenitor initiation, which has yet to be further characterized. Curiously, akin to *Eomes*, *Smarcd3* (*BAF60c*) expression in the mouse precedes *Mesp1* upregulation and is essential for heart formation (Lickert et al., 2004). Regulatory elements from the mouse *Smarcd3* locus actively drive reporter expression in the zebrafish ALPM (Yuan et al., 2018), while zebrafish *Smarcd3* function has been linked to paraxial muscle differentiation through interaction with brachyury/*Ntl* (Ochi et al., 2008). These data might indicate that *Smarcd3* orthologs act as co-factors to T-box factors such as *Eomes* or other yet-to-be-determined transcription factors. How universal this interplay is for cardiac progenitor formation or within the LPM in general warrants further investigation.

The subsequent migration of cardiac progenitors to the midline and the formation of the linear heart tube depends on several factors, including platelet-derived growth factor (PDGF) and Robo-Slit signaling providing extrinsic and intrinsic migration cues (Bloomekatz et al., 2017; Fish et al., 2011; Qian et al., 2005; Zhao and Mommersteeg, 2018). In zebrafish (*sox32/cas*) and mouse (*Sox17*) endoderm mutants, multiple heart tubes form within the

bilateral ALPM, indicating that cardiac progenitors have an intrinsic propensity to form a rudimentary heart (Alexander et al., 1999; Dickmeis et al., 2001; Kanai-Azuma et al., 2002; Kikuchi et al., 2001; Lickert et al., 2002). As a universal trait, the developing heart incorporates cells from two ALPM-associated progenitor fields, the so-called first versus second heart fields (FHF and SHF, respectively) (Abu-Issa and Kirby, 2008; Meilhac et al., 2004; Stolfi et al., 2010; Tirosh-Finkel et al., 2006). While the FHF descendants set up the initial heart tube with atrium and ventricle for systemic circulation, the addition of SHF progenitors extends the heart on both poles (de Pater et al., 2009; Felker et al., 2018; Grimes and Kirby, 2009; Hami et al., 2011; Lasic and Scott, 2011; Zhou et al., 2011). As a fundamental building block of all vertebrate hearts, the interplay of FHF and SHF influences cardiac conductivity and facilitates sequential contraction (Mosimann et al., 2015); however, why two progenitor pools are required for heart formation remains uncertain. SHF descendants contribute to the increasingly complex compartmentalization in the heart of terrestrial vertebrates, culminating in a right ventricle that is dedicated to pulmonary circulation (Kelly, 2012; Koshiba-Takeuchi et al., 2009; Swedlund and Lescroart, 2019; Vincent and Buckingham, 2010).

Endothelium

In vertebrates, blood and endothelium form concomitantly with the heart. While expressing an overlapping set of genes, endothelial and hematopoietic progenitors in ALPM and PLPM develop seemingly disconnected from each other but temporally in sync. Endothelium and blood arise, at least partially, from bipotent hemangioblasts, as well as from fate-restricted angioblasts and hematopoietic progenitors (Choi et al., 1998; Murray, 1932; Sabin, 1917; Vogeli et al., 2006). The zebrafish *npas4l/cloche* mutant is virtually devoid of blood and endothelium (with exception of few surviving angioblasts), as evident by the broad lack of *scl*, *lmo2* and *etv2* expression (Marass et al., 2019; Reischauer et al., 2016; Stainier et al., 1995). While a clear functional *Npas4l* ortholog is currently unknown outside of fishes, these findings place *Npas4l* at the top of the developmental hierarchy controlling the formation of endothelial/hematopoietic progenitors. Among the earliest conserved endothelial/hematopoietic transcription factors is the ETS factor *Etv2* that, together with *Scf/Tal1*, governs endothelial/hematopoietic and hemangioblast formation in mouse, chick and zebrafish (Craig and Sumanas, 2016; Oh et al., 2015). With over a dozen family members expressed at different developmental time points downstream of *Etv2*, ETS factors play a continued role in endothelial differentiation towards a functional vascular network with veins and arteries. For example, the expression of *Fli1*, *Erg* and *Ets1* provides powerful endothelial markers in various model systems (Craig and Sumanas, 2016). In addition to transcription factors, vascular-endothelial growth factor (VEGF) signaling is guiding endothelial differentiation (Simons et al., 2016). Reflecting this role, VEGF receptor genes such as *Vegfr2* and *Flk1* and their paralogs are among the earliest genes contributing to hemangioblast formation (Chung et al., 2002; Ema et al., 2003; Loh et al., 2016; Thompson et al., 1998). Nonetheless, despite a wealth of insights into the mechanisms of vascular system formation, how *Etv2* and its related factors (and the even more upstream-acting *Npas4l* in zebrafish) are selectively activated within the cardiovascular-primed LPM remains unknown.

Blood

Blood emerges in several discrete waves of hematopoiesis at distinct time points and locations within the embryo, and its development is

closely intertwined with endothelium formation (Davidson and Zon, 2004; Orkin and Zon, 2008). In teleosts and amphibians, a specialized primitive wave of myeloid progenitors emerges in the ALPM that might be an ancestral trait (Davidson and Zon, 2004; Herbomel et al., 1999; Ohinata et al., 1990). The first primitive wave of PLPM-derived blood consists of transient, embryonic erythrocytes that stem from *Scf/Tal1*-, *Lmo2*- and *Gata1*-expressing progenitors (Davidson and Zon, 2004; Mead et al., 2001; Orkin and Zon, 2008). An intermediate wave of erythro-myeloid progenitors form encased within the developing vessels in zebrafish (Bertrand et al., 2007), and several yolk sack and placenta cell populations have been attributed with intermittent hematopoietic potential in mice (Orkin and Zon, 2008; Palis et al., 1999; Zhang et al., 2018). Finally, *Runx1*-expressing definitive hematopoietic stem cell (HSC) progenitors bud off from the ventral wall of the dorsal aorta (so-called hemogenic endothelium) through an endothelial-to-hematopoietic transition in zebrafish (Bertrand et al., 2010; Kissa and Herbomel, 2010) and in mice (Boisset et al., 2010; Zovein et al., 2008), while a somite-based contribution of aortic wall and HSCs has also been reported in zebrafish (Qiu et al., 2016). In addition to hemangioblasts, the repeated interdependence of hematopoietic waves on endothelial cells possibly hints at a joint evolutionary origin (Pascual-Anaya et al., 2013). Such scenarios have received further support from the ontogeny of macrophage lineages (Sanz-Morejón et al., 2019; Shigeta et al., 2019) and from observations made in a variety of invertebrates (Cloney, 1982; Cloney and Grimm, 1970; Hartenstein and Mandal, 2006; Monahan-Earley et al., 2013; Munoz-Chapuli, 2011; Munoz-Chapuli et al., 2005; Scimone et al., 2018; Shida et al., 2003). Together with the joint expression of key genes in endothelial and hematopoietic progenitors, a common origin of all cardiovascular lineages within the LPM provides the developmental context to tie these interdependent cell fates together.

Lymphatics

Related to endothelium and blood, the origin of lymphatic vessels seems more complex. While trunk and cardiac lymphatics have been shown to originate from LPM-derived lineages, in particular from veins in mouse and zebrafish (Lioux et al., 2020; Maruyama et al., 2019; Nicenboim et al., 2015; Semo et al., 2016), recent work in the mouse indicates that *Pax3:Cre*-expressing paraxial mesoderm is a major source of trunk and cardiac lymphatic vessels (Stone and Stainier, 2019). Similarly, *Pax3:Cre*-expressing cells as paraxial mesoderm contribute to at least parts of the endothelium in the mouse forelimb (He et al., 2003; Huang et al., 2003; Hutcheson et al., 2009; Mayeuf-Louchart et al., 2014; Pardanaud et al., 1996; Pouget et al., 2006; Yvernogeu et al., 2019). Whether *Pax3*-based lineage tracing in these scenarios is strictly paraxial mesoderm specific (Engleka et al., 2005), and whether a non-LPM origin for lymphatics and individual endothelial lineages is a universal trait across vertebrates, remain to be elucidated.

Craniofacial muscle lineages

In line with the surprising lineage diversity of the LPM, detailed lineage tracing studies in the mouse have revealed that the ALPM progenitors that form SHF also contribute to neck and craniofacial muscles alongside paraxial mesoderm and neural crest contributions to their connective tissue (Bothe and Dietrich, 2006; Lescroart et al., 2010; Meilhac et al., 2004; Nathan et al., 2008; Tirosh-Finkel et al., 2006). Although the nomenclature of mesodermal domains in the developing head suffers from disparities across the literature, at least part of the cardiopharyngeal field (CPF) designates an ALPM-centered progenitor pool that, in addition to forming the heart, also

contributes to craniofacial and neck muscles (Diogo et al., 2015). Comparative anatomical and genetic studies across chordates have demonstrated joint cardiac and branchiomeric muscle formation, together with overlapping expression patterns in the anterior mesoderm of key regulators, including *Nkx2.5*, *Isl1* and *Tbx1* (Diogo et al., 2015; Felker et al., 2018; Gopalakrishnan et al., 2015; Heude et al., 2018; Lescroart et al., 2015; Michailovici et al., 2015; Paffett-Lugassy et al., 2017; Stolfi et al., 2010; Wang et al., 2019b). The evolutionary timeline of additional cranial muscle groups that are distinct from trunk muscle trajectories coincides with the adaption of multi-chambered hearts (Comai et al., 2019; Diogo et al., 2015; Heude et al., 2018; Theis et al., 2010). The first traces of a CPF are even detectable in cephalochordates, by the expression of several T-box transcription factors, including *Tbx110* and *Tbx20* in the ventrolaterally located mesoderm of amphioxus (Holland et al., 2008; Onimaru et al., 2011). More insights into the CPF promises to reveal new insights into vertebrate head and neck evolution, and how seemingly disparate mesodermal populations in the head, such as the cephalic or cranial paraxial mesoderm, are interconnected (Bertrand et al., 2011a).

Kidney

In amniotes, the kidney develops in a distinct temporal sequence via three different stages: pronephros, mesonephros and metanephros (adult kidney). In teleosts and amphibians, the mesonephros functions as the adult kidney. The kidney primordia emerge as bilateral fields expressing *Wt1*, *Lhx1*, *Pax2* and *Pax8* in the PLPM during early somitogenesis (Heller and Brändli, 1999; Mudumana et al., 2008; Nelson et al., 2014; Serluca and Fishman, 2001; Tena et al., 2007; Terashima et al., 2014). During differentiation, besides the rostrally positioned glomerulus, the nephric tubule epithelium is specified along the A-P axis in several segments (McMahon, 2016; Naylor et al., 2016; Serluca and Fishman, 2001). Curiously, the mediolateral position of kidney progenitors relative to the paraxial mesoderm is distinct between fish and amniotes: in amniotes, kidney progenitors form directly adjacent to the paraxial somites as the most medially located LPM stripe (also referred to as intermediate mesoderm). Conversely, in fish, kidney progenitors form lateral to the endothelium-hematopoietic progenitors in the LPM, clearly embedding kidney origins in the context of LPM formation.

Limb skeleton and connective tissue

A powerful example of the evolutionary adaptability of the LPM is the connective tissue and skeleton of the paired appendages, which has been repeatedly reviewed (Hiscock et al., 2017; Petit et al., 2017; Zeller et al., 2009). Fore- and hindlimb buds emerge from the somatic LPM at specific positions along the A-P axis. RA signaling and Hox genes are involved in properly positioning the progenitor fields (Moreau et al., 2019). In close interplay with the ectoderm secreting FGF ligands (i.e. Fgf8), LPM-expressed *Tbx5* and *Tbx4*, among other factors, contribute to initiating limb formation in the ALPM and PLPM, respectively (Bruneau et al., 2001; Koshiba-Takeuchi et al., 2009; Minguillon et al., 2012; Nishimoto and Logan, 2016; Rallis et al., 2003). The limb skeleton and connective tissue have been predominantly fate-mapped to an LPM origin, while limb musculature is contributed by paraxial/somitic mesoderm (Nishimoto and Logan, 2016; Tanaka, 2016b). Curiously, *Tbx5* is required for both forelimb and heart development, and its expression encompasses the forelimb and heart field progenitors that emerge adjacently within the LPM (Bickley and Logan, 2014; Rallis et al., 2003). Whether *Tbx5* expression is driven by a joint program in both progenitors or if each progenitor field responds to separate inputs remains uncertain (Minguillon et al., 2012).

Coelomic epithelium and associated structures

The epithelial lining of the coelomic cavities, the so-called mesothelium, is also LPM derived. The mesothelium covers the body cavities (parietal layers) and the organs within (visceral layers), which have been linked to somatic and splanchnic LPM origins, respectively (Mutsaers and Wilkosz, 2007). In mice, *Wt1* and *Gata4*, as well as *Msln* expression, provide the earliest (E9.0) genetic and lineage markers for the visceral coelomic epithelium, which is detectable lateral to the urogenital progenitors (Ariza et al., 2016; Armstrong et al., 1993; Cano et al., 2013; Chau et al., 2014; Delgado et al., 2014; Que et al., 2008; Rinkevich et al., 2012). The coelomic epithelium is increasingly recognized as the source of a wide range of cell types (Ariza et al., 2016). In particular, smooth muscles surrounding the gastrointestinal and respiratory tract, and the vascular system, as well as additional fibroblast-like lineages, have been tracked in mice (Ariza et al., 2018; Asahina et al., 2011; Cano et al., 2013; Carmona et al., 2013; Chau et al., 2011; Ijpenberg et al., 2007; Pérez-Pomares et al., 2004; Que et al., 2008; Rinkevich et al., 2012; Sinha and Santoro, 2018; Wilm et al., 2005) and chick (Winters et al., 2012). Genetic lineage tracing in zebrafish further supports a conserved LPM origin for the visceral intestinal smooth muscles (Gays et al., 2017). Nonetheless, which smooth muscle lineages (or if all) feature a LPM origin remains unresolved.

The spleen develops from condensations of the *Wt1*-positive coelomic epithelium in mice and humans (Burn et al., 2008; Endo et al., 2015; Hecksher-Sorensen et al., 2004), and visceral white adipose tissue (WAT) depots in mice have been suggested to derive from LPM, as indicated by genetic lineage tracing with *Wt1:creERT2* and *HoxB6:creERT2* (Chau et al., 2014; Krueger et al., 2014; Sanchez-Gurmaches et al., 2015; Sebo et al., 2018; Zhou et al., 2008). Finally, gonadal structures have been assigned to have a common origin in the adrenogonadal primordium, which in mouse and rat arises from a thickening of the coelomic epithelium (Hatano et al., 1996; Ikeda et al., 1994). In these models, *Gata4*, *Tbx18*, *Tcf21* and *Wt1* are among the earliest activated genes expressed throughout the genital ridge, recapitulating a gene expression signature observed in other regions of the coelomic epithelium (Airik et al., 2006; Bohnenpoll et al., 2013; Cui et al., 2004; Häfner et al., 2015; Hammes et al., 2001; Hu et al., 2013; Karl and Capel, 1998; Liu et al., 2015). Lineage tracing in mouse with *Cre* driver lines including *Wt1:creERT2* (Liu et al., 2015) and *Tbx18:creERT2* (Bohnenpoll et al., 2013) have shown that coelomic epithelium-derived precursor cells give rise to several cell types within the primitive gonads, such as the Sertoli cells in the testis and the follicular cells in the ovary. During gonadal differentiation, the primordial germ cells (PGCs) arrive at the genital ridge and are retained within the forming gonads (Barton et al., 2016). Despite these fascinating links to LPM origins, how the initial mesothelium-associated lineages arise within the LPM remains to be charted.

Concluding remarks

The LPM connects diverse organ systems in the vertebrate body plan. How individual LPM-derived lineages emerge during development is of major interest for controlled stem cell reprogramming. Two principal approaches promise the generation of therapeutically relevant, human LPM derivatives. First, direct reprogramming into specified LPM fates has been achieved with defined combinations of developmental transcription factors in iPSCs, ESCs and somatic cells, as exemplified with the programming of fibroblasts into beating cardiomyocytes using *GATA4*, *HAND2*, *MEF2C* and *TBX5* (Sadahiro et al., 2015; Song et al., 2012; Takasato et al., 2014). Second, the stepwise recapitulation of developmental signaling towards a LPM

gene expression signature can be achieved in ES cells, as demonstrated with timed exposure to TGF β and BMP (Loh et al., 2016; Mendjan et al., 2014). Nonetheless, characterizing and categorizing LPM-derived cells through reprogramming still relies on limited marker signatures (Loh et al., 2016; Mendjan et al., 2014; Orkin and Zon, 2008; Takasato and Little, 2015). Nonetheless, LPM-based organoid models promise to provide a potent source of clinically relevant cell types and new platforms to probe the basic mechanisms of LPM patterning (Holloway et al., 2019). Together, these new and exciting models enable elucidation of the mechanisms driving LPM emergence from embryonic mesendoderm. Easily rivaling the cell fate potential of the neural crest (Mayor and Theveneau, 2013), we are slowly unraveling the cellular properties that render the LPM capable of forming its diverse descendant cell fates and organ systems.

Acknowledgements

We thank Dr Christopher Hess, Dr Lionel Christiaen, Dr Janine M. Ziermann and Dr Patrick Tschopp for valuable input on individual topics, and the members of the Mosimann lab for critical comments on the manuscript. We sincerely apologize to all our colleagues whose contributions to LPM biology we were unable to cite due to the complexity and breadth of the covered topics.

Competing interests

The authors declare no competing or financial interests.

Funding

The authors' research is supported by Kanton Zürich, by a ZUNIV FAN project grant, by the Blutspende SRK Zürich, by the Department of Pediatrics, University of Colorado School of Medicine and by the Children's Hospital Colorado Foundation. Deposited in PMC for immediate release.

Development at a Glance

A high-resolution version of the poster is available for downloading in the online version of this article at <http://dev.biologists.org/content/147/12/dev175059/F1.poster.jpg>

References

- Abu-Issa, R. and Kirby, M. L. (2008). Patterning of the heart field in the chick. *Dev. Biol.* **319**, 223-233. doi:10.1016/j.ydbio.2008.04.014
- Airik, R., Bussen, M., Singh, M. K., Petry, M. and Kispert, A. (2006). *Tbx18* regulates the development of the ureteral mesenchyme. *J. Clin. Invest.* **116**, 663-674. doi:10.1172/JCI26027
- Alexander, J., Rothenberg, M., Henry, G. L. and Stainier, D. Y. (1999). Casanova plays an early and essential role in endoderm formation in zebrafish. *Dev. Biol.* **215**, 343-357. doi:10.1006/dbio.1999.9441
- Ariza, L., Carmona, R., Cañete, A., Cano, E. and Muñoz-Chápuli, R. (2016). Coelomic epithelium-derived cells in visceral morphogenesis. *Dev. Dyn.* **245**, 307-322. doi:10.1002/dvdy.24373
- Ariza, L., Cañete, A., Rojas, A., Muñoz-Chápuli, R. and Carmona, R. (2018). Role of the Wilms' tumor suppressor gene *Wt1* in pancreatic development. *Dev. Dyn.* **247**, 924-933. doi:10.1002/dvdy.24636
- Armstrong, J. F., Pritchard-Jones, K., Bickmore, W. A., Hastie, N. D. and Bard, J. B. L. (1993). The expression of the Wilms' tumour gene, *WT1*, in the developing mammalian embryo. *Mech. Dev.* **40**, 85-97. doi:10.1016/0925-4773(93)90090-K
- Arnold, S. J. and Robertson, E. J. (2009). Making a commitment: cell lineage allocation and axis patterning in the early mouse embryo. *Nat. Rev. Mol. Cell Biol.* **10**, 91-103. doi:10.1038/nrm2618
- Asahina, K., Zhou, B., Pu, W. T. and Tsukamoto, H. (2011). Septum transversum-derived mesothelium gives rise to hepatic stellate cells and perivascular mesenchymal cells in developing mouse liver. *Hepatology* **53**, 983-995. doi:10.1002/hep.24119
- Azpiazua, N. and Frasch, M. (1993). *tinman* and *bagpipe*: two homeo box genes that determine cell fates in the dorsal mesoderm of *Drosophila*. *Genes Dev.* **7**, 1325-1340. doi:10.1101/gad.7.7b.1325
- Bailey, F. and Miller, A. (1921). *Text-Book of Embryology*, 4th edn. New York: William Wood and Co.
- Barton, L. J., LeBlanc, M. G. and Lehmann, R. (2016). Finding their way: themes in germ cell migration. *Curr. Opin. Cell Biol.* **42**, 128-137. doi:10.1016/j.cob.2016.07.007
- Becker, D., Eid, R. and Schughart, K. (1996). The limb/LPM enhancer of the murine *Hoxb6* gene: reporter gene analysis in transgenic embryos and studies of

- DNA-protein interactions. *Pharm. Acta Helv.* **71**, 29-35. doi:10.1016/0031-6865(95)00049-6
- Bertrand, J. Y., Kim, A. D., Violette, E. P., Stachura, D. L., Cisson, J. L. and Traver, D.** (2007). Definitive hematopoiesis initiates through a committed erythromyeloid progenitor in the zebrafish embryo. *Development* **134**, 4147-4156. doi:10.1242/dev.012385
- Bertrand, J. Y., Chi, N. C., Santoso, B., Teng, S., Stainier, D. Y. and Traver, D.** (2010). Haematopoietic stem cells derive directly from aortic endothelium during development. *Nature* **464**, 108-111. doi:10.1038/nature08738
- Bertrand, S., Camasses, A., Somorjai, I., Belgacem, M. R., Chabrol, O., Escande, M.-L., Pontarotti, P. and Escriva, H.** (2011a). Amphioxus FGF signaling predicts the acquisition of vertebrate morphological traits. *Proc. Natl. Acad. Sci. USA* **108**, 9160-9165. doi:10.1073/pnas.1014235108
- Bertrand, S., Escriva, H., Williams, N. A., Holland, N. D. and Holland, L. Z.** (2011b). Evolutionary crossroads in developmental biology: amphioxus. *Development* **138**, 4819-4830. doi:10.1242/dev.066720
- Bickley, S. R. B. and Logan, M. P. O.** (2014). Regulatory modulation of the T-box gene *Tbx5* links development, evolution, and adaptation of the sternum. *Proc. Natl. Acad. Sci. USA* **111**, 17917-17922. doi:10.1073/pnas.1409913111
- Bloomekatz, J., Singh, R., Prall, O. W., Dunn, A. C., Vaughan, M., Loo, C.-S., Harvey, R. P. and Yelon, D.** (2017). Platelet-derived growth factor (PDGF) signaling directs cardiomyocyte movement toward the midline during heart tube assembly. *Elife* **6**, e21172. doi:10.7554/eLife.21172
- Bodmer, R.** (1993). The gene tinman is required for specification of the heart and visceral muscles in *Drosophila*. *Development* **118**, 719-729.
- Bohnenpoll, T., Bettenhausen, E., Weiss, A.-C., Foik, A. B., Trowe, M.-O., Blank, P., Airik, R. and Kispert, A.** (2013). *Tbx18* expression demarcates multipotent precursor populations in the developing urogenital system but is exclusively required within the ureteric mesenchymal lineage to suppress a renal stromal fate. *Dev. Biol.* **380**, 25-36. doi:10.1016/j.ydbio.2013.04.036
- Boisset, J.-C., van Cappellen, W., Andrieu-Soler, C., Galjart, N., Dzierzak, E. and Robin, C.** (2010). In vivo imaging of haematopoietic cells emerging from the mouse aortic endothelium. *Nature* **464**, 116-120. doi:10.1038/nature08764
- Bondue, A., Lapouge, G., Paulissen, C., Semeraro, C., Iacovino, M., Kyba, M. and Blanpain, C.** (2008). *Mesp1* acts as a master regulator of multipotent cardiovascular progenitor specification. *Cell Stem Cell* **3**, 69-84. doi:10.1016/j.stem.2008.06.009
- Bothe, I. and Dietrich, S.** (2006). The molecular setup of the avian head mesoderm and its implication for craniofacial myogenesis. *Dev. Dyn.* **235**, 2845-2860. doi:10.1002/dvdy.20903
- Bruneau, B. G., Nemer, G., Schmitt, J. P., Charron, F., Robitaille, L., Caron, S., Conner, D. A., Gessler, M., Nemer, M., Seidman, C. E. et al.** (2001). A murine model of Holt-Oram syndrome defines roles of the T-Box transcription factor *Tbx5* in cardiogenesis and disease. *Cell* **106**, 709-721. doi:10.1016/S0092-8674(01)00493-7
- Burn, S. F., Boot, M. J., de Angelis, C., Doohan, R., Arques, C. G., Torres, M. and Hill, R. E.** (2008). The dynamics of spleen morphogenesis. *Dev. Biol.* **318**, 303-311. doi:10.1016/j.ydbio.2008.03.031
- Bussmann, J., Bakkers, J. and Schulte-Merker, S.** (2007). Early endocardial morphogenesis requires *Scf/Tal1*. *PLoS Genet.* **3**, e140. doi:10.1371/journal.pgen.0030140
- Cano, E., Carmona, R. and Muñoz-Chápuli, R.** (2013). *Wt1*-expressing progenitors contribute to multiple tissues in the developing lung. *Am. J. Physiol. Cell. Mol. Physiol.* **305**, L322-L332. doi:10.1152/ajplung.00424.2012
- Carmona, R., Cano, E., Mattiotti, A., Gaztambide, J. and Muñoz-Chápuli, R.** (2013). Cells derived from the coelomic epithelium contribute to multiple gastrointestinal tissues in mouse embryos. *PLoS ONE* **8**, e55890. doi:10.1371/journal.pone.0055890
- Chau, Y.-Y., Brownstein, D., Mjoseng, H., Lee, W.-C., Buza-Vidas, N., Nerlov, C., Jacobsen, S. E., Perry, P., Berry, R., Thornburn, A. et al.** (2011). Acute multiple organ failure in adult mice deleted for the developmental regulator *Wt1*. *PLoS Genet.* **7**, e1002404. doi:10.1371/journal.pgen.1002404
- Chau, Y.-Y., Bandiera, R., Serrels, A., Martínez-Estrada, O. M., Qing, W., Lee, M., Slight, J., Thornburn, A., Berry, R., McHaffie, S. et al.** (2014). Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. *Nat. Cell Biol.* **16**, 367-375. doi:10.1038/ncb2922
- Choi, K., Kennedy, M., Kazarov, A., Papadimitriou, J. C. and Keller, G.** (1998). A common precursor for hematopoietic and endothelial cells. *Development* **125**, 725-732.
- Chung, Y. S., Zhang, W. J., Arentson, E., Kingsley, P. D., Palis, J. and Choi, K.** (2002). Lineage analysis of the hemangioblast as defined by *FLK1* and *SCL* expression. *Development* **129**, 5511-5520. doi:10.1242/dev.00149
- Clements, D., Taylor, H. C., Herrmann, B. G. and Stott, D.** (1996). Distinct regulatory control of the *Brachyury* gene in axial and non-axial mesoderm suggests separation of mesoderm lineages early in mouse gastrulation. *Mech. Dev.* **56**, 139-149. doi:10.1016/0925-4773(96)00520-5
- Cloney, R. A.** (1982). Ascidian larvae and the events of metamorphosis. *Am. Zool.* **22**, 817-826. doi:10.1093/icb/22.4.817
- Cloney, R. A. and Grimm, L.** (1970). Transcellular emigration of blood cells during ascidian metamorphosis. *Zeitschrift für Zellforsch. und Mikroskopische Anat.* **107**, 157-173. doi:10.1007/BF00335222
- Comai, G., Heude, E., Mella, S., Paisant, S., Pala, F., Gallardo, M., Langa, F., Kardon, G., Gopalakrishnan, S. and Tajbakhsh, S.** (2019). A distinct cardiopharyngeal mesoderm genetic hierarchy establishes antero-posterior patterning of esophagus striated muscle. *Elife* **8**, e47460. doi:10.7554/eLife.47460
- Costello, I., Pimeisl, I.-M., Dräger, S., Bikoff, E. K., Robertson, E. J. and Arnold, S. J.** (2011). The T-box transcription factor *Eomesodermin* acts upstream of *Mesp1* to specify cardiac mesoderm during mouse gastrulation. *Nat. Cell Biol.* **13**, 1084-1091. doi:10.1038/ncb2304
- Craig, M. P. and Sumanas, S.** (2016). ETS transcription factors in embryonic vascular development. *Angiogenesis* **19**, 275-285. doi:10.1007/s10456-016-9511-z
- Cui, S., Ross, A., Stallings, N., Parker, K. L., Capel, B. and Quaggin, S. E.** (2004). Disrupted gonadogenesis and male-to-female sex reversal in *Pod1* knockout mice. *Development* **131**, 4095-4105. doi:10.1242/dev.01266
- Davidson, A. J. and Zon, L. I.** (2004). The "definitive" (and 'primitive') guide to zebrafish hematopoiesis. *Oncogene* **23**, 7233-7246. doi:10.1038/sj.onc.1207943
- Davidson, A. J., Ernst, P., Wang, Y., Dekens, M. P. S. S., Kingsley, P. D., Palis, J., Korsmeyer, S. J., Daley, G. Q. and Zon, L. I.** (2003). *cdx4* mutants fail to specify blood progenitors and can be rescued by multiple *hox* genes. *Nature* **425**, 300-306. doi:10.1038/nature01973
- de Pater, E., Clijsters, L., Marques, S. R., Lin, Y.-F. F., Garavito-Aguilar, Z. V., Yelon, D. and Bakkers, J.** (2009). Distinct phases of cardiomyocyte differentiation regulate growth of the zebrafish heart. *Development* **136**, 1633-1641. doi:10.1242/dev.030924
- Deimling, S. J. and Drysdale, T. A.** (2011). *Fgf* is required to regulate anterior-posterior patterning in the *Xenopus* lateral plate mesoderm. *Mech. Dev.* **128**, 327-341. doi:10.1016/j.mod.2011.06.002
- Delgado, I., Carrasco, M., Cano, E., Carmona, R., García-Carbonero, R., Marín-Gómez, L. M., Soria, B., Martín, F., Cano, D. A., Muñoz-Chápuli, R. et al.** (2014). *GATA4* loss in the septum transversum mesenchyme promotes liver fibrosis in mice. *Hepatology* **59**, 2358-2370. doi:10.1002/hep.27005
- Deshwar, A. R., Onderisin, J. C., Aleksandrova, A., Yuan, X., Burrows, J. T. A. and Scott, I. C.** (2016). *Mespaa* can potentially induce cardiac fates in zebrafish. *Dev. Biol.* **418**, 17-27. doi:10.1016/j.ydbio.2016.08.022
- Dickmeis, T., Mourrain, P., Saint-Etienne, L., Fischer, N., Aanstad, P., Clark, M., Strähle, U. and Rosa, F.** (2001). A crucial component of the endoderm formation pathway, *CASANOVA*, is encoded by a novel *sox*-related gene. *Genes Dev.* **15**, 1487-1492. doi:10.1101/gad.196901
- Diogo, R., Kelly, R. G., Christiaen, L., Levine, M., Ziermann, J. M., Molnar, J. L., Noden, D. M. and Tzahor, E.** (2015). A new heart for a new head in vertebrate cardiopharyngeal evolution. *Nature* **520**, 466-473. doi:10.1038/nature14435
- Duester, G.** (2008). Retinoic acid synthesis and signaling during early organogenesis. *Cell* **134**, 921-931. doi:10.1016/j.cell.2008.09.002
- Ema, M., Faloon, P., Zhang, W. J., Hirashima, M., Reid, T., Stanford, W. L., Orkin, S., Choi, K. and Rossant, J.** (2003). Combinatorial effects of *Flk1* and *Tal1* on vascular and hematopoietic development in the mouse. *Genes Dev.* **17**, 380-393. doi:10.1101/gad.1049803
- Endo, A., Ueno, S., Yamada, S., Uwabe, C. and Takakuwa, T.** (2015). Morphogenesis of the spleen during the human embryonic period. *Anat. Rec.* **298**, 820-826. doi:10.1002/ar.23099
- Engleka, K. A., Gitler, A. D., Zhang, M., Zhou, D. D., High, F. A. and Epstein, J. A.** (2005). Insertion of *Cre* into the *Pax3* locus creates a new allele of *Spotch* and identifies unexpected *Pax3* derivatives. *Dev. Biol.* **280**, 396-406. doi:10.1016/j.ydbio.2005.02.002
- Erter, C. E., Wilm, T. P., Basler, N., Wright, C. V. and Solnica-Krezel, L.** (2001). *Wnt8* is required in lateral mesendodermal precursors for neural posteriorization in vivo. *Development* **128**, 3571-3583.
- Felker, A., Prummel, K. D. K. D., Merks, A. M. A. M., Mickoleit, M., Brombacher, E. C. E. C., Huisken, J., Panáková, D. and Mosimann, C.** (2018). Continuous addition of progenitors forms the cardiac ventricle in zebrafish. *Nat. Commun.* **9**, 2001. doi:10.1038/s41467-018-04402-6
- Ferretti, E. and Hadjantonakis, A.-K.** (2019). Mesoderm specification and diversification: from single cells to emergent tissues. *Curr. Opin. Cell Biol.* **61**, 110-116. doi:10.1016/j.cob.2019.07.012
- Firulli, A. B., McFadden, D. G., Lin, Q., Srivastava, D. and Olson, E. N.** (1998). Heart and extra-embryonic mesodermal defects in mouse embryos lacking the bHLH transcription factor *Hand1*. *Nat. Genet.* **18**, 266-270. doi:10.1038/ng0398-266
- Fish, J. E., Wythe, J. D., Xiao, T., Bruneau, B. G., Stainier, D. Y. R., Srivastava, D. and Woo, S.** (2011). A *Slit/miR-218/Robo* regulatory loop is required during heart tube formation in zebrafish. *Development* **138**, 1409-1419. doi:10.1242/dev.060046
- Furthauer, M., Van Celst, J., Thisse, C. and Thisse, B.** (2004). *Fgf* signalling controls the dorsoventral patterning of the zebrafish embryo. *Development* **131**, 2853-2864. doi:10.1242/dev.01156

- Gays, D., Hess, C., Camporeale, A., Ala, U., Provero, P., Mosimann, C. and Santoro, M. M. (2017). An exclusive cellular and molecular network governs intestinal smooth muscle cell differentiation in vertebrates. *Development* **144**, 464-478. doi:10.1242/dev.133926
- Gessert, S., Kühl, M. and Kühl, M. (2010). The multiple phases and faces of wnt signaling during cardiac differentiation and development. *Circ. Res.* **107**, 186-199. doi:10.1161/CIRCRESAHA.110.221531
- Gopalakrishnan, S., Comai, G., Sambasivan, R., Francou, A., Kelly, R. G. and Tajbakhsh, S. (2015). A cranial mesoderm origin for esophagus striated muscles. *Dev. Cell* **34**, 694-704. doi:10.1016/j.devcel.2015.07.003
- Grimes, A. C. and Kirby, M. L. (2009). The outflow tract of the heart in fishes: anatomy, genes and evolution. *J. Fish Biol.* **74**, 983-1036. doi:10.1111/j.1095-8649.2008.02125.x
- Gurdon, J. B. (1995). The formation of mesoderm and muscle in *Xenopus*. In *Organization of the Early Vertebrate Embryo*, pp. 51-59. Boston, MA: Springer.
- Häfner, R., Bohnenpoll, T., Rudat, C., Schultheiss, T. M. and Kispert, A. (2015). *Fgf2* is required for the expansion of the early adrenocortical primordium. *Mol. Cell. Endocrinol.* **413**, 168-177. doi:10.1016/j.mce.2015.06.022
- Halpern, M. E., Ho, R. K., Walker, C. and Kimmel, C. B. (1993). Induction of muscle pioneers and floor plate is distinguished by the zebrafish no tail mutation. *Cell* **75**, 99-111. doi:10.1016/S0092-8674(05)80087-X
- Hami, D., Grimes, A. C., Tsai, H. J. and Kirby, M. L. (2011). Zebrafish cardiac development requires a conserved secondary heart field. *Development* **138**, 2389-2398. doi:10.1242/dev.061473
- Hammerschmidt, M., Pelegri, F., Mullins, M. C., Kane, D. A., Brand, M., van Eeden, F. J., Furutani-Seiki, M., Granato, M., Haffter, P., Heisenberg, C. P. et al. (1996). Mutations affecting morphogenesis during gastrulation and tail formation in the zebrafish, *Danio rerio*. *Development* **123**, 143-151.
- Hammes, A., Guo, J. K., Lutsch, G., Leheste, J. R., Landrock, D., Ziegler, U., Gubler, M. C. and Schedl, A. (2001). Two splice variants of the wilms' tumor 1 gene have distinct functions during sex determination and nephron formation. *Cell* **106**, 319-329. doi:10.1016/S0092-8674(01)00453-6
- Hartenstein, V. and Mandal, L. (2006). The blood/vascular system in a phylogenetic perspective. *BioEssays* **28**, 1203-1210. doi:10.1002/bies.20497
- Hatano, O., Takakusu, A., Nomura, M. and Morohashi, K. (1996). Identical origin of adrenal cortex and gonad revealed by expression profiles of Ad4BP/SF-1. *Genes Cells* **1**, 663-671. doi:10.1046/j.1365-2443.1996.00254.x
- He, L., Papoutsis, M., Huang, R., Tomarev, S. I., Christ, B., Kurz, H. and Wiltig, J. (2003). Three different fates of cells migrating from somites into the limb bud. *Anat. Embryol. (Berl)*. **207**, 29-34. doi:10.1007/s00429-003-0327-4
- Hecksher-Sorensen, J., Watson, R. P., Lettice, L. A., Serup, P., Eley, L., De Angelis, C., Ahlgren, U. and Hill, R. E. (2004). The splanchnic mesodermal plate directs spleen and pancreatic laterality, and is regulated by *Bapx1/Nkx3.2*. *Development* **131**, 4665-4675. doi:10.1242/dev.01364
- Heisenberg, C.-P. and Solnica-Krezel, L. (2008). Back and forth between cell fate specification and movement during vertebrate gastrulation. *Curr. Opin. Genet. Dev.* **18**, 311-316. doi:10.1016/j.gde.2008.07.011
- Heller, N. and Brändli, A. W. (1999). *Xenopus Pax-2/5/8* orthologues: Novel insights into PaxGene evolution and identification of Pax-8 as the earliest marker for otic and pronephric cell lineages. *Dev. Genet.* **24**, 208-219. doi:10.1002/aid-dvg4>3.0.CO;2-J
- Herbomel, P., Thisse, B. and Thisse, C. (1999). Ontogeny and behaviour of early macrophages in the zebrafish embryo. *Development* **126**, 3735-3745.
- Heude, E., Tesarova, M., Sefton, E. M., Jullian, E., Adachi, N., Grimaldi, A., Zikmund, T., Kaiser, J., Kardon, G., Kelly, R. G. et al. (2018). Unique morphogenetic signatures define mammalian neck muscles and associated connective tissues. *Elife* **7**, e40179. doi:10.7554/eLife.40179
- Hild, M., Dick, A., Rauch, G. J., Meier, A., Bouwmeester, T., Haffter, P. and Hammerschmidt, M. (1999). The *smad5* mutation *somitabun* blocks *Bmp2b* signaling during early dorsoventral patterning of the zebrafish embryo. *Development* **126**, 2149-2159.
- Hill, C. S. (2018). Spatial and temporal control of NODAL signaling. *Curr. Opin. Cell Biol.* **51**, 50-57. doi:10.1016/j.ceb.2017.10.005
- Hiscock, T. W., Tschopp, P. and Tabin, C. J. (2017). On the formation of digits and joints during limb development. *Dev. Cell* **41**, 459-465. doi:10.1016/j.devcel.2017.04.021
- Holland, N. D. (2018). Formation of the initial kidney and mouth opening in larval amphioxus studied with serial blockface scanning electron microscopy (SBSEM). *Evodevo* **9**, 16. doi:10.1186/s13227-018-0104-3
- Holland, L. Z., Holland, N. D. and Gilland, E. (2008). Amphioxus and the evolution of head segmentation. *Integr. Comp. Biol.* **48**, 630-646. doi:10.1093/icb/ich060
- Holley, S. A. and Ferguson, E. L. (1997). Fish are like flies are like frogs: conservation of dorsal-ventral patterning mechanisms. *BioEssays* **19**, 281-284. doi:10.1002/bies.950190404
- Holloway, E. M., Capeling, M. M. and Spence, J. R. (2019). Biologically inspired approaches to enhance human organoid complexity. *Development* **146**. doi:10.1242/dev.166173
- Hu, Y.-C., Okumura, L. M. and Page, D. C. (2013). *Gata4* is required for formation of the genital ridge in mice. *PLoS Genet.* **9**, e1003629. doi:10.1371/journal.pgen.1003629
- Huang, R., Zhi, Q. and Christ, B. (2003). The relationship between limb muscle and endothelial cells migrating from single somite. *Anat. Embryol. (Berl)* **206**, 283-289. doi:10.1007/s00429-002-0289-y
- Huber, T. L., Kouskoff, V., Fehling, H. J., Palis, J. and Keller, G. (2004). Haemangioblast commitment is initiated in the primitive streak of the mouse embryo. *Nature* **432**, 625-630. doi:10.1038/nature03122
- Hutcheson, D. A., Zhao, J., Merrell, A., Haldar, M. and Kardon, G. (2009). Embryonic and fetal limb myogenic cells are derived from developmentally distinct progenitors and have different requirements for beta-catenin. *Genes Dev.* **23**, 997-1013. doi:10.1101/gad.1769009
- Ijpenberg, A., Pérez-Pomares, J. M., Guadix, J. A., Carmona, R., Portillo-Sánchez, V., Macías, D., Hohenstein, P., Miles, C. M., Hastie, N. D. and Muñoz-Chápuli, R. (2007). *Wt1* and retinoic acid signaling are essential for stellate cell development and liver morphogenesis. *Dev. Biol.* **312**, 157-170. doi:10.1016/j.ydbio.2007.09.014
- Ikeda, Y., Shen, W. H., Ingraham, H. A. and Parker, K. L. (1994). Developmental expression of mouse steroidogenic factor-1, an essential regulator of the steroid hydroxylases. *Mol. Endocrinol.* **8**, 654-662. doi:10.1210/mend.8.5.8058073
- Itoh, N., Ohta, H., Nakayama, Y. and Konishi, M. (2016). Roles of FGF signals in heart development, health, and disease. *Front. Cell Dev. Biol.* **4**, 110. doi:10.3389/fcell.2016.00110
- José-Edwards, D. S., Oda-Ishii, I., Kugler, J. E., Passamaneck, Y. J., Katikala, L., Nibu, Y. and Di Gregorio, A. (2015). *Brachyury*, *Foxa2* and the cis-regulatory origins of the notochord. *PLoS Genet.* **11**, e1005730. doi:10.1371/journal.pgen.1005730
- Kanai-Azuma, M., Kanai, Y., Gad, J. M., Tajima, Y., Taya, C., Kurohmaru, M., Sanai, Y., Yonekawa, H., Yazaki, K., Tam, P. P. L. et al. (2002). Depletion of definitive gut endoderm in *Sox17*-null mutant mice. *Development* **129**, 2367-2379.
- Karl, J. and Capel, B. (1998). Sertoli cells of the mouse testis originate from the coelomic epithelium. *Dev. Biol.* **203**, 323-333. doi:10.1006/dbio.1998.9068
- Kelly, R. G. (2012). The second heart field. *Curr. Top. Dev. Biol.* **100**, 33-65. doi:10.1016/B978-0-12-387786-4.00002-6
- Kelly, R. G., Buckingham, M. E. and Moorman, A. F. (2014). Heart fields and cardiac morphogenesis. *Cold Spring Harb. Perspect. Med.* **4**, a015750. doi:10.1101/cshperspect.a015750
- Kessler, D. S. and Melton, D. A. (1994). Vertebrate embryonic induction: mesodermal and neural patterning. *Science* **266**, 596-604. doi:10.1126/science.7939714
- Kikuchi, Y., Agathon, A., Alexander, J., Thisse, C., Waldron, S., Yelon, D., Thisse, B. and Stainier, D. Y. (2001). *casanova* encodes a novel Sox-related protein necessary and sufficient for early endoderm formation in zebrafish. *Genes Dev.* **15**, 1493-1505. doi:10.1101/gad.892301
- Kishimoto, Y., Lee, K. H., Zon, L., Hammerschmidt, M. and Schulte-Merker, S. (1997). The molecular nature of zebrafish swirl: *BMP2* function is essential during early dorsoventral patterning. *Development* **124**, 4457-4466.
- Kissa, K. and Herbomel, P. (2010). Blood stem cells emerge from aortic endothelium by a novel type of cell transition. *Nature* **464**, 112-115. doi:10.1038/nature08761
- Kitajima, S., Takagi, A., Inoue, T. and Saga, Y. (2000). *MesP1* and *MesP2* are essential for the development of cardiac mesoderm. *Development* **127**, 3215-3226.
- Koshiba-Takeuchi, K., Mori, A. D., Kaynak, B. L., Cebra-Thomas, J., Sukonnik, T., Georges, R. O., Latham, S., Beck, L., Henkelman, R. M., Black, B. L. et al. (2009). Reptilian heart development and the molecular basis of cardiac chamber evolution. *Nature* **461**, 95-98. doi:10.1038/nature08324
- Kozmik, Z., Holland, L. Z., Schubert, M., Lacalli, T. C., Kreslova, J., Vleck, C. and Holland, N. D. (2001). Characterization of amphioxus *Amphivent*, an evolutionarily conserved marker for chordate ventral mesoderm. *Genesis* **29**, 172-179. doi:10.1002/gene.1021
- Krueger, K. C., Costa, M. J., Du, H. and Feldman, B. J. (2014). Characterization of cre recombinase activity for in vivo targeting of adipocyte precursor cells. *Stem Cell Reports* **3**, 1147-1158. doi:10.1016/j.stemcr.2014.10.009
- Lane, M. C. and Smith, W. C. (1999). The origins of primitive blood in *Xenopus*: implications for axial patterning. *Development* **126**, 423-434.
- Lasagni, L., Angelotti, M. L., Ronconi, E., Lombardi, D., Nardi, S., Peired, A., Becherucci, F., Mazzinghi, B., Sisti, A., Romoli, S. et al. (2015). Podocyte regeneration driven by renal progenitors determines glomerular disease remission and can be pharmacologically enhanced. *Stem Cell Reports* **5**, 248-263. doi:10.1016/j.stemcr.2015.07.003
- Lawson, K. A., Meneses, J. J. and Pedersen, R. A. (1991). Clonal analysis of epiblast fate during germ layer formation in the mouse embryo. *Development* **113**, 891-911.
- Lazic, S. and Scott, I. C. (2011). *Mef2cb* regulates late myocardial cell addition from a second heart field-like population of progenitors in zebrafish. *Dev. Biol.* **354**, 123-133. doi:10.1016/j.ydbio.2011.03.028
- Lengerke, C., Wingert, R., Beeretz, M., Grauer, M., Schmidt, A. G., Konantz, M., Daley, G. Q. and Davidson, A. J. (2011). Interactions between *Cdx* genes and retinoic acid modulate early cardiogenesis. *Dev. Biol.* **354**, 134-142. doi:10.1016/j.ydbio.2011.03.027

- Lescroart, F., Kelly, R. G., Le Garrec, J.-F., Nicolas, J.-F., Meilhac, S. M. and Buckingham, M. (2010). Clonal analysis reveals common lineage relationships between head muscles and second heart field derivatives in the mouse embryo. *Development* **137**. doi:10.1242/dev.050674
- Lescroart, F., Hamou, W., Francou, A., Théveniau-Ruissy, M., Kelly, R. G. and Buckingham, M. (2015). Clonal analysis reveals a common origin between nonsomite-derived neck muscles and heart myocardium. *Proc. Natl. Acad. Sci. USA* **112**, 1446-1451. doi:10.1073/pnas.1424538112
- Lickert, H., Kutsch, S., Kanzler, B., Tamai, Y., Taketo, M. M. and Kemler, R. (2002). Formation of multiple hearts in mice following deletion of β -catenin in the embryonic endoderm. *Dev. Cell* **3**, 171-181. doi:10.1016/S1534-5807(02)00206-X
- Lickert, H., Takeuchi, J. K., von Both, I., Walls, J. R., McAuliffe, F., Lee Adamson, S., Mark Henkelman, R., Wrana, J. L., Rossant, J. and Bruneau, B. G. (2004). Baf60c is essential for function of BAF chromatin remodelling complexes in heart development. *Nature* **432**, 107-112. doi:10.1038/nature03071
- Lioux, G., Liu, X., Temiño, S., Oxendine, M., Ayala, E., Ortega, S., Kelly, R. G., Oliver, G. and Torres, M. (2020). A second heart field-derived vasculogenic niche contributes to cardiac lymphatics. *Dev. Cell* **52**, 350-363.e6. doi:10.1016/j.devcel.2019.12.006
- Liu, C., Peng, J., Matzuk, M. M. and Yao, H. H.-C. (2015). Lineage specification of ovarian theca cells requires multicellular interactions via oocyte and granulosa cells. *Nat. Commun.* **6**, 6934. doi:10.1038/ncomms7934
- Loh, K. M. M., Chen, A., Koh, P. W. W., Deng, T. Z. Z., Sinha, R., Tsai, J. M. M., Barkal, A. A. A., Shen, K. Y. Y., Jain, R., Morganti, R. M. M. et al. (2016). Mapping the pairwise choices leading from pluripotency to human bone, heart, and other mesoderm cell types. *Cell* **166**, 451-467. doi:10.1016/j.cell.2016.06.011
- Marass, M., Beisaw, A., Gerri, C., Luzzani, F., Fukuda, N., Günther, S., Kuenne, C., Reischauer, S. and Stainier, D. Y. R. (2019). Genome-wide strategies reveal target genes of Npas4l associated with vascular development in zebrafish. *Development* **146**, dev173427. doi:10.1242/dev.173427
- Martin, J. F. and Olson, E. N. (2000). Identification of a prx1 limb enhancer. *Genesis* **26**, 225-229. doi:10.1002/(SICI)1526-968X(200004)26:4<225::AID-GENE10>3.0.CO;2-F
- Martinez-Arias, A. and Stevenon, B. (2018). On the nature and function of organizers. *Development* **145**, dev159525. doi:10.1242/dev.159525
- Maruyama, K., Miyagawa-Tomita, S., Mizukami, K., Matsuzaki, F. and Kurihara, H. (2019). Isl1-expressing non-venous cell lineage contributes to cardiac lymphatic vessel development. *Biol. Cell* **452**, 134-143. doi:10.1016/j.ydbio.2019.05.002
- Mayeuf-Louchart, A., Lagha, M., Danckaert, A., Rocancourt, D., Relaix, F., Vincent, S. D. and Buckingham, M. (2014). Notch regulation of myogenic versus endothelial fates of cells that migrate from the somite to the limb. *Proc. Natl. Acad. Sci. USA* **111**, 8844-8849. doi:10.1073/pnas.1407606111
- Mayor, R. and Theveneau, E. (2013). The neural crest. *Development* **140**, 2247-2251. doi:10.1242/dev.091751
- McDole, K., Guignard, L., Amat, F., Berger, A., Malandain, G., Royer, L. A., Turaga, S. C., Branson, K. and Keller, P. J. (2018). In toto imaging and reconstruction of post-implantation mouse development at the single-cell level. *Cell* **175**, 859-876.e33. doi:10.1016/j.cell.2018.09.031
- McMahon, A. P. (2016). Development of the mammalian kidney. *Curr. Top. Dev. Biol.* **117**, 31-64. doi:10.1016/bs.ctdb.2015.10.010
- Mead, P. E., Deconinck, A. E., Huber, T. L., Orkin, S. H. and Zon, L. I. (2001). Primitive erythropoiesis in the *Xenopus* embryo: the synergistic role of LMO-2, SCL and GATA-binding proteins. *Development* **128**, 2301-2308.
- Meilhac, S. M., Esner, M., Kelly, R. G., Nicolas, J.-F. and Buckingham, M. E. (2004). The clonal origin of myocardial cells in different regions of the embryonic mouse heart. *Dev. Cell* **6**, 685-698. doi:10.1016/S1534-5807(04)00133-9
- Mendjan, S., Mascetti, V. L. L., Ortmann, D., Ortiz, M., Karjosukarso, D. W. W., Ng, Y., Moreau, T. and Pedersen, R. A. A. (2014). NANOG and CDX2 pattern distinct subtypes of human mesoderm during exit from pluripotency. *Cell Stem Cell* **15**, 310-325. doi:10.1016/j.stem.2014.06.006
- Michailovici, I., Eigler, T. and Tzahor, E. (2015). Craniofacial muscle development. *Curr. Top. Dev. Biol.* **115**, 3-30. doi:10.1016/bs.ctdb.2015.07.022
- Minguillon, C., Nishimoto, S., Wood, S., Vendrell, E., Gibson-Brown, J. J. and Logan, M. P. O. (2012). Hox genes regulate the onset of Tbx5 expression in the forelimb. *Development* **139**, 3180-3188. doi:10.1242/dev.084814
- Monahan-Earley, R., Dvorak, A. M. and Aird, W. C. (2013). Evolutionary origins of the blood vascular system and endothelium. *J. Thromb. Haemost.* **11** Suppl. 1, 46-66. doi:10.1111/jth.12253
- Moore, A. W., Barbel, S., Jan, L. Y. and Jan, Y. N. (2000). A genomewide survey of basic helix-loop-helix factors in *Drosophila*. *Proc. Natl. Acad. Sci. USA* **97**, 10436-10441. doi:10.1073/pnas.170301897
- Moreau, C., Caldarelli, P., Rocancourt, D., Roussel, J., Denans, N., Pourquie, O. and Gros, J. (2019). Timed collinear activation of Hox genes during gastrulation controls the avian forelimb position. *Curr. Biol.* **29**, 35-50.e4. doi:10.1016/j.cub.2018.11.009
- Mosimann, C., Panáková, D., Werdich, A. A. A., Musso, G., Burger, A., Lawson, K. L. K., Carr, L. A. L. A., Nevis, K. R. K. R., Sabeh, M. K. K., Zhou, Y. et al. (2015). Chamber identity programs drive early functional partitioning of the heart. *Nat. Commun.* **6**, 8146. doi:10.1038/ncomms9146
- Mudumana, S. P., Hentschel, D., Liu, Y., Vasilyev, A. and Drummond, I. A. (2008). odd skipped related1 reveals a novel role for endoderm in regulating kidney versus vascular cell fate. *Development* **135**, 3355-3367. doi:10.1242/dev.022830
- Mullins, M. C., Hammerschmidt, M., Kane, D. A., Odenthal, J., Brand, M., van Eeden, F. J., Furutani-Seiki, M., Granato, M., Haffter, P., Heisenberg, C. P. et al. (1996). Genes establishing dorsoventral pattern formation in the zebrafish embryo: the ventral specifying genes. *Development* **123**, 81-93.
- Munoz-Chapuli, R. (2011). Evolution of angiogenesis. *Int. J. Dev. Biol.* **55**, 345-351. doi:10.1387/ijdb.103212rm
- Munoz-Chapuli, R., Carmona, R., Guadix, J. A., Macias, D. and Perez-Pomares, J. M. (2005). The origin of the endothelial cells: an evo-devo approach for the invertebrate/vertebrate transition of the circulatory system. *Evol. Dev.* **7**, 351-358. doi:10.1111/j.1525-142X.2005.05040.x
- Murray, P. D. F. (1932). The development in vitro of the blood of the early chick embryo. *Proc. R. Soc. B Biol. Sci.* **111**, 497-521. doi:10.1098/rspb.1932.0070
- Mutsaers, S. E. and Wilkosz, S. (2007). Structure and function of mesothelial cells. *Cancer Treat. Res.* **134**, 1-19. doi:10.1007/978-0-387-48993-3_1
- Nathan, E., Monovich, A., Tirosh-Finkel, L., Harrelson, Z., Rousso, T., Rinon, A., Harel, I., Evans, S. M. and Tzahor, E. (2008). The contribution of Islet1-expressing splanchnic mesoderm cells to distinct branchiomeric muscles reveals significant heterogeneity in head muscle development. *Development* **135**, 647-657. doi:10.1242/dev.007989
- Naylor, R. W., Skvarca, L. B., Thisse, C., Thisse, B., Hukriede, N. A. and Davidson, A. J. (2016). BMP and retinoic acid regulate anterior-posterior patterning of the non-axial mesoderm across the dorsal-ventral axis. *Nat. Commun.* **7**, 12197. doi:10.1038/ncomms12197
- Nelson, A. C., Cutty, S. J., Niini, M., Stemple, D. L., Flicek, P., Houart, C., Bruce, A. E. and Wardle, F. C. (2014). Global identification of Smad2 and Eomesodermin targets in zebrafish identifies a conserved transcriptional network in mesoderm and a novel role for Eomesodermin in repression of ectodermal gene expression. *BMC Biol.* **12**, 81. doi:10.1186/s12915-014-0081-5
- Nguyen, V. H., Schmid, B., Trout, J., Connors, S. A., Ekker, M. and Mullins, M. C. (1998). Ventral and lateral regions of the zebrafish gastrula, including the neural crest progenitors, are established by a bmp2b / swirl Pathway of Genes. *Dev. Biol.* **110**, 93-110. doi:10.1006/dbio.1998.8927
- Nicenboim, J., Malkinson, G., Lupo, T., Asaf, L., Sela, Y., Mayselless, O., Gibbs-Bar, L., Senderovich, N., Hashimshony, T., Shin, M. et al. (2015). Lymphatic vessels arise from specialized angioblasts within a venous niche. *Nature* **522**, 56-61. doi:10.1038/nature14425
- Niederreither, K. and Dollé, P. (2008). Retinoic acid in development: towards an integrated view. *Nat. Rev. Genet.* **9**, 541-553. doi:10.1038/nrg2340
- Nishimatsu, S. and Thomsen, G. H. (1998). Ventral mesoderm induction and patterning by bone morphogenetic protein heterodimers in *Xenopus* embryos. *Mech. Dev.* **74**, 75-88. doi:10.1016/S0925-4773(98)00070-7
- Nishimoto, S. and Logan, M. P. O. (2016). Subdivision of the lateral plate mesoderm and specification of the forelimb and hindlimb forming domains. *Semin. Cell Dev. Biol.* **49**, 102-108. doi:10.1016/j.semcdb.2015.11.011
- Ochi, H., Hans, S. and Westerfield, M. (2008). Smarcd3 regulates the timing of zebrafish myogenesis onset. *J. Biol. Chem.* **283**, 3529-3536. doi:10.1074/jbc.M708594200
- Oh, S.-Y., Kim, J. Y. and Park, C. (2015). The ETS Factor, ETV2: a master regulator for vascular endothelial cell development. *Mol. Cells* **38**, 1029-1036. doi:10.14348/molcells.2015.0331
- Ohinata, H., Tochinali, S. and Katagiri, C. (1990). Occurrence of nonlymphoid leukocytes that are not derived from blood islands in *Xenopus laevis* larvae. *Dev. Biol.* **141**, 123-129. doi:10.1016/0012-1606(90)90107-T
- Onimaru, K., Shoguchi, E., Kuratani, S. and Tanaka, M. (2011). Development and evolution of the lateral plate mesoderm: comparative analysis of amphioxus and lamprey with implications for the acquisition of paired fins. *Dev. Biol.* **359**, 124-136. doi:10.1016/j.ydbio.2011.08.003
- Orkin, S. H. and Zon, L. I. (2008). Hematopoiesis: an evolving paradigm for stem cell biology. *Cell* **132**, 631-644. doi:10.1016/j.cell.2008.01.025
- Ormestad, M., Astorga, J. and Carlsson, P. (2004). Differences in the embryonic expression patterns of mouse Foxf1 and -2 match their distinct mutant phenotypes. *Dev. Dyn.* **229**, 328-333. doi:10.1002/dvdy.10426
- Paffett-Lugassy, N., Novikov, N., Jeffrey, S., Abrial, M., Guner-Ataman, B., Sakhiveli, S., Burns, C. E. and Burns, C. G. (2017). Unique developmental trajectories and genetic regulation of ventricular and outflow tract progenitors in the zebrafish second heart field. *Development* **144**, 4616-4624. doi:10.1242/dev.153411
- Palis, J., Robertson, S., Kennedy, M., Wall, C. and Keller, G. (1999). Development of erythroid and myeloid progenitors in the yolk sac and embryo proper of the mouse. *Development* **126**, 5073-5084.
- Pardanaud, L., Luton, D., Prigent, M., Bourcheix, L. M., Catala, M. and Dieterlen-Lievre, F. (1996). Two distinct endothelial lineages in ontogeny, one of them related to hemopoiesis. *Development* **122**, 1363-1371.

- Pascual-Anaya, J., Albuixech-Crespo, B., Somorjai, I. M. L., Carmona, R., Oisi, Y., Álvarez, S., Kuratani, S., Muñoz-Chápuli, R. and García-Fernández, J. (2013). The evolutionary origins of chordate hematopoiesis and vertebrate endothelia. *Dev. Biol.* **375**, 182-192. doi:10.1016/j.ydbio.2012.11.015
- Pérez-Pomares, J. M., Carmona, R., González-Iriarte, M., Macías, D., Guadix, J. A. and Muñoz-Chápuli, R. (2004). Contribution of mesothelium-derived cells to liver sinusoids in avian embryos. *Dev. Dyn.* **229**, 465-474. doi:10.1002/dvdy.10455
- Petit, F., Sears, K. E. and Ahituv, N. (2017). Limb development: a paradigm of gene regulation. *Nat. Rev. Genet.* **18**, 245-258. doi:10.1038/nrg.2016.167
- Pouget, C., Gautier, R., Teillet, M.-A. and Jaffredo, T. (2006). Somite-derived cells replace ventral aortic hemangioblasts and provide aortic smooth muscle cells of the trunk. *Development* **133**, 1013-1022. doi:10.1242/dev.02269
- Prummel, K. D., Hess, C., Nieuwenhuize, S., Parker, H. J., Rogers, K. W., Kozmikova, I., Racioppi, C., Brombacher, E. C., Czarkwiani, A., Knapp, D. et al. (2019). A conserved regulatory program initiates lateral plate mesoderm emergence across chordates. *Nat. Commun.* **10**, 3857. doi:10.1038/s41467-019-11561-7
- Qian, L., Liu, J. and Bodmer, R. (2005). Slit and Robo control cardiac cell polarity and morphogenesis. *Curr. Biol.* **15**, 2271-2278. doi:10.1016/j.cub.2005.10.037
- Qiu, J., Fan, X., Wang, Y., Jin, H., Song, Y., Han, Y., Huang, S., Meng, Y., Tang, F. and Meng, A. (2016). Embryonic hematopoiesis in vertebrate somites gives rise to definitive hematopoietic stem cells. *J. Mol. Cell Biol.* **8**, 288-301. doi:10.1093/jmcb/mjw024
- Que, J., Wilm, B., Hasegawa, H., Wang, F., Bader, D. and Hogan, B. L. M. (2008). Mesothelium contributes to vascular smooth muscle and mesenchyme during lung development. *Proc. Natl. Acad. Sci. USA* **105**, 16626-16630. doi:10.1073/pnas.0808649105
- Ralliss, C., Bruneau, B. G., Del Buono, J., Seidman, C. E., Seidman, J. G., Nissim, S., Tabin, C. J. J., Logan, M. P. O. P., Ashby, P. R., Coutelle, O. et al. (2003). Tbx5 is required for forelimb bud formation and continued outgrowth. *Development* **130**, 2741-2751. doi:10.1242/dev.00473
- Reischauer, S., Stone, O. A., Villaseñor, A., Chi, N., Jin, S.-W., Martin, M., Lee, M. T., Fukuda, N., Marass, M., Witty, A. et al. (2016). Cloche is a bHLH-PAS transcription factor that drives haemato-vascular specification. *Nature* **535**, 294-298. doi:10.1038/nature18614
- Rinkevich, Y., Mori, T., Sahoo, D., Xu, P.-X., Bermingham, J. R. and Weissman, I. L. (2012). Identification and prospective isolation of a mesothelial precursor lineage giving rise to smooth muscle cells and fibroblasts for mammalian internal organs and their vasculature. *Nat. Cell Biol.* **14**, 1251-1260. doi:10.1038/ncb2610
- Ro, H. and Dawid, I. B. (2009). Organizer restriction through modulation of Bozozok stability by the E3 ubiquitin ligase Lnx-like. *Nat. Cell Biol.* **11**, 1121-1127. doi:10.1038/ncb1926
- Rojas, A., De Val, S., Heidt, A. B., Xu, S.-M., Bristow, J. and Black, B. L. (2005). Gata4 expression in lateral mesoderm is downstream of BMP4 and is activated directly by Forkhead and GATA transcription factors through a distal enhancer element. *Development* **132**, 3405-3417. doi:10.1242/dev.01913
- Rosenquist, G. C. (1970). Location and movements of cardiogenic cells in the chick embryo: the heart-forming portion of the primitive streak. *Dev. Biol.* **22**, 461-475. doi:10.1016/0012-1606(70)90163-6
- Rossant, J. and Tam, P. P. L. (2009). Blastocyst lineage formation, early embryonic asymmetries and axis patterning in the mouse. *Development* **136**, 701-713. doi:10.1242/dev.017178
- Sabin, F. R. (1917). Preliminary note on the differentiation of angioblasts and the method by which they produce blood-vessels, blood-plasma and red blood-cells as seen in the living chick. 1917. *J. Hematother Stem Cell Res* **11**, 5-7. doi:10.1089/152581602753448496
- Sadahiro, T., Yamanaka, S. and Ieda, M. (2015). Direct cardiac reprogramming: progress and challenges in basic biology and clinical applications. *Circ. Res.* **116**, 1378-1391. doi:10.1161/CIRCRESAHA.116.305374
- Saga, Y., Kitajima, S. and Miyagawa-Tomita, S. (2000). Mesp1 expression is the earliest sign of cardiovascular development. *Trends Cardiovasc. Med.* **10**, 345-352. doi:10.1016/S1050-1738(01)00069-X
- Sanchez-Gurmaches, J., Hsiao, W.-Y. and Guertin, D. A. (2015). Highly selective in vivo labeling of subcutaneous white adipocyte precursors with Prx1-Cre. *Stem Cell Reports* **4**, 541-550. doi:10.1016/j.stemcr.2015.02.008
- Sanz-Morejón, A., García-Redondo, A. B., Reuter, H., Marques, I. J., Bates, T., Galardi-Castilla, M., Große, A., Manig, S., Langa, X., Ernst, A. et al. (2019). Wilms tumor 1b expression defines a pro-regenerative macrophage subtype and is required for organ regeneration in the zebrafish. *Cell Rep.* **28**, 1296-1306.e6. doi:10.1016/j.celrep.2019.06.091
- Satou, Y., Imai, K. S. and Satoh, N. (2004). The ascidian Mesp gene specifies heart precursor cells. *Development* **131**, 2533-2541. doi:10.1242/dev.01145
- Saykali, B., Mathiah, N., Nahaboo, W., Racu, M.-L., Hammou, L., Defrance, M. and Migeotte, I. (2019). Distinct mesoderm migration phenotypes in extra-embryonic and embryonic regions of the early mouse embryo. *Elife* **8**, e42434. doi:10.7554/eLife.42434.050
- Schier, A. F. and Talbot, W. S. (2001). Nodal signaling and the zebrafish organizer. *Int. J. Dev. Biol.* **45**, 289-297.
- Schier, A. F. and Talbot, W. S. (2005). Molecular genetics of axis formation in zebrafish. *Annu. Rev. Genet.* **39**, 561-613. doi:10.1146/annurev.genet.37.110801.143752
- Schulte-Merker, S., van Eeden, F. J., Halpern, M. E., Kimmel, C. B. and Nüsslein-Volhard, C. (1994). no tail (ntl) is the zebrafish homologue of the mouse T (Brachyury) gene. *Development* **120**, 1009-1015.
- Scialdone, A., Tanaka, Y., Jawaid, W., Moignard, V., Wilson, N. K., Macaulay, I. C., Marioni, J. C. and Göttgens, B. (2016). Resolving early mesoderm diversification through single-cell expression profiling. *Nature* **535**, 289-293. doi:10.1038/nature18633
- Scimone, M. L., Wurtzel, O., Malecek, K., Fincher, C. T., Oderberg, I. M., Kravarik, K. M. and Reddien, P. W. (2018). foxF-1 Controls specification of non-body wall muscle and phagocytic cells in planarians. *Curr. Biol.* **28**, 3787-3801.e6. doi:10.1016/j.cub.2018.10.030
- Sebo, Z. L., Jeffery, E., Holtrup, B. and Rodeheffer, M. S. (2018). A mesodermal fate map for adipose tissue. *Development* **145**, dev166801. doi:10.1242/dev.166801
- Selleck, M. A. and Stern, C. D. (1991). Fate mapping and cell lineage analysis of Hensen's node in the chick embryo. *Development* **112**, 615-626.
- Semo, J., Nicenboim, J. and Yaniv, K. (2016). Development of the lymphatic system: new questions and paradigms. *Development* **143**, 924-935. doi:10.1242/dev.132431
- Serluca, F. C. and Fishman, M. C. (2001). Pre-pattern in the pronephric kidney field of zebrafish. *Development* **128**, 2233-2241.
- Shida, K., Terajima, D., Uchino, R., Ikawa, S., Ikeda, M., Asano, K., Watanabe, T., Azumi, K., Nonaka, M., Satou, Y. et al. (2003). Hemocytes of *Ciona intestinalis* express multiple genes involved in innate immune host defense. *Biochem. Biophys. Res. Commun.* **302**, 207-218. doi:10.1016/S0006-291X(03)00113-X
- Shigeta, A., Huang, V., Zuo, J., Besada, R., Nakashima, Y., Lu, Y., Ding, Y., Pellegrini, M., Kulkarni, R. P., Hsiai, T. et al. (2019). Endocardially derived macrophages are essential for valvular remodeling. *Dev. Cell* **0**, 617-630.e3. doi:10.1016/j.devcel.2019.01.021
- Sidi, S., Goutel, C., Peyriéras, N. and Rosa, F. M. (2003). Maternal induction of ventral fate by zebrafish radar. *Proc. Natl. Acad. Sci. USA* **100**, 3315-3320. doi:10.1073/pnas.0530115100
- Simons, M., Gordon, E. and Claesson-Welsh, L. (2016). Mechanisms and regulation of endothelial VEGF receptor signalling. *Nat. Rev. Mol. Cell Biol.* **17**, 611-625. doi:10.1038/nrm.2016.87
- Sinha, S. and Santoro, M. M. (2018). New models to study vascular mural cell embryonic origin: implications in vascular diseases. *Cardiovasc. Res.* **114**, 481-491. doi:10.1093/cvr/cvy005
- Song, K., Nam, Y.-J., Luo, X., Qi, X., Tan, W., Huang, G. N., Acharya, A., Smith, C. L., Tallquist, M. D., Neilson, E. G. et al. (2012). Heart repair by reprogramming non-mycocytes with cardiac transcription factors. *Nature* **485**, 599-604. doi:10.1038/nature11139
- Stainier, D. Y., Weinstein, B. M., Detrich, H. W., Zon, L. I., Fishman, M. C., Detrich, H. W., Ill, Zon, L. I. and Fishman, M. C. (1995). Cloche, an early acting zebrafish gene, is required by both the endothelial and hematopoietic lineages. *Development* **121**, 3141-3150.
- Stolfi, A., Gainous, T. B., Young, J. J., Mori, A., Levine, M. and Christiaen, L. (2010). Early chordate origins of the vertebrate second heart field. *Science* **329**, 565-568. doi:10.1126/science.1190181
- Stone, O. A. and Stainier, D. Y. R. (2019). Paraxial mesoderm is the major source of lymphatic endothelium. *Dev. Cell* **50**, 247-255.e3. doi:10.1016/j.devcel.2019.04.034
- Swedlund, B. and Lescroart, F. (2019). Cardiopharyngeal progenitor specification: multiple roads to the heart and head muscles. *Cold Spring Harb. Perspect. Biol.* a036731. doi:10.1101/cshperspect.a036731
- Takasato, M. and Little, M. H. (2015). The origin of the mammalian kidney: implications for recreating the kidney in vitro. *Development* **142**, 1937-1947. doi:10.1242/dev.104802
- Takasato, M., Er, P. X., Becroft, M., Vanslabrouck, J. M., Stanley, E. G., Elefanty, A. G. and Little, M. H. (2014). Directing human embryonic stem cell differentiation towards a renal lineage generates a self-organizing kidney. *Nat. Cell Biol.* **16**, 118-126. doi:10.1038/ncb2894
- Tam, P. P. and Beddington, R. S. (1987). The formation of mesodermal tissues in the mouse embryo during gastrulation and early organogenesis. *Development* **99**, 109-126.
- Tanaka, M. (2016a). Developmental mechanism of limb field specification along the anterior-posterior axis during vertebrate evolution. *J. Dev. Biol.* **4**, 18. doi:10.3390/jdb4020018
- Tanaka, M. (2016b). Fins into limbs: Autopod acquisition and anterior elements reduction by modifying gene networks involving 5'Hox, Gli3, and Shh. *Dev. Biol.* **413**, 1-7. doi:10.1016/j.ydbio.2016.03.007
- Technau, U. and Scholz, C. B. (2003). Origin and evolution of endoderm and mesoderm. *Int. J. Dev. Biol.* **47**, 531-539.
- Tena, J. J., Neto, A., de la Calle-Mustienes, E., Bras-Pereira, C., Casares, F. and Gómez-Skarmeta, J. L. (2007). Odd-skipped genes encode repressors that control kidney development. *Dev. Biol.* **301**, 518-531. doi:10.1016/j.ydbio.2006.08.063

- Terashima, A. V., Mudumana, S. P. and Drummond, I. A.** (2014). Odd skipped related 1 is a negative feedback regulator of nodal-induced endoderm development. *Dev. Dyn.* **243**, 1571-1580. doi:10.1002/dvdy.24191
- Theis, S., Patel, K., Valasek, P., Otto, A., Pu, Q., Harel, I., Tzahor, E., Tajbakhsh, S., Christ, B. and Huang, R.** (2010). The occipital lateral plate mesoderm is a novel source for vertebrate neck musculature. *Development* **137**, 2961-2971. doi:10.1242/dev.049726
- Thompson, M. A., Ransom, D. G., Pratt, S. J., MacLennan, H., Kieran, M. W., Detrich, H. W., Vail, B., Huber, T. L., Paw, B., Brownlie, A. J. et al.** (1998). The *cloche* and *spadetail* genes differentially affect hematopoiesis and vasculogenesis. *Dev. Biol.* **197**, 248-269. doi:10.1006/dbio.1998.8887
- Tirosh-Finkel, L., Elhanany, H., Rinon, A. and Tzahor, E.** (2006). Mesoderm progenitor cells of common origin contribute to the head musculature and the cardiac outflow tract. *Development* **133**, 1943-1953. doi:10.1242/dev.02365
- Tremblay, M., Sanchez-Ferras, O. and Bouchard, M.** (2018). GATA transcription factors in development and disease. *Development* **145**, dev164384. doi:10.1242/dev.164384
- Vincent, S. D. and Buckingham, M. E.** (2010). How to make a heart. *Curr. Top. Dev. Biol.* **90**, 1-41. doi:10.1016/S0070-2153(10)90001-X
- Vogeli, K. M., Jin, S. W., Martin, G. R. and Stainier, D. Y.** (2006). A common progenitor for haematopoietic and endothelial lineages in the zebrafish gastrula. *Nature* **443**, 337-339. doi:10.1038/nature05045
- Wang, W., Niu, X., Stuart, T., Jullian, E., Mauck, W. M., Kelly, R. G., Satija, R. and Christiaen, L.** (2019a). A single-cell transcriptional roadmap for cardiopharyngeal fate diversification. *Nat. Cell Biol.* **21**, 674-686. doi:10.1038/s41556-019-0336-z
- Wang, H., Holland, P. W. H. and Takahashi, T.** (2019b). Gene profiling of head mesoderm in early zebrafish development: insights into the evolution of cranial mesoderm. *Evodevo* **10**, 14. doi:10.1186/s13227-019-0128-3
- Warga, R. M. and Nüsslein-Volhard, C.** (1999). Origin and development of the zebrafish endoderm. *Development* **126**, 827-838.
- Wilkinson, D. G., Bhatt, S. and Herrmann, B. G.** (1990). Expression pattern of the mouse *T* gene and its role in mesoderm formation. *Nature* **343**, 657-659. doi:10.1038/343657a0
- Wilm, B., Ipenberg, A., Hastie, N. D., Burch, J. B. E. and Bader, D. M.** (2005). The serosal mesothelium is a major source of smooth muscle cells of the gut vasculature. *Development* **132**, 5317-5328. doi:10.1242/dev.02141
- Winters, N. I., Thomson, R. T. and Bader, D. M.** (2012). Identification of a novel developmental mechanism in the generation of mesothelia. *Development* **139**, 2926-2934. doi:10.1242/dev.082396
- Xu, P.-F., Houssin, N., Ferri-Lagneau, K. F., Thisse, B. and Thisse, C.** (2014). Construction of a vertebrate embryo from two opposing morphogen gradients. *Science* **344**, 87-89. doi:10.1126/science.1248252
- Yabe, T., Hoshijima, K., Yamamoto, T. and Takada, S.** (2016). Quadruple zebrafish mutant reveals different roles of *Mesp* genes in somite segmentation between mouse and zebrafish. *Development* **143**. doi:10.1242/dev.133173
- Yuan, X., Song, M., Devine, P., Bruneau, B. G., Scott, I. C. and Wilson, M. D.** (2018). Heart enhancers with deeply conserved regulatory activity are established early in zebrafish development. *Nat. Commun.* **9**, 4977. doi:10.1038/s41467-018-07451-z
- Yvernogeau, L., Gautier, R., Petit, L., Khoury, H., Relaix, F., Ribes, V., Sang, H., Charbord, P., Souyri, M., Robin, C. et al.** (2019). In vivo generation of haematopoietic stem/progenitor cells from bone marrow-derived haemogenic endothelium. *Nat. Cell Biol.* **21**, 1334-1345. doi:10.1038/s41556-019-0410-6
- Zaffran, S., Kuchler, A., Lee, H. H. and Frasch, M.** (2001). *biniou* (*FoxF*), a central component in a regulatory network controlling visceral mesoderm development and midgut morphogenesis in *Drosophila*. *Genes Dev.* **15**, 2900-2915.
- Zeller, R., López-Ríos, J. and Zuniga, A.** (2009). Vertebrate limb bud development: moving towards integrative analysis of organogenesis. *Nat. Rev. Genet.* **10**, 845-858. doi:10.1038/nrg2681
- Zhang, Y., Gao, S., Xia, J. and Liu, F.** (2018). Hematopoietic hierarchy - an updated roadmap. *Trends Cell Biol.* **28**, 976-986. doi:10.1016/j.tcb.2018.06.001
- Zhao, J. and Mommersteeg, M. T. M.** (2018). Slit-Robo signalling in heart development. *Cardiovasc. Res.* **114**, 794-804. doi:10.1093/cvr/cvy061
- Zhou, B., Ma, Q., Rajagopal, S., Wu, S. M., Domian, I., Rivera-Feliciano, J., Jiang, D., von Gise, A., Ikeda, S., Chien, K. R. et al.** (2008). Epicardial progenitors contribute to the cardiomyocyte lineage in the developing heart. *Nature* **454**, 109-113. doi:10.1038/nature07060
- Zhou, Y., Cashman, T. J., Nevis, K. R., Obregon, P., Carney, S. A., Liu, Y., Gu, A., Mosimann, C., Sondalle, S., Peterson, R. E. et al.** (2011). Latent TGF-beta binding protein 3 identifies a second heart field in zebrafish. *Nature* **474**, 645-648. doi:10.1038/nature10094
- Zovein, A. C., Hofmann, J. J., Lynch, M., French, W. J., Turlo, K. A., Yang, Y., Becker, M. S., Zanetta, L., Dejana, E., Gasson, J. C. et al.** (2008). Fate tracing reveals the endothelial origin of hematopoietic stem cells. *Cell Stem Cell* **3**, 625-636. doi:10.1016/j.stem.2008.09.018