

Chapter 2

Establishment of Anterior–Posterior Axis in the Mouse Embryo

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Abstract The anterior–posterior (A–P) axis is the first established and morphologically discernible axis of the body during mouse development. From embryonic day (E) 4.5 to E6.5 of mouse embryos, the formation of the distal visceral endoderm (DVE) followed by that of the anterior visceral endoderm (AVE) breaks the A–P symmetry of the embryo. The DVE progenitor cells arise in primitive endoderm (PrE) cells of the late blastocyst with an asymmetrical distribution. This asymmetry may contribute to the determination of the A–P axis in later embryos. At E5.5, DVE cells mature, and migrate from the distal tip to the future anterior side. The DVE migration guides the migration of newly formed AVE and trigger the extensive movement of visceral endoderm (VE) cells in a wide area. Our observations revise the earlier model about AVE development, namely, that the AVE is directly derived from the DVE.

Keywords Anterior–posterior axis • AVE • Blastocyst • DVE • Implantation

2.1 Introduction

Vertebrates have three principal body axes: the anterior–posterior (A–P), dorsal–ventral (D–V), and left–right (L–R) axes. In many animal species, the A–P axis is the first morphologically discernible body axis. How and at which stage of development is the A–P axis determined? The answer depends on the animal species. Establishment of the A–P axis is based on early molecular asymmetry. In *Drosophila melanogaster*, the A–P axis is defined during oogenesis by the asymmetrical deposition of maternal mRNAs along two poles of the oocyte (Huynh and St. Johnston 2004).

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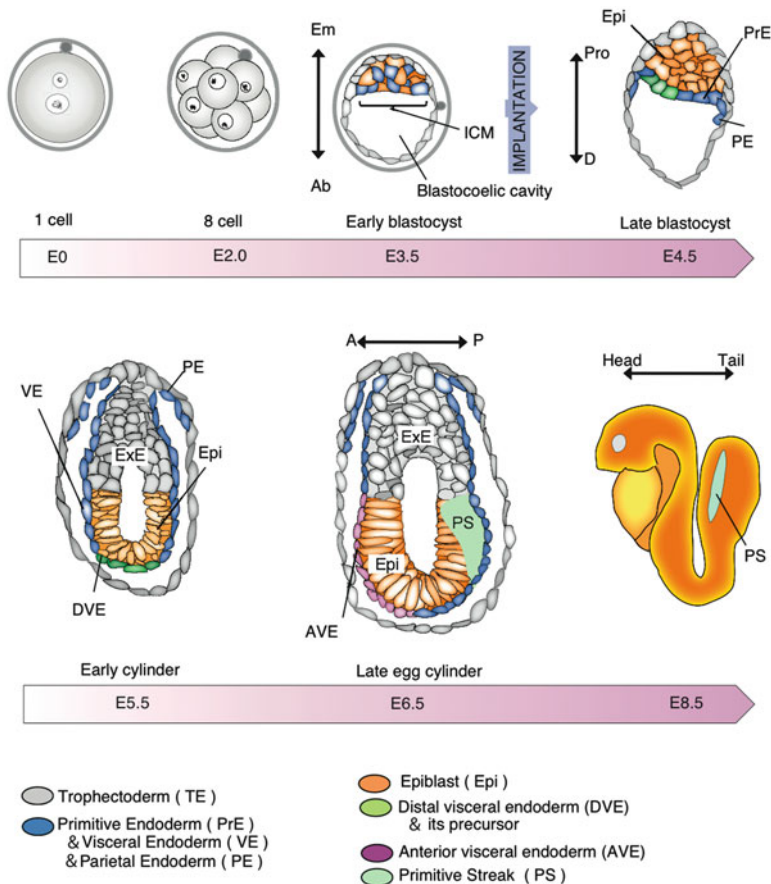


Fig. 2.1 Axis formation of early mouse embryo development. In the early blastocyst, the Em–Ab (embryo–abembryo) axis is defined by the position of the inner cell mass (ICM). After the implantation, the Em–Ab axis and the Pro–D axis of the late blastocyst are aligned in the same direction. The proximal side corresponds to the mesometrial side in the uterus. From E5.5 to E6.5, the anterior–posterior (A–P) axis of an embryo is established by DVE migration, which is followed by AVE formation. The cell types in the embryos are color coded. AVE anterior visceral endoderm, DVE distal visceral endoderm, E embryonic day, Epi epiblast, Exe extra-embryonic ectoderm, PrE primitive ectoderm, PE parietal endoderm, PS primitive streak, VE visceral endoderm, Em–Ab embryonic–abembryonic axis, Pro–D proximal–distal axis, A–P anterior–posterior axis

In the mouse, the initial process to develop A–P asymmetry has been poorly understood, although several recent reports showed that early A–P molecular asymmetry can be traced back at least to the peri-implantation embryos.

The fertilized mouse egg undergoes cell divisions, increasing the number of blastomeres, and reaches the early blastocyst stage at E3.5 (Fig. 2.1). The early blastocyst is composed of two types of cells: inner cell mass (ICM) and trophoblast (TE). The ICM contributes to the future embryonic tissues whereas TE contributes

to placental tissues (Yamanaka et al. 2006). The orientation of ICM and its cavity defines the embryonic–abembryonic (Em–Ab) axis of the blastocyst. In the late blastocyst, the Em–Ab axis corresponds to the proximal–distal (Pro–D) axis, in reference to the site of implantation within the mesometrial tissue of the uterus. At this stage, the ICM has contributed to two cell lineages: the PrE and the epiblast (Epi). The PrE first appears as an epithelial monolayer adjacent to the blastocoelic cavity. By E5.5, the PrE gives rise to the VE, lining the surface of the Epi, and to the parietal endoderm (PE), which is located along the TE. A subset of VE cells that are located at the distal tip of the embryo at E5.5 is called the DVE. DVE cells start to migrate toward the future anterior side. At E6.5, AVE cells are indeed located on the anterior side (Rossant and Tam 2009; Takaoka and Hamada 2012). The AVE-derived signals induce head structures on the nearby Epi and primitive streak (PS) on the opposite side; this is followed by the development of head–tail patterning and segmentation in embryos (Tam and Loebel 2007) (Fig. 2.1).

In this chapter, I discuss the mechanisms of A–P axis formation in mouse embryo development concerning cell fate specification, dynamics of cellular arrangements, and effective molecular signaling (Fig. 2.2).

2.2 Origin of DVE in the Blastocyst

DVE cells express several genes such as Nodal antagonists *Lefty1* and *Cer1l* (Meno et al. 1996; Perea-Gomez et al. 2002; Yamamoto et al. 2004), as well as Wnt antagonist *Dkk1* (Kimura-Yoshida et al. 2005). It has been thought that the A–P axis is firmly established when DVE cells located at the distal tip of the embryo migrate toward the future anterior side at E5.5. By this time, the expression domains of the Nodal antagonists *Lefty1* and *Cer1l* in the VE have already been shifted toward the future anterior side. Although the aforementioned asymmetrical cell organization clearly indicates the A–P difference, recent investigations based on fate mapping of *Lefty1*-expressing cells and live imaging of individual cells suggested that DVE cells are derived from *Lefty1*-expressing cells of the late blastocyst (Fig. 2.2). *Lefty1*-expressing cells arise as a small cluster in the PrE of late blastocysts. This asymmetrical expression may determine the future direction of the A–P axis, and the origin of the A–P axis can be traced back to the peri-implantation stage from the egg cylinder stage.

How is asymmetrical *Lefty1* expression induced to a subset of PrE cells? Three possible models can be considered. Expression of *Lefty1* is regulated by Nodal signaling in PrE cells via the activation of an enhancer (APE) located in the upstream region of the *Lefty1* gene, in response to *Nodal*/*Foxh1* signal inputs. Thus, a possible model is that a component of Nodal signaling system is expressed in an asymmetrical manner. However, Nodal ligand, Nodal-downstream transcription factor FoxH1, and Nodal co-receptor Cripto are uniformly expressed in the Epi and VE cells from the late-blastocyst to early-egg cylinder stage. (Takaoka et al. 2006). An unknown factor required for Nodal signaling may be expressed asymmetrically.

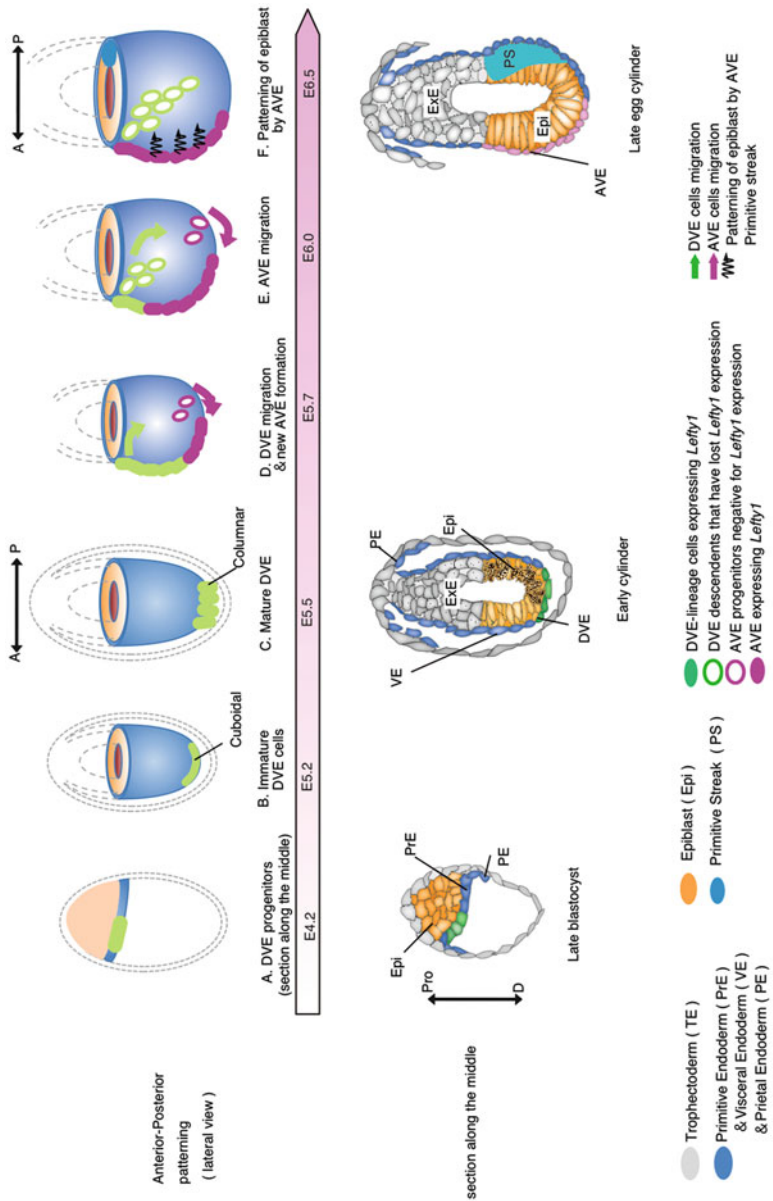


Fig. 2.2 A–P axis formation during mouse embryo development: origins and migrations of the DVE and the AVE in embryo patterning along the A–P axis. The DVE lineage is shown in *green* and the AVE lineage is shown in *purple cells*; *solid coloring* indicates cells that express *Lefty1*, whereas coloring only in outline indicates cells without *Lefty1* expression. **(a)** At E4.2, *Lefty1* is expressed in the DVE progenitors (*green*). **(b)** Immature DVE cells, which maintain *Lefty1* expression but are negative for other DVE markers such as *Cer1l* and *Hex*, are found at the distal tip of the embryo at E5.2. **(c)** At E5.5, matured DVE cells express *Lefty1* and other DVE markers. Shapes of DVE cells change to columnar. DVE cells migrate to the future anterior side of the embryo. **(d)** At E5.7, DVE cells migrate away from the distal tip, and VE cells negative for *Lefty1* expression (*open magenta shapes*) move to the distal tip and become new AVE cells. **(e)** At E6.0, DVE cells that have reached the embryonic/extra-embryonic junction migrate laterally and lose expression of DVE markers, including *Lefty1*. AVE cells remain newly generated at the distal tip and also migrate toward the proximal side. **(f)** At E6.5, the AVE occupies the anterior side of the embryo, and creates A–P patterning in the Epi. AVE anterior visceral endoderm, DVE distal visceral endoderm, E embryonic day, *Epi* epiblast, *Exe* extra-embryonic ectoderm, *PrE* primitive ectoderm, *PS* primitive streak, *VE* visceral endoderm, *Pro–D* proximal–distal axis, *A–P* anterior–posterior axis

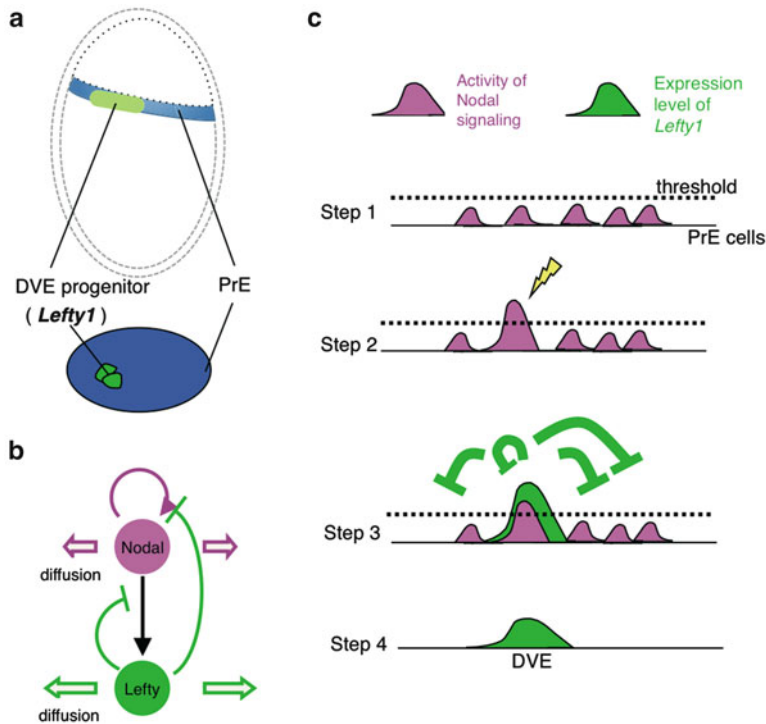


Fig. 2.3 Model for the self-enhancement lateral inhibition (SELI) mechanism in DVE formation. (a) Observation: *Lefty1*-positive cells (green), putative DVE progenitors, appear as a very small population of PrE cells (blue). (b) Scheme of cross-regulation between Nodal and Lefty 1. Lefty1 (green) is induced by Nodal signaling (magenta), and Nodal signaling is inhibited by a negative feedback. (c) Model: PrE cells have a threshold for the Nodal signaling activity that allows *Lefty1* activation (step 1). By a stochastic mechanism, the activity of Nodal signaling exceeds the threshold in a fraction of PrE cells (yellow arrows, step 2). Then, Lefty1 expression is activated in these cells, and the activated Lefty1 inhibits Nodal signaling in other PrE cells (step 3). The DVE is formed (step 4)

The second model assumes crosstalk of these signaling systems with other signaling pathways. Wnt is a candidate signaling system that crosstalks with other systems. The nuclear localization of β -catenin, which is indicative of active Wnt signaling, was observed in late blastocysts detected in a single Epi cell that faces the PrE (Chazaud and Rossant 2006). In addition, investigation on microarray profiling of β -catenin mutant embryos identified *Cripto*, a Nodal co-receptor, as a β -catenin target gene (Morkel et al. 2003). These results suggest that *Nodal* signaling is readily activated with Wnt signal input.

The third model, the restriction of *Lefty1* expression to a subset of ICM cells, involves a self-enhancement lateral inhibition (SELI) mechanism, which amplifies a small difference of *Nodal* signaling activities into a robust asymmetry, as has been demonstrated for the left–right embryo patterning (Nakamura et al. 2006; Nakamura and Hamada 2012) (Fig. 2.3). Lefty1 is induced by Nodal signaling, and Nodal is

regulated by the *Activin/Nodal* signaling-dependent enhancer of *Nodal* (ASE) in a subset of ICM cells (Granier et al. 2011). These coordinated activities of *Nodal* and its feedback inhibitor *Lefty* meet the requirements for the SELI system.

2.3 Maturation of DVE and DVE Migration

From E4.5 to E5.5, expression of *Lefty1* is cell autonomously maintained in the DVE progenitor to mature DVE cells. At E5.5, a greater variety of genes such as *Cer11*, *Hex*, and *Dkk1* are expressed in the DVE, suggesting that signaling systems change as the DVE cells become mature. In this signaling system, bone morphogenetic protein (BMP) signaling plays an important role. *BMP4*, which is expressed in ExE (extra-embryonic ectoderm) cells, generates a gradient of BMP signaling in the embryonic Epi and VE tissues. The DVE progenitors are confined to the distal tip of embryos corresponding to the BMP signaling-negative portion from E5.2 to E5.5. The BMP signaling thus restricts the DVE region to the distal tip of embryos. Indeed, ExE-removed embryos show an expansion of the DVE region (Rodriguez et al. 2005; Yamamoto et al. 2009) (Fig. 2.4).

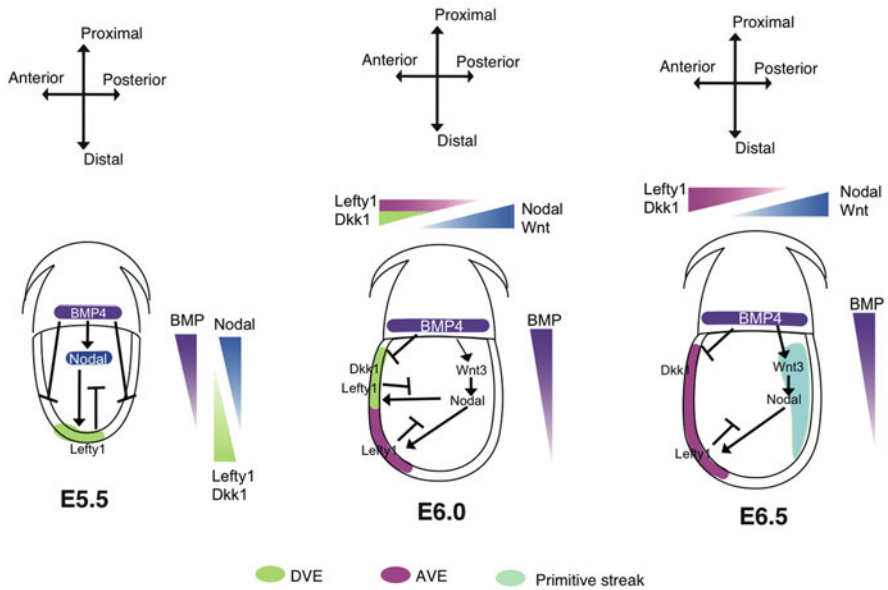


Fig. 2.4 Changes in the network of signaling systems during the developmental stages for DVE migration and AVE formation. Major changes in the spatial organization of the signaling system are caused by the migrations of DVE (green) and AVE (magenta) cells. After E5.5, the DVE migration transforms the P–D differences in the signaling systems into the A–P differences. At E6.0 and E6.5, signals from the AVE specify the nearby Epi by inhibiting Nodal signaling and Wnt signaling. On the opposite side far from the AVE, Nodal and Wnt signaling remains active, which results in the formation of the primitive streak (light blue). Activities of bone morphogenetic protein (BMP), Nodal, and Wnt are indicated by purple and blue triangles, respectively

Alongside their maturation, DVE cells migrate to the future anterior side of the early egg cylinder embryos. Immediately before their migration, three morphological changes take place in the DVE cells. The first is “visceral endoderm thickening” (VET), which makes the entire VE a monolayer of tall columnar cells (Rivera-Perez et al. 2003; Srinivas 2006; Takaoka et al. 2011) (Fig. 2.2).

Second, lamellipodia- and filopodia-like structures are formed in migrating DVE cells (Rakeman and Anderson 2006; Migeotte et al. 2010). In the VE-specific conditional mutant embryo lacking the Rho family GTPase Rac1, a component of WAVE complex (a regulator of the actin cytoskeleton), the lamellipodia- and filopodia-like structures fail to form. As a result, DVE cells fail to migrate away from the distal tip. In *Nap1* mutant embryos also, lacking a component of WAVE complex, DVE cells fail to migrate (Rakeman and Anderson 2006). These observations indicate that dynamic cytoskeletal reorganization regulated by the WAVE complex is required for the correct DVE migration.

Third, at a more macroscopic level, DVE cells form multicellular rosettes. Rosettes of five or more cells, sharing a central vertex, are formed in the simple epithelium of VE during the migration of DVE. Formation of the cellular rosettes depends on PCP signaling, and is supposed to buffer the structural disturbance in cell packing in an epithelium caused by DVE migration (Trichas et al. 2012).

2.4 The Direction of the A–P Axis

At E5.5, DVE cells migrate to the future anterior side. It is a critical issue whether the direction of A–P is determined before the DVE migration. First, several studies suggest that embryos have A–P asymmetry before the DVE migration. One suggestion is that the expression domains of the Nodal antagonists *Lefty1* and *Cer11* are already shifted toward the future anterior side before E5.5. Forced expression of Nodal antagonist *Lefty1* at E5.2 causes asymmetry in Nodal signaling and initiates the migration of DVE (Yamamoto et al. 2004). Similarly, Wnt antagonist and *Dkk1* expression domains change dynamically between before and after DVE migration, and the ectopic activation of *Dkk1* can alter the direction of DVE cell migration (Kimura-Yoshida et al. 2005). These reports suggested that embryos may have A–P pre-patterning before E5.5. However, DVE still migrates unilaterally toward the proximal side in mutant mice that lack both *Lefty1* and *Cer11* (Perea-Gomez et al. 2002; Yamamoto et al. 2004) or those lacking *Dkk1* (del Barco Barrantes et al. 2003). The lack of migration defects in these mutant embryos may be caused by functional redundancy between Nodal-dependent and Wnt-dependent mechanisms. The process that determines the direction of the A–P axis may involve parallel mechanisms.

2.5 Role of DVE and AVE

Recent investigations have indicated that the descendant of the DVE contributed mainly to the most proximal portion of AVE and VE in the lateral region, but not to the entire AVE (Fig. 2.2). Time-lapse observation of DVE migration and AVE formation showed that the extensive movement of VE cells is initiated by DVE migration at E5.5 (Takaoka et al. 2011). While DVE cells migrate, the majority of AVE cells are newly formed at the distal end, migrate toward the proximal side following DVE migration, and eventually occupy the entire region of the AVE (Takaoka et al. 2011) (Fig. 2.2).

What is the role of the DVE in AVE formation? In DVE-ablated embryos caused by genetic manipulation, AVE cells are newly formed at the distal end but fail to migrate. Under this condition, extensive movement of VE cells does not occur, and the migration of the AVE cells is stalled (Takaoka et al. 2011). For instance, in mutant embryos lacking *Cripto*, a coreceptor of Nodal, the AVE is formed in the absence of DVE but does not migrate at all (Chu and Shen 2010). These observations suggest that the DVE guides the AVE to the anterior side by initiating extensive movement of visceral endoderm cells.

AVE cells function as head organizer by expressing a few signal protein antagonists, that is, Nodal antagonists *Lefty1* and *Cerl1*, and Wnt antagonist *Dkk1*. These antagonists protect nearby Epi cells from posterior-inducing Wnt and Nodal signaling (Fig. 2.4), specifying AVE-underlain Epi to head tissue. In fact, explant culture assays have shown that Epi cells without VE will adopt the posterior identity, whereas implanted AVE cause Epi to assume an anterior identity (Kimura et al. 2000).

2.6 Reinterpretation of Embryo Phenotypes Defective in A–P Axis Formation

It had been believed that the mature DVE is the direct precursor for the entire AVE and its migration toward the future anterior side away from the distal tip is the mechanism of AVE formation (Beddington and Robertson 1999) (Fig. 2.5). However, the recent observation that DVE does not contribute to the major part of AVE renders it necessary to reinterpret the phenotypes of previously reported mutant mouse embryos based on the following four criteria: (1) DVE formation; (2) DVE migration; (3) AVE formation; and (4) AVE migration (Table 2.1).

In *Nodal*-null (Waldrip et al. 1998; Mesnard et al. 2006) and *Smad2*-null (Waldrip et al. 1998) mutants, the Epi is specified to neural tissues precociously, and neither DVE nor AVE forms (Fig. 2.6). In *Cripto*-null (Ding et al. 1998; Chu and Shen 2010) and *Eomes* VE-conditional null embryos, *Cerl1*, a DVE marker, is expressed at very reduced levels or not at all at E5.5. *Cerl1*-positive AVE cells are newly formed close to the distal tip of the mutant embryo from E6.0 to E6.5, but they fail to migrate proximally and remain at the distal tip of the embryo, as in the

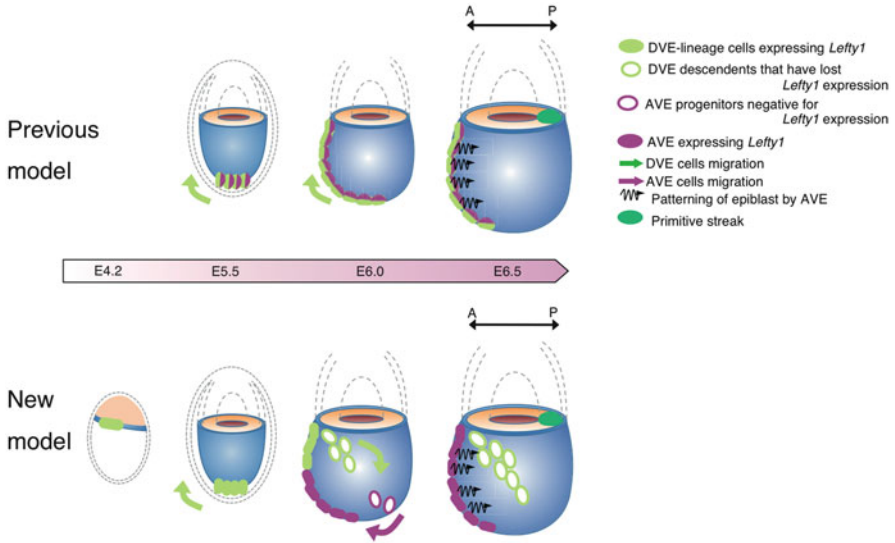


Fig. 2.5 Comparison of previously proposed model and current model concerning the roles of DVE in AVE formation. Previous model (*upper*): The DVE is specified at the distal tip of the embryo at E5.5, then migrates toward the anterior and proximal side to form the AVE. It has been thought that all AVE cells are derived from DVE. New model (*lower*): Origin of the DVE can be traced back to the *Lefty1*-positive primitive endoderm cells. The migration of DVE cells triggers global VE movements, and AVE cells are newly produced at the distal tip. In the proximally located migrating cells, DVE markers are lost. At E6.5, newly formed AVE cells occupy the anterior side of VE cells

DVE-ablated embryo (Takaoka et al. 2011; Morris et al. 2012) (Fig. 2.6). In other mutants also, such as *Otx2*-null (Kimura-Yoshida et al. 2005), *Rac1*-null (Sugihara et al. 1998; Migeotte et al. 2010), and *Pten*-null (Bloomekatz et al. 2012) mutants, the DVE is formed at the distal dip at E5.5, but fails to migrate. Thus, cells that express DVE/AVE markers remain close to the distal tip of the embryo at E6.0 and E6.5 (Fig. 2.6). These observations indicate that the major role of DVE is to guide the AVE migration.

2.7 Conclusion

The A–P axis of mouse embryos is fully established by the directed movement of DVE and AVE cells, the latter known as s head organizer. DVE progenitor cells are distributed on one side of the primitive endoderm cells at E4.2. The direction of the A–P axis of later embryos may depend on this asymmetry. At E5.5, DVE cells that express Nodal antagonists *Lefty1* and *Cer1*, and Wnt antagonist *Dkk1*,

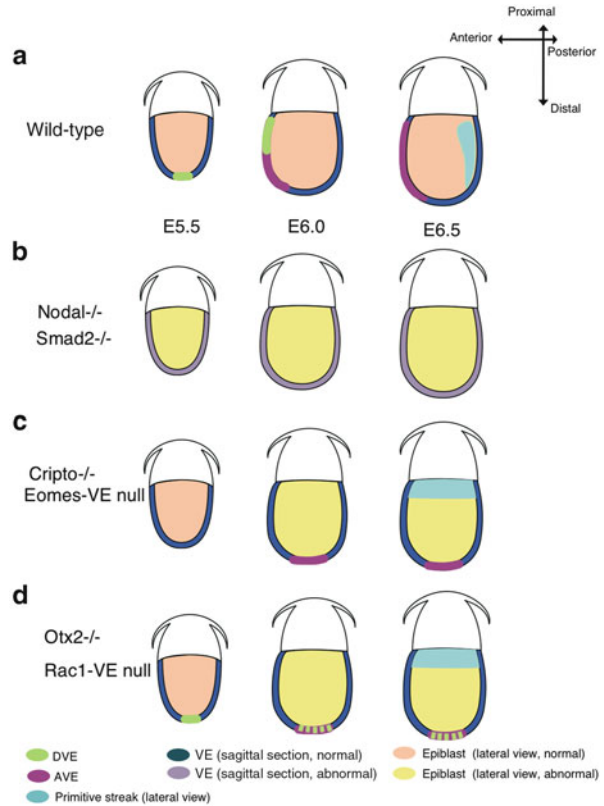
Table 2.1 Reinterpretation of mutant mouse phenotypes that include defective anterior visceral endoderm (AVE) formation

Gene	Genetic modification	DVE formation at E5.5	DVE migration	AVE formation at E6.5	AVE migration	References
<i>Nodal</i>	Null	No	–	No	–	Brennan et al. (2001), Camus et al. (2006) and Mesnard et al. (2006)
<i>Smad2</i>	Null	No	–	No	–	Nomura and Li (1998) and Brennan et al. (2001)
<i>Cripto</i>	Null	No	–	Yes	No	Ding et al. (1998), Kimura et al. (2001) and Chu and Shen (2010)
<i>Eomes</i>	VE-specific null	Low	No	Yes	No	Nowotschin et al. (2013)
<i>Otx2</i>	Null	Yes	No	Yes	No	Kimura et al. (2000, 2001) and Kimura-Yoshida et al. (2005)
<i>Rac1</i>	VE-specific null	Yes	No	Yes	No	Migeotte et al. (2010)
<i>Lefty1</i>	Null	Expansion	Yes	Yes	Yes	Yamamoto et al. (2004)
<i>Lefty1</i> <i>Cer1l</i>	Double null	N.D.	N.D.	Yes	Delay	Perea-Gomez et al. (2002) and Yamamoto et al. (2004)

become mature and migrate to the future anterior side. Immediately before their migration, morphological changes occur in the VE cells, namely, visceral endoderm thickening, formation of lamellipodia- and filopodia-like processes, and organization of multicellular rosettes. DVE migration toward the future anterior side has the role of guiding the AVE cells to the anterior side of the egg cylinder embryo, and triggers extensive rearrangement of visceral endoderm cells in a wide area.

Important questions that remain to be answered are these: how are DVE progenitors selected among PrE cells in the blastocyst, and at which stage of development is the direction of DVE migration determined?

Fig. 2.6 Grouping of mouse mutant phenotypes defective in the A–P axis development. (a) Wild-type embryos. (b) Precocious neural differentiation occurs in the Epi; thus, the DVE and the AVE fail to form throughout E5.5 and E6.5 stages. (c) The DVE does not form at E5.5. The AVE is newly formed at the distal tip at E6.0 but fails to migrate. As a result, Epi cells with posterior identity develop at the proximal side of the embryo. (d) The DVE forms at the distal tip of the embryo at E5.5 but fails to migrate. Cells positive for DVE/AVE markers remain at the distal tip at E6.0 and E6.5. As a result, Epi cells with posterior identity develop at the proximal side of the embryo, similar to (c)



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