ABSTRACT  An increasing amount of evidence suggests that in mouse there are two signalling centres required for the formation of a complete neural axis: the anterior visceral endoderm (AVE), and the node and its derivatives. Embryological and genetic studies suggest that the AVE has a head-inducing activity. In contrast, the node appears to act first as a head inducer in synergy with the AVE initiating anterior neural patterning at early stages of mouse development, and later, node derivatives are necessary for maintenance and embellishment of anterior neural character. Hex and Hesx1 are homeobox genes that are expressed in relevant tissues involved in anterior patterning. The analysis of the Hex and Hesx1 mutant mice has revealed that the lack of these genes has little or no effect on the early steps of anterior neural induction. However, both genes are required subsequently for the proper expansion of the forebrain region. We suggest that disturbance in the specification of an Fgf8 signalling centre in the anterior neural ridge may account for the anterior defects observed in these mutants.

KEY WORDS: Hex, Hesx1, forebrain, Fgf8, mouse.

Introduction

Classical experiments by Spemann and Mangold (1924) identified a specific group of cells in the dorsal lip of the blastopore of the amphibian gastrula, the organizer, which was sufficient to induce a complete secondary axis when grafted into the ventral region of a host embryo. Histological analysis revealed that in this ectopic axis the notochord derived from the grafted tissue but the neural tube was composed mostly of host cells, thus demonstrating that the dorsal blastopore lip contained an activity capable of changing the fate of the surrounding tissues. Spemann also showed that the inducing activities of the organizer were stage dependent. Transplantation of the early gastrula organizer induced complete ectopic axis whilst grafts of equivalent tissues of a late gastrula organizer induced partial secondary axes lacking the head region (Spemann, 1931). These experiments promoted the idea that separate head and trunk organizers existed.

Based on the cell fate and inductive properties of the grafted tissue, homologous organizers have been described in all vertebrates: the embryonic shield in zebrafish, Hensen’s node in chick and the node in mouse. As in Amphibia, the zebrafish and chick organizers contained head and trunk inductive activities that together can induce a complete ectopic axis (Waddington, 1933; Storey et al., 1992; Zoltewicz and Gerhart, 1997; Saude et al., 2000). In mouse, transplantation of the node has been conducted using donor tissue isolated from full-length and early-streak mouse embryos. Although, secondary neural axes were induced, the midbrain and forebrain regions were absent (Beddington, 1994; Tam and Steiner, 1999). These results indicate that in the mouse the induction of the anterior aspects of the neural tube requires developmental information not provided solely by the node and its derivatives.

Gene targeting studies in mice have identified a number of homeobox genes and signalling molecules required for head formation (Beddington and Robertson, 1999). Chimeric analysis has demonstrated the requirement of these genes in the visceral endoderm for the initiation of forebrain and midbrain development. Based on these results and ablation experiments in mouse, a two step model for anterior neural induction has been proposed. This model suggests that the anterior visceral endoderm (AVE) is responsible for the initial induction of the rostral identity in adjacent ectoderm, and that subsequently this identity is maintained and elaborated by axial mesendoderm (AME). However, recent ge-
The establishment of an Fgf8 signalling centre in the anterior neural ridge expansion of the prospective forebrain region requires the establishment of anterior neural character, and suggests that the definitive endoderm (ADE), derived from the node, is required for the maintenance of anterior neural character, and suggest that the expansion of the prospective forebrain region requires the establishment of an Fgf8 signalling centre in the anterior neural ridge (ANR) at early somite stages.

**AVE is required for anterior patterning**

At 5.5 dpc, the mouse embryo is comprised of an inner cell layer called epiblast, which gives rise to the embryo proper and the mesodermal constituent of extraembryonic tissues, and an outer cell layer of visceral endoderm destined to populate only the visceral yolk sac (Fig. 1). Cell lineage studies have shown that the antecedents of the AVE are located at the distal tip of the 5.0 dpc embryo and are fated to move anteriorly by the onset of gastrulation at 6.5 dpc. This “rotation” of distal visceral endoderm cells to its final anterior position is probably in concert with movements of the proximal anterior epiblast towards the posterior side of the embryo where the primitive streak will form. Soon after the onset of gastrulation epiblast cells ingress through the streak to form new cell layers: the embryonic and extraembryonic mesoderm and the definitive endoderm. The mesoderm is intercalated between the endoderm and ectoderm. The definitive endoderm is inserted into the visceral endoderm layer, thus displacing it into the extraembryonic region.

Different lines of evidence have shown the necessity of extraembryonic tissues, and more specifically the AVE, if a normal head is to be formed (Beddington and Robertson, 1999). Genetic evidence supporting a role of the AVE in anterior patterning has been obtained from the analysis of the Hnf3ß, Otx2 and Lim1 mutants (Table 1). Embryos homozygous for mutations in these genes exhibit brain deletions rostral to the otic vesicle (Ang and Rossant, 1994; Acampora et al., 1995; Shawlot and Behringer, 1995). The lack of brain tissue occurs early during gastrulation due to a failure in induction of the anterior neural plate. Rostral neural markers such as Six3, Pax2 (Acampora et al., 1998; Rhinn et al., 1998), Otx2 and En (Ang and Rossant, 1994; Shawlot and Behringer, 1995) were absent or reduced in these mutants at 7.5 dpc. Originally, these anterior defects were supposed to be due to the absence or abnormality of the node and prechordal plate (Bally-Cuif and Boncinelli, 1997). However, recent studies have shown that the expression of AVE markers is either reduced and/or mislocalised in these mutants. In 7.5 dpc Lim1<sup>−/−</sup> mutants, the Cerl expression domain is reduced and located near the distal tip of the embryo, presumably in cells which may correspond to the AVE that failed to move anteriorly (Shawlot et al., 1998). In Otx2<sup>−/−</sup> mutants...
not only Cerrl but also Lim1 and Hesx1 expression domains in the AVE are abnormally localised in the distal region of the embryo at 6.5 dpc (Acampora et al., 1998; Rhinn et al., 1998). In Hnf3ß-/- embryos, diminished Cerrl expression is detected in approximately 50% of 7.5 dpc mutants. At 6.5 dpc Hnf3ß -/- embryos show accumulation of visceral endodermal cells at the distal tip of the embryo (Ang and Rossant, 1994; Klingensmith et al., 1999), which may be due to a disturbance in cell movements that normally move distal visceral endoderm at 5.5 dpc to an anterior-proximal position at the onset of gastrulation (Fig. 1). However, defects in the patterning and/or localisation of the AVE of these mutants do not demonstrate the requirement of these genes in the visceral endoderm for anterior neural induction.

Previous studies have shown that ES cells injected into a host blastocyst colonise all epiblast derivatives, but very rarely the visceral endoderm (Beddington and Robertson, 1989). Taking advantage of this developmental bias, it was possible to generate chimeric embryos where the embryo proper was of one genotype and the visceral endoderm of another. For example, chimeric embryos composed predominantly of Otx2+/+ epiblast cells developing within Otx2-/- visceral endoderm (Otx2+/+ <-> Otx2-) gave rise to chimeras showing identical brain deletions to those observed in the Otx2-/- mutants. In contrast, the converse experiment (Otx2-/- <-> Otx2+/-) has shown that wild-type visceral endoderm can rescue the early anterior neural defects in chimeric embryos at 7.5 dpc, thus providing irrefutable evidence that Otx2 is first required in visceral endoderm for normal brain formation (Rhinn et al., 1998; Acampora et al., 1998). Likewise, the function of nodal, Hnf3ß, and Lim1 function in the visceral endoderm is necessary for normal forebrain and midbrain development (Varlet et al., 1997; Dufort et al., 1998; Shawlot et al.,...
Embryological evidence for a role of the AVE in anterior neural patterning has been provided from ablation experiments in mouse. Removal of the anterior region of the visceral endoderm during the earlier stages of gastrulation either prevents or severely impairs the expression of the hindbrain marker Gbx2 (Thomas and Beddington, 1996). Together these experiments indicate that the AVE is required to establish the anterior identity of the neural plate.

**AVE is not sufficient for anterior neural induction**

Although there is much evidence to support the necessity of the AVE for normal induction of the midbrain and forebrain regions of the neural tube, the mouse AVE is not sufficient for this inductive process. Recent transplantation experiments in mouse have shown that the AVE and the early gastrula organizer (EGO) are both required for the induction of anterior neural structures. The term EGO has been used by P. Tam and co-workers to define a group of posterior epiblast cells located at the tip of the primitive streak of the early-streak mouse embryos that display cell fates, gene expression and patterning activity characteristic of the morphologically recognisable node at full-length streak stages (Tam et al., 1997). Fragments of the posterior epiblast containing the EGO transplanted to the lateral region of the late-streak embryo are able to recruit host cells to form a partial neural axis, but one that lacks the AVE markers mislocalised at the distal tip of the early-streak mutant embryos. Interestingly, the embryonic ectoderm fails to express the brain markers Otx2, Hesx1 and En1 (Huelsken et al., 2000).

In contrast, in Fgfl8-/- mutants the EGO is properly formed as judged by normal expression of the early node markers T, Lim1, Hnf3β and Gsc. The AVE is also correctly specified but fails to be displaced proximally into the extraembryonic region at streak stages, presumably because there is no anterior movement of definitive endoderm cells. This results in an expansion of the forebrain and midbrain markers Hesx1, Six3 and Otx2 and absence of the hindbrain marker Gbx2, thus resembling a head without a trunk (Sun et al., 1999). Likewise, Cripto-/- mutants show expression of the EGO markers T, Lim1, Fgfl8 and Gsc in the proximal epiblast, and the AVE is properly specified but mislocalised distally at 6.5 dpc. As in the Fgfl8-/- mutants, the overlying ectoderm expresses only forebrain and midbrain markers (Ding et al., 1998). Taken together with the analyses of Wnt3 and β-catenin mutants, these experiments indicate that the absence of the early node results in a failure of the AVE to induce anterior neural character in the overlying epiblast, suggesting that the AVE is not sufficient for initiating anterior patterning on its own.

However, heterospecific transplantation experiments have shown that the prestreak rabbit AVE is able to induce anterior neural character in prospective epidermal and extraembryonic cells in chick host embryos (Knoetgen et al., 1999). Differences in
neural inducing activity between the mouse and rabbit AVE might be correlated with the size of the tissue used in the graft. The prestreak rabbit embryo is about 2.5 times larger than the mouse embryo at the same stage, and thus the amount of inducing signals produced by the grafted rabbit AVE may be sufficient to induce neural character, whilst the mouse AVE may not. Alternatively, factors other than the mass effect, such as competence of the responding tissue or the manner in which the tissues are grafted, might explain these differences in the inducing activity of the mouse and rabbit AVE. It should be noted that in these transplantation experiments what is thought to be the chick equivalent of the AVE the hypoblast, also fails to induce anterior neurectoderm.

**AVE and EGO cooperate in the initial induction of the anterior neural plate**

From the results discussed above, it seems likely that the initiation of anterior neural induction requires the cooperation of the inductive activities of two signalling centres: the AVE and the EGO. Important questions that remain to be answered are when does this cooperation takes place during mouse development and which signals are involved. Genetic evidence and grafting experiments suggest that the initiation of anterior neural patterning might occur at the onset of gastrulation. At 6.5 dpc, the absence of a normal EGO results in failure of the AVE to bestow anterior character in the overlying ectoderm later in development (Liu et al., 1999; Huelsken et al., 2000). Whereas the epiblast overlying the AVE acquires anterior neural character when the EGO is correctly specified (Ding et al., 1998; Sun et al., 1999). However, it is possible that the AVE and EGO together might sensitise the epiblast before overt gastrulation starts so that it can be induced to form neural tissue.

Fate map studies of late prestreak or early streak embryos have shown that there is a net caudal movement of proximal epiblast towards the primitive streak during gastrulation (Lawson et al., 1991). The translocation of the primordial germ cell precursors, which derive from the most proximal epiblast, to the posterior side of the early streak embryo suggests that these unilateral movements of proximal epiblast occur very early in gastrulation (Lawson and Hage, 1994). As mentioned above, the EGO is localised at the distal tip of the primitive streak of the early gastrula, thus suggesting that cells that form the EGO might come from the proximal epiblast. Clonal analysis of proximal epiblast has shown that 6.0 dpc epiblast cells located within 60 µm of the embryonic/extraembryonic boundary, while contributing the bulk of their descendants to extraembryonic mesoderm, can also contribute to the distal tip of the primitive streak, axial mesendoderm and node region (K. Lawson, personal communication). The expression patterns of T and *nodal* are also suggestive of the node being derived from the proximal epiblast. *T* is expressed in the proximal rim of the epiblast at prestreak stages, and later in the primitive streak and node region (Wilkinson et al., 1990; Thomas et al., 1998). nodal is expressed throughout the embryonic epiblast before gastrulation and becomes restricted to the primitive streak and node region as gastrulation proceeds. However, recently it has been reported that distinct regulatory elements drive nodal expression in the proximal versus the distal epiblast, thus suggesting a regionalisation of the embryonic epiblast before the onset of gastrulation (Norris and Robertson, 1999). Likewise, the expression patterns of Wnt3, β-catenin, Cripto and Fgf8 at prestreak stages suggest that proximal and distal epiblast cells have distinct molecular identities (Ding et al., 1998; Liu et al., 1999; Sun et al., 1999; Huelsken et al., 2000). In this scenario it is tempting to speculate that the AVE and the proximal epiblast might initiate the patterning of the prospective anterior neural plate prior to the onset of gastrulation or mesoderm formation. As a result of this early induction at prestreak stages the epiblast might become competent to respond to anteriorising signals later in development. The continuing influence of the AVE on the overlying epiblast during prestreak and streak stages would allow that region to acquire anterior neural character and express forebrain and midbrain markers. More posterior epiblast, away from the anteriorising activity of the AVE, would be under the influence of posteriorising signals emanating from the node, primitive streak and/or mesoderm as gastrulation proceeds, and would give rise to hindbrain and spinal cord regions of the neural plate.

The nature of the signals involved in this interaction has been investigated mainly in *Xenopus*. The current model proposes that the formation of anterior neural structures requires the inhibition of both TGFβ and Wnt signalling pathways by secreted factors such as cerberus, frzb-1, dickkopf-1, chordin and noggin (Glinka
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et al., 1997; Niehrs, 1999; Piccolo et al., 1999). In mouse, the genes encoding TGFβ and Wnt inhibitors are expressed in relevant tissues for head formation such as the AVE, the node and its derivatives (Beddington and Robertson, 1999; Glinka et al., 1998; Niehrs, 1999). However, gene inactivation studies for some of these genes have shown no effect on the initiation of anterior neural patterning. Embryos deficient for either Cerl, Noggin or chordin, for example, did not display any head abnormalities (Simpson et al., 1999; Bachiller et al., 2000). Even the Noggin;Chordin double homozygous mutants showed anterior truncations compatible with a function in the maintenance of the anterior character rather than in the initial neural induction. (Bachiller et al., 2000). These data suggest that either the level of genetic redundancy in the mouse embryo is very high or alternatively, other signals might be involved in the initial steps of anterior neural induction.

The maintenance of anterior neural character requires ADE

Once the initial patterning of the neural plate is set up by the activities of the early node and AVE, this has to be maintained and refined later in mouse development. Different lines of evidence have invoked the anterior mesendoderm as maintaining the anterior character of the neural plate. The anterior axial mesendoderm (AME) is composed of different cell populations including ADE fated to form the liver, the prechordal and the anterior notochordal plate (Sulik et al., 1994; Thomas et al., 1998). Tissue recombination experiments have shown that positive signals emanating from the anterior mesendoderm are required for the stabilisation of Otx2 expression whilst negative signals from posterior mesendoderm can actively repress Otx2 expression in the explants (Ang et al., 1994). Likewise, anterior mesendoderm induces the expression of Engrailed genes in explant cultures (Ang and Rossant, 1993). Chimeric analysis has provided genetic evidence for an essential role of the AME in brain formation. These studies have demonstrated the necessity of Lim1 in the AME to maintain anterior character in the overlying neurectoderm (Shawlot et al., 1999). The severe AME defects observed in the Otx2−/− mutants also suggest an important role of this gene in the AME for normal brain formation (Acampora et al., 1998; Rhinn et al., 1998). Analysis of the Hex null mutant mouse has allowed us to dissect further the function of the ADE in anterior patterning (Martinez-Barbera et al., 2000a).

Hex is expressed in the AVE of prestreak embryos and, as gastrulation proceeds, expression appears in a second domain of definitive endoderm cells at the distal tip of the elongating streak (Fig. 2 A-D; Thomas et al., 1998). Hex−/− embryos exhibit varying degrees of anterior truncation ranging from none to a severe lack of forebrain tissue (Fig. 3 A-C). Interestingly, even in the most severely affected Hex−/− mutants, the brain truncations are restricted to the forebrain tissue (Fig. 3 A-C). Intriguingly, even in the most severely affected Hex−/− mutants, the brain truncations are restricted to the forebrain tissue rostral to the zona limitans intrathalamica (ZLI), the boundary between dorsal and ventral thalamus (Rubenstein et al., 1998). Analysis of Hex and Six3 expression during neurulation revealed that the presumptive forebrain region was correctly patterned at 7.5 dpc as expression of these neural markers in the anterior neural ectoderm was indistinguishable from wild-type littermates (Fig. 4 A-D). Therefore, the Hex−/− embryos show anterior defects that are clearly different to those in the Hnf3β, Otx2 and Lim1 mutants regarding the extent and the onset of brain deletions.

These differences suggest that the mechanisms responsible for the anterior defects in the Hex mutants are different to those in the

Fig. 5. AVE is properly specified in the Hex and Hesx1 mutants. Whole-mount in situ hybridisation to Cerl. (A) Midstreak wild-type embryo showing Cerl expression in the AVE (arrow) and definitive endoderm (arrowheads). (B) Cerl expression domain in the AVE appears normal in Hex−/− embryos, but Cerl is not expressed in the definitive endoderm of these embryos. (C,D) Lim1 expression is reduced in the AME and appears expanded in the node region of the Hex−/− mutants when compared with wild-type littermates. (E,F) Midstreak wild-type (E) and Hesx1−/− (F) embryos exhibit normal Cerl expression in the AVE (arrow) and definitive endoderm (arrowhead). Bar, 75 μm.
Hnf3β, Otx2 and Lim1 mutants, where the AVE is incorrectly patterned and/or fails to move from the distal tip of the early embryo. This leads to a failure in the induction of the forebrain and midbrain at 7.5 dpc (Dufort et al., 1998; Rhinn et al., 1998; Acampora et al., 1998; Shawlot et al., 1999). In contrast, in the 7.5 dpc Hex−/− mutants, the expression of the AVE markers Cerrl, Lim1 and Mrg1/Cited2 was normal (Fig. 5 A-D; data not shown), and the forebrain and midbrain regions were unaffected in the 7.5 dpc Hex−/− mutants. Therefore, Hex is most likely not required in the AVE for normal forebrain formation.

What then is causing the forebrain defects in the Hex mutants? At midstreak stages Hex is expressed at the distal tip of the primitive streak, in the ectoderm and endoderm layers immediately adjacent to the prospective node region (Fig. 2A; Thomas et al., 1998; Lawson et al., 1991). As gastrulation proceeds, this Hex expression domain in definitive endodermal cells extends rostrally from the presumptive node to merge with the AVE and displace it towards the extraembryonic region (Fig. 2B; Thomas and Beddington, 1996; Thomas et al., 1998). In the Hex−/− embryos the definitive endoderm was not properly patterned as Cerrl expression domain was absent in this tissue (Fig. 5 A,B). Moreover, injection of Hex−/− ES cells into wild-type blastocysts produced chimeric embryos with forebrain defects similar to those observed in the Hex−/− mutants (Fig. 6 A,B). Since injected ES cells give rise predominantly to epiblast derived tissues (Beddington and Robertson, 1989), these chimeric studies indicate that Hex is required in the ADE for normal forebrain development. In agreement with this, removal of anterior foregut endoderm in chick embryos results in similar forebrain deletions to those observed in the Hex−/− mutants (Withington et al., 2000).

Defects in the AME in the Hex mutants were apparent from the lack of Cerrl expression not only in the definitive endoderm, but also in the prechordal and notochordal plates. In addition, Hnf3β and Lim1 expression was reduced in the AME of late-streak Hex−/− embryos, and this reduction coincided with an expansion of the Hnf3β and Lim1 expression domain in the node, thus suggesting a failure in AME cells to exit the node region and move anteriorly (Fig. 5 C,D). However, Hnf3β expression was found to be normal in Hex−/− mutants at later stages of development. Therefore, it is possible that only the most rostral part of the AME, possibly the ADE and prechordal plate, are affected in the Hex mutants. Interestingly, the boundary between the notochord and the prechordal plate appears to coincide with the ZLI, which is the caudal limit of the forebrain truncations in the Hex mutants (Rubenstein et al., 1998). In summary, the analysis of the Hex mutants has provided genetic evidence for the requirement of the ADE for normal forebrain formation.

The expansion of the forebrain requires the establishment of an Fgf8 signalling centre in the ANR

How do defects in the ADE lead to the forebrain truncations observed in the Hex mutants? At the moment this is not known. However, it is possible that disturbances in vertical signalling from the ADE and/or prechordal plate to the overlying anterior neural ectoderm might impair the formation of signalling centres in the forebrain responsible for its further expansion and maturation (Rubenstein et al., 1998). One of these local inductive sources in the forebrain is the ANR, the junction between the most anterior neural plate and the non-neural ectoderm at the early somite stage (Shimamura and Rubenstein, 1997). Ablation of the ANR and tissue recombination experiments in mouse and rat suggest that the ANR is required for the induction and/or maintenance of Bf1 expression in the anterolateral neural plate, a gene essential for normal growth and differentiation of the telencephalon, and for the specification of dopaminergic neurons in the rostral forebrain (Xuan et al., 1995; Shimamura and Rubenstein, 1997; Ye et al., 1998). Interestingly, Fgf8, a secreted factor expressed in the ANR, can substitute for the ANR in both these respects (Shimamura and
Rubenstein, 1997; Ye et al., 1998). In Hex−/− mutants, Fgf8 expression in the ANR is absent or significantly reduced by the 8-10 somite stage (Fig. 7 A-D). Therefore, the forebrain truncations in the Hex−/− mutants might be due to compromising the formation of the ANR. As described below, results obtained from the analysis of the Hesx1 null mutant mouse support this interpretation (Martinez-Barbera et al., 2000b).

Hesx1 (also known as Rpx) is a member of the paired-like class of homeobox genes that is expressed in the rostral region of the embryonic neural plate, and in the AME underlying it. At 8.5 dpc, Hesx1 is still expressed in the rostral neural ectoderm, and is also detected in the oral ectoderm and anterior foregut. Later, Hesx1 expression becomes restricted to Rathke’s pouch (Fig. 2 E-H; Hermesz et al., 1996; Thomas and Beddington, 1996). Hesx1 deficient embryos show forebrain truncations that are very similar if not identical to those observed in the Hex−/− mutants (Fig. 3 D-F; Dattani et al., 1998). The forebrain defects in the Hesx1−/− mutants appear to have a caudal limit in the ZLI, which has been suggested to be the posterior boundary of the Hesx1 expression domain in the anterior neural plate of the early somite mouse embryo (Inoue et al., 2000). The onset of the forebrain defects also occurs at the early somite stage, when the Six3 expression domain in prospective forebrain becomes reduced (Fig. 4 E-H). However, Cerl expression in the AVE, ADE, prechordal and anterior notochordal plate is unperturbed in Hesx1−/− embryos (Fig. 5 E,F; data not shown). Likewise, Lim1 and Shh expression in the AME is unaffected in the Hesx1 mutants (Martinez-Barbera et al., 2000b).

Chimeric analysis has shown that Hesx1 is required in an epiblast derived tissue, most likely the anterior neural ectoderm, for normal forebrain formation (Fig. 6 C,D). Interestingly, Fgf8 expression in the ANR is reduced in the Hesx1 mutants (Fig. 7 E,F; Dattani et al., 1998).

The extent and timing of the forebrain defects in Hex+/− and Hesx1−/− embryos appear to fit with a disturbance of Fgf8 expression in the ANR and the variability of the rostral defects in these mutants may reflect the amount of Fgf8 signalling that persists. Certainly, embryos carrying an Fgf8 hypomorphic allele display variable forebrain defects, including small telencephalic vesicles and absence, or reduction, of the dorsal midline septum of the telencephalon (Meyers et al., 1998). Likewise, Oto mutants show forebrain defects associated with a reduction of Fgf8 expression in the ANR (Zoltewicz et al., 1999). Therefore, these data suggest that either the lack of Hex in the ADE or Hesx1 in the anterior neural ectoderm severely impairs the formation of the Fgf8 signalling centre in the ANR, which results in variable degrees of forebrain truncation. Therefore, the sequence of inductive steps required to make forebrain may be the following: The AVE, in synergy with the early node organizer, initiates the induction and patterning of the forebrain, while the AME emanating later from the node maintains and refines this initial pattern (Ang et al., 1994; Thomas and Beddington, 1996; Acampora et al., 1998; Tam and Steiner, 1999; Shawlot et al., 1999; Liu et al., 1999). Subsequently, local signalling centres (like the ANR) are established in the forebrain region to complete the growth and differentiation of the forebrain anlage (Rubenstein et al., 1998).

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References

Forebrain formation in mouse


