HESX1 and Septo-Optic Dysplasia

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Development of the Forebrain and Anterior Pituitary Gland

Animal studies have recently shed a considerable amount of light on the normal development of the forebrain and pituitary gland. There is now good evidence that anterior patterning in the extraembryonic endoderm (anterior visceral endoderm [AVE]) of the early mammalian conceptus occurs before there is any sign of primitive streak formation, i.e., before gastrulation. The latter is the process resulting in the formation of the primitive streak, the notochord, and the three germ layers that lead to the development of all embryonic tissues and organs [1]. This AVE has been shown to be functional in providing the embryo with anterior character and is vital for normal forebrain development. To date, we know that expression of several genes, including Otx2, Lim1, goosecoid, cerberus-related 1, and Hex, is restricted to a medial strip of the AVE underlying approximately the anterior third of the epiblast at least 12 hours before the primitive streak has formed. As the streak forms, the most anterior extreme of the AVE (in the region where the heart will develop) starts to express Mrg1. Slightly more posteriorly, where it overlies epiblast fated to give rise to oral ectoderm and forebrain, Hesxl (also known as Rpx) is expressed. Hence, as gastrulation starts, the AVE already exhibits a restricted pattern of expression of transcription factors. Mutations in a number of these genes, first expressed in the AVE and only subsequently in epiblast derivatives, affect anterior development in the mouse, with variable defects in forebrain development. These include Hesxl, Lim1, and Otx2 [2–4].

In man, the first known event in the development of the nervous system is neural induction or neurulation, whereby the neural plate, the embryonic precursor of the brain, forms in the third week of gestation. Neural plate formation is induced by the developing notochord. The notochord first forms as a median cellular cord known as the notochordal process. It then acquires a lumen called the notochordal canal. The process grows cranially between the ectoderm and endoderm until it reaches the prechordal plate, a small circular area of columnar endodermal cells which is firmly attached to the overlying ectoderm. The notochordal process then degenerates to form the notochordal plate, and this then infolds to form the notochord. The notochord defines the primitive axis of the embryo and gives it some rigidity. The developing notochord induces the overlying ectoderm to thicken and form the neural plate, the primordium of the central nervous system. The ectoderm of the neural plate, the neurectoderm, gives rise to the brain and spinal cord.

The neural plate forms as a result of the cellular interaction between the ectoderm and the mesoderm of the gastrula-stage embryo and is a planar sheet of pseudostratified neuroepithelium produced during gastrulation. The neural plate becomes regionally patterned along each of its axes and is converted into the neural tube which then differentiates into the central nervous system structures in the brain and spinal cord. Again, restricted patterns of differential gene expression are evident at the anterior neural plate stage in the human embryo, and these foreshadow the later development of morphological and functional subdivisions of the neural tube. By the fourth week of gestation, a series of ring-like constrictions mark the approximate boundaries between the primordia of the major brain regions: the forebrain or prosencephalon, midbrain or mesencephalon, and hindbrain or rhombencephalon. As the rostral neuropore closes at about 25 days of gestation, the optic vesicles appear as two lateral outgrowths on each side of the forebrain, and are the primordia of the retinae and optic nerves. A second pair of diverticula arise more dorsally and rostrally; these are the cerebral or telencephalic vesicles which are the primordia of the cerebral hemispheres, their cavities forming the lateral ventricles.

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During the fifth week, the forebrain partly divides into two regions, the telencephalon and the diencephalon. The diencephalon will give rise to the thalamus and hypothalamus.

Fate map studies in a number of species such as the chick, Xenopus, Axolotl, and Zebrafish have shown that the prospective telencephalon occupies the rostral end of the neural plate, partly overlapping the anterior neural ridge. Distributed laterally along the anterior neural ridge are sites fated to form the olfactory bulbs and the lateral, dorsal, and medial regions of cerebral cortex. Of note is the finding that the site destined to form the anterior pituitary or adenohypophysis also maps onto the anterior neural ridge. Additionally, in Xenopus, the mid-anterior ridge produces a triangular wedge of tissue extending at the midline from the chiasma ridge to the lamina terminalis and laterally into the optic stalks (for review, see [5]).

Several lines of molecular and genetic evidence now suggest that medial and ventral specification of the forebrain is regulated by the prechordal plate, an axial mesendodermal structure. Forebrain development is highly complex and it is clear that a number of genes are implicated in this process. These include Sonic Hedgehog, Fgf8, Hexx1, HNF3β, Nkx2.1, Nkx2.2, Lim1, Otx1, Otx2, Cerberus, goosecoid, Pax6, Six3, Emx1, and Emx2. The exact role of many of these genes remains to be defined. Nevertheless, since the forebrain, eyes, optic chiasm, olfactory bulbs, adenohypophysis, and hypothalamus originate from the same region in the embryo, defects of some of the genes expressed in the anterior neural ridge could potentially lead to developmental defects of these structures. However, it is important to stress that many of these genes have multiple spatial and temporal domains of expression throughout the embryo and are not solely concerned with forebrain and pituitary development.

The pituitary gland is a midline structure consisting of the anterior, intermediate, and posterior lobes of varying size and complexity in different species. It has a dual embryonic origin. Fate map studies in the chick and Xenopus have demonstrated that the derivatives of the oral roof ectoderm (which include the pituitary and nasal epithelium) are initially derived from the anterior neural ridge (ANR). As the embryonic head turns, the ANR is displaced ventrally and forms the stomodeum, the ectoderm which gives rise to the roof of the mouth and its derived structures [6,7]. In the mouse, the onset of pituitary organogenesis coincides with a thickening of this initially uniform stomodeal ectoderm on embryonic day (E)8.5 which then invaginates on E9.0 to form Rathke’s pouch. The anterior and intermediate lobes of the pituitary derive from this structure. The posterior lobe is derived as a result of the evagination of the neural ectoderm (infundibulum) at the base of the developing diencephalon in direct contact with Rathke’s pouch. Hence, in the mouse, the anterior and intermediate lobes of the pituitary gland form at embryonic day 8.5 (E8.5) from Rathke’s pouch and this makes direct cell-cell contact with the neuroepithelium of the nascent diencephalon at E8.5–9 [8]. In man, the diverticulum forming Rathke’s pouch projects dorsally from the roof of the stomodeum around the fourth week of gestation and grows towards the brain. By the fifth week, the pouch has elongated, has become constricted at its attachment to the oral epithelium and has come into contact with the infundibulum. The apposition of Rathke’s pouch and the diencephalon is maintained throughout the early stages of pituitary organogenesis, and this close relationship has long suggested that inductive tissue interactions are involved in the process. Between E10.5 and E12 in the mouse, the pouch epithelium continues to proliferate as it closes and separates from the underlying oral ectoderm. Subsequent to these initial patterning events, the progenitors of the hormone-secreting cell types proliferate ventrally from the pouch between E12.5–E15.5 to populate what will form the anterior lobe (for review see [9]). The remnants of the dorsal portion of the pouch form the intermediate lobe destined to form melanotropes. The size of the intermediate lobe varies markedly between species, and, in man, its exact role remains unclear.

The development of the anterior pituitary gland is now known to be dependent on various intrinsic and extrinsic transcription factors and signalling molecules. Extrinsic factors include Tif1, BMP4, and Fgf8 [10–13], which are expressed in the diencephalon and not Rathke’s pouch, but are nevertheless implicated in normal pituitary development. It seems that Rathke’s pouch develops in a two-step process that requires at least two sequential inductive signals from the diencephalon. First, the induction and formation of the pouch rudiment is dependent upon BMP4 that is present only in the hypothalamus and not in Rathke’s pouch. Secondly, FGF8, which is also present in the hypothalamus and not in Rathke’s pouch, activates the key regulatory genes Lhx3 and Lhx4 (see below), and these are essential for subsequent development of the pouch rudiment into a definitive pouch [12].

A number of transcription factors are expressed within the pituitary primordium itself. These include Six3 [13], Pax6 [14], and Hexx1/Rpx [15,16], all of which continue to be expressed in Rathke’s pouch. Concurrent with organ commitment, two LIM-homeodomain factors, Lhx3 or P-Lim [17,18], and Lhx4 [19], are also expressed in Rathke’s pouch. Deletion of the Lhx3/P-Lim gene in mice results in the failure of the pituitary gland to grow and differentiate, although Rathke’s pouch forms [20], whereas a double Lhx3/Lhx4 mutant results in a failure of formation of Rathke’s pouch [19]. The OTX-related factor...