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Review

Distinct roles of homeoproteins in brain topographic mapping and in neural circuit formation

Olivier Stettler[a,*], Kenneth L. Moya[b,c]

[a] Laboratoire CRRET EAC 7149, Université Paris-Est Créteil, 61, Av. du Général de Gaulle, 94010 Créteil Cedex, France
[b] Collège de France, Center for Interdisciplinary Research in Biology, UMR CNRS 7241/INSERM U1050, 11 place Marcelin Berthelot, 75005 Paris, France
[c] Labex Memolife, PSL Research University, France

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ABSTRACT

The construction of the brain is a highly regulated process, requiring coordination of various cellular and molecular mechanisms that together ensure the stability of the cerebrum architecture and functions. The mature brain is an organ that performs complex computational operations using specific sensory information from the outside world and this requires precise organization within sensory networks and a separation of sensory modalities during development. We review here the role of homeoproteins in the arealization of the brain according to sensorimotor functions, the micropartition of its cytoarchitecture, and the maturation of its sensory circuitry. One of the most interesting observation about homeoproteins in recent years concerns their ability to act both in a cell-autonomous and non-cell-autonomous manner. The highlights in the present review collectively show how these two modes of action of homeoproteins confer various functions in shaping cortical maps.

Contents

1. Introduction: canonical and non-canonical functions of homeoproteins during building of the brain

The formation of functional brain areas is a process that starts with the regional specification of the neuroepithelium, followed by differentiation of neuronal types according to their lineage, and finally by the establishment of precise connections between areas that are functionally linked [1–4]. Homeoproteins (HPs) have long been known as key molecular determinants capable of specifying distinct embryonic territories during early body development [5–14]. This is exemplified in the nervous system where the HPs function as transcription factors that can early (i.e. before embryonic day 12 in the mouse) control specific cell differentiation programs and the size and physiological fate of brain areas [3,5,7,15–20] (see Section 2). However, HPs can also have later effects during the course of the development of the brain (i.e. at late embryonic and perinatal stages in the mouse) by controlling the proper formation and the stabilization of neuronal connections [20–28]. For instance and as shown below (Section 2), the HP Lhx2 drives the precise connections of thalamocortical axons within the somatosensory barrel field cortex [20]. Two other recent examples of HPs that participate in neuronal circuits development are provided by Engrailed which guides retinal axons and regulates the retinocollicular map formation [21,24,25] (Section 3), and by Otx2 which stabilizes the connections from the two eyes in the binocular visual cortex [26,27] (Section 4).

A number of data now support the notion that, in a developmental context, HPs can function in two different ways, as gene transcription factors, and less classically, as protein

* Corresponding author at: EAC 7149, Laboratoire CRRET, 61, Av. du Général de Gaulle, 94010 Créteil Cedex, France. Tel.: +33 1 45 17 18 13.
E-mail address: olivier.stettler@u-pec.fr (O. Stettler).

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translational modulators [29,30]. Homeoprotein transcription factors bind to DNA through a highly conserved structure, called the homeodomain, which is 60 amino acids in length and is structured in three alpha helices [30]. Additionally, interaction of the eukaryotic translation initiation factor eIF4E, with one or another of the putative eIF4E-binding sites flanking the homeodomain is thought to be responsible for HP translational activities [21,29,31]. Translational activity was first demonstrated for bicoid which regulates the translation of *caudal* mRNA from the anterior pole of the fly embryo through eIF4E binding [32]. The canonical eIF4E binding motif (YXXXXLΦ)[33] was subsequently found in the homeodomain protein PRH that inhibits eIF4E-dependent mRNA transport, and in 199 other HPs, which thus potentially act as regulators of eIF4E-dependent mRNA translation. In addition to bicoid and PRH, a direct interaction with eIF4E has so far been demonstrated for the HPs HoxA9, Emx2, OTX2 and Engrailed-1 and Engrailed-2 [24,29]. Another non-classical trait of HPs of potential importance, in particular during late development of the brain, is their capability to act as signaling molecules between cells. Thus far, all HP that have been tested for their signaling property (i.e. 10 of more than 200) [30] have been shown to pass from cell to cell, allowing direct access to the cytosol and eventually the nucleus of recipient cell [30]. Most neurodevelopmental studies related to HPs have nonetheless focused on their classical cell autonomous functions; the possibility that HPs act both at a cell autonomous and non-cell autonomous level in a same developmental process is not excluded. A future challenge will be to examine or re-examine how these two HPs modus operandi are coordinated during brain development (Section 5). This review aims to highlight recent data that extend our knowledge of the role of these proteins, regardless of their mode of action, as organizers of neural circuitry and neural maps. In order to focus our discussion on brain areas where both cell autonomous and non-cell autonomous functions of HPs have been described, the present review is limited to the role of HPs in the forebrain and midbrain regions. Consequently, the cerebellum for which the HPs Engrailed-1 and -2 act nonetheless as master transcriptional regulators of the patterning of gene expression and of afferent topography, is considered elsewhere [23,34].

2. Homeoproteins define neocortical territories and neural circuitry

The position of borders between brain regions is of primary physiological importance as it determines the neural tissue that will be allocated to specific brain functions. These borders are local transitions within the cerebral microarchitecture, the latter being formed of distinct populations of neurons and afferent inputs. Many studies aimed at understanding how boundaries are implemented have focused on the neocortex [1,4,15,20,35,36], a part of the brain with functional specializations that are highly conserved in mammals. The neocortex is organized into distinct primary sensory subdivisions (S1, A1, V1, M1 for somatosensory, auditory, visual, and motor cortex respectively) referred to as cortical areas or fields. These areas reproduce locally, through specific cytoarchitecture and/or chemoarchitecture and gene expression patterns, the topographic organization of peripheral sensory receptors to which they are connected [1,35] (see Lockmane and Garel, in this issue). The central representation of the periphery is very precise so that nearest neighbor relationships between primary sensory fields are maintained, in the subcortical relays and in the neocortex, thus forming the so-called topographic maps. The specification and differentiation of neocortical areas arises under the combined influences of extrinsic mechanisms, driven by afferent pathways that convey sensory information from the periphery (e.g. from the brainstem and thalamic relays), and genetic regulation, intrinsic to the neocortex. A significant number of studies have shown that sensory deprivation by removal of sensory innervation from a body part during a critical period of development alters both functionally and physically the cortical representation of the body part [37–40]. Manipulating the periphery or its subcortical relays produces highly stereotyped changes in the organization of the neocortex in various mammals suggesting that the extrinsic mechanisms themselves are under a tight genetic control [28]. Among the various transcription factors (TFs), morphogens, and signaling molecules participating in neocortical arealization and compartmentalization are the HPs and TFs Emx2 (empty spiracles homeobox 2) and Pax6 (paired box 6) [4,41]. These two proteins have important functions along with the non-HP TFs COUP-TFI (also known as NR2f1) and sp8 in establishing the layout of neocortex subfields in the rostrocaudal axis [42–44]. Gradients of Emx2 and Pax6 expressed by cortical progenitor cells in the ventricular zone (VZ) of the neocortical primordium may act primarily in the formation of a cortical protomap [41,45,46]. Neuroepithelial cells specified by TFs in the cortical primordium then proliferate and differentiate to form a complex six-layered neocortical structure with regionally diverse cytoarchitectures. Positional informations initially driven within the protomap by Emx2 and Pax6 in particular, foreshadow the location and size of cortical subfields that will subsequently form. Acting as cortical field organizer, and/or by conferring specific identities to progenitors cells, HPs are involved in the final targeting of thalamo-cortical axons (TCA) inputs that innervate distinct cortical areas [20,28,36,47].

In the rodent VZ, Emx2 is expressed in a high Posterior-Medial to low Anterior-Lateral gradient and impart caudal areal identity [48,49], while Pax6 is expressed in an opposing pattern with a low P-M to high A-L gradient, and impart rostral identity to the cortical primordium [50] (Fig. 1a). In the mouse, reduction of V1 has been proposed as a possible consequence of Emx2 loss of function [45,50,51] (Fig. 1). And, V1 extension anteriorly at the expense of S1 and the fronto-motor area has been observed after Emx2 gain of function [15,45]. The same V1 shift was predicted after loss of Pax6 function [15,42,41], but this has not been confirmed in a conditional KO of Pax6 that does however show the expected reduction of S1 size [36] (Fig. 1). Under physiological conditions, EMX2 repression of PAX6 specification of rostral identity contributes to reduced rostral areas [45]. Thus Emx2 and Pax6 operate by concentration-dependent mechanisms in cortical progenitors to specify the sizes and positioning of the primary cortical areas that establish area-specific TCA projections. A recent study using viable Pax6 conditional knockout (cKO) showed that mice with a cortex-specific Pax6 deletion not only displayed a substantially reduced S1 but also a partial loss of the body sensory representation [36].

Tactile receptors distributed over the body are represented in somatotopic maps within S1. Rodent S1 has a large area allocated to posterior medial barrel subfield (PMBSF), and the anterior lateral barrel subfield (ALBSF) which receive sensory inputs from the facial whiskers [52]. Barrels in these fields consist in clusters of terminal arbors (the barrel core) of VPN (ventro posterior thalamic nucleus) afferents, synapsing onto the dendrites of spiny stellate neurons that form the barrel wall in layer 4 of the S1. Each barrel receives input from a single whisker and the barrel field is organized to represent the topographic distribution of the facial whiskers (see Lockmane and Garel, and Vitali and Jabaudon, in this issue).

Pax6 cKO show sharply reduced PMBSF and ALBSF (Fig. 1b); the magnitude of this reduction is even greater than observed for the whole S1 suggesting that the portion of S1 allocated to the barrel field is specifically reduced in these TG mice [36]. These mice also show the loss of specific parts of the cortical barrel field (Fig. 1b) that may be due to an exaggerated competition among VPN TCA for limited cortical space. Finally, the reduced S1 in Pax6 cKO alters the VPN thalamic relay resulting in its re-patterning to match the