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Clonal origin of the mammalian forebrain from widespread oriented mixing of early regionalized neuroepithelium precursors

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Abstract

The forebrain is formed by remodeling and growth of the anterior neural plate. This morphogenesis occurs in response to inductive signals during gastrulation and neurulation but is poorly understood at the cellular level. Here, we have used the LaacZ method of single cells labeling to visualize, at E12.5, clones originated at early stages of mouse forebrain development. The largest clones show that single progenitors can give rise to neuroepithelial cells dispersed across the forebrain. A significant fraction of the clones, and even relatively small ones, populated both the diencephalon and the telencephalon, indicating that the clonal separation between diencephalic and telencephalic progenitors is transient and/or partial. However, two groups of large clones, populating either the diencephalon or the telencephalon, dispersed within their respective domains, suggesting an early regionalization between some diencephalic and telencephalic progenitors. Widespread oriented mixing within these territories and then clonal expansion into smaller domains probably follow this initial regionalization. These data are consistent with a model of progressive specification of forebrain domains. We propose that the ordered expansion of early regionalized progenitor pools for the diencephalon and telencephalon could establish a potential link between early inductive signals and forebrain morphogenesis.

Keywords: Cell lineage; Clonal analysis; Diencephalon; Dispersion; Forebrain; *laacZ*; Mouse embryo; Neural progenitor; Telencephalon

Introduction

The forebrain is organized into diencephalon and telencephalon. The diencephalon includes the thalamus and hypothalamus. The ventral telencephalon is organized into three ganglionic bulges, termed lateral, medial and caudal ganglionic eminences (LGE, MGE and CGE) that give rise to the striatum, pallidum and amygdala as well as interneurons that migrate to the more dorsal cerebral cortex and other forebrain territories (hippocampus, olfactory bulbs, thalamus) (Nadarajah and Parnavelas, 2002). In the embryo, the forebrain is formed by remodeling and growth of the anterior neural plate in response to patterning signals during gastrulation and neurulation (reviewed in Rallu et al., 2002). The regionalization of forebrain domains starts to be established in the neural plate. At this stage, the expression pattern of transcription factors determining forebrain cell fates defines three major domains, corresponding to the future diencephalon, eye and telencephalon (Wilson and Houart, 2004). The following steps lead to a segment-like genetic organization of the forebrain, called the prosomeric model, essentially conserved among vertebrates (Puelles and Rubenstein, 1993, 2003).

The formation of the forebrain involves a set of coordinated cell movements and proliferation patterns, but the relationship between cell behaviors and determination steps has remained unclear. In fact, there is an important gap in our knowledge regarding the behavior of cells receiving early signals in the neural plate and their lineage relationship with cells undergoing later morphogenetic movements. Fate maps of the mouse epiblast at the onset of gastrulation (E6.5) show that the forebrain is not separated from more caudal regions due to a longitudinal dispersion of clones (Lawson et al., 1991, 1992; Quinlan et al., 1995). At E7.5 in the mouse or at stage 4 in the chick, clones are more regionalized and forebrain progenitors are identified as a rostral region of the neural fate map (Fernandez-Garre et al., 2002; Tam, 1989). Next, progenitors

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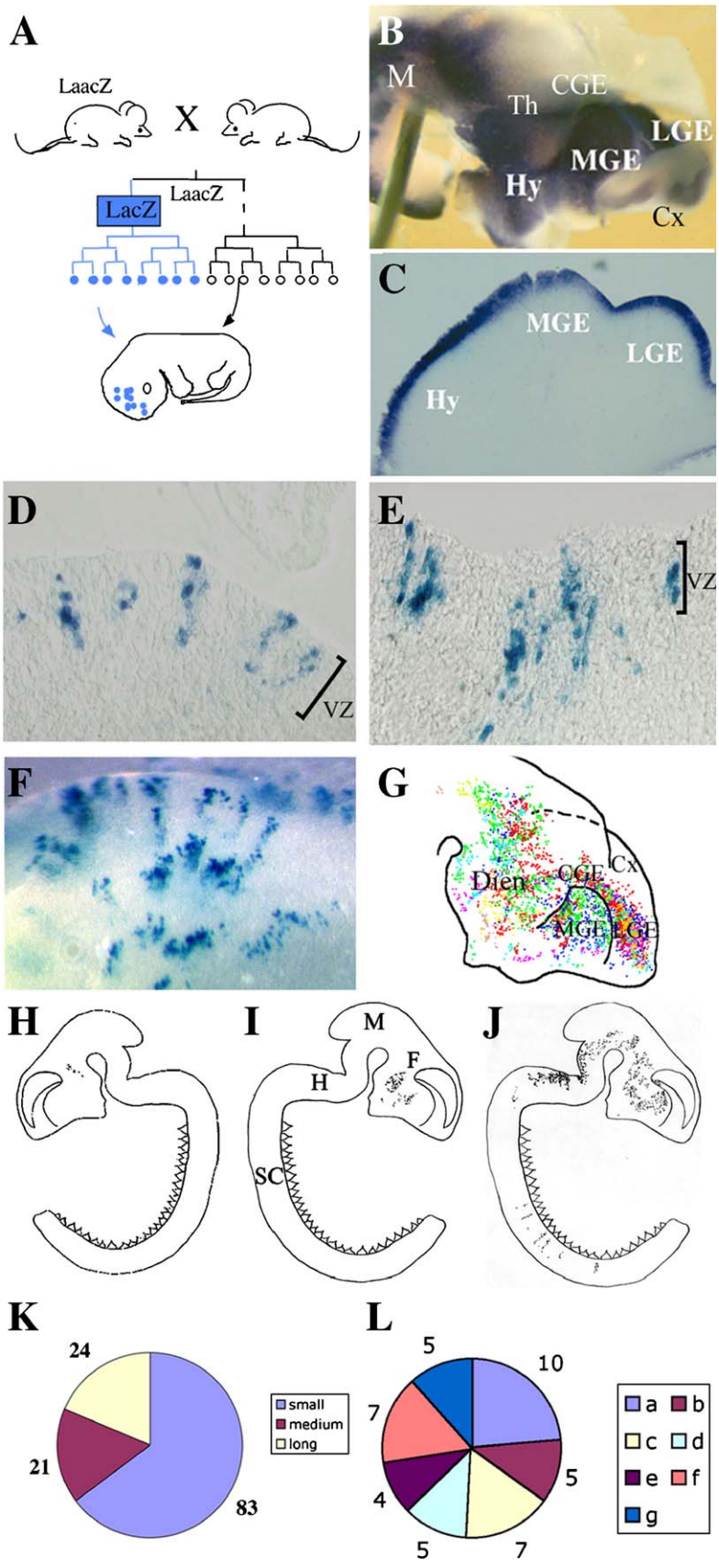
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