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Research Report

The dorsal pallium in zebrafish, *Danio rerio* (Cyprinidae, Teleostei)

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ABSTRACT

Zebrafish as a neurogenetic model system depends on the correct neuroanatomical understanding of its brain organization. Here, we address the unresolved question regarding a possible zebrafish homologue of the dorsal pallial division, the region that in mammals gives rise to the isocortex. Analyzing the distributions of nicotine adenine dinucleotide phosphate diphorase (NADPHd) activity and parvalbumin in the anterior zebrafish telencephalon, we show that against previous assumptions the central (Dc) zone possesses its own germinative region in the dorsal proliferative zone. We define the central (Dc) zone as topologically corresponding to the dorsal pallial division of other vertebrates (mammalian isocortex). In addition, we confirm through BrdU-labeling experiments that the posterior (Dp) zone is formed by radial migration and homologous to the mammalian piriform cortex. Based on our results, we propose a new developmental and organizational model of the zebrafish pallium—one which is the result of a complex outward–inward folding.

1. Introduction

The mammalian isocortex is considered the *crowning* achievement of evolution because it forms the neurological substrate for cognitive and emotive human mental processes (Rakic, 2009). It develops from what is called the dorsal pallial division. Searching for the evolutionary origin of this structure has been one of the most challenging questions in comparative neurology (Medina and Abellan, 2009). A dorsal pallial division homologous to the mammalian isocortex evolved with jawed vertebrates (gnathostomes) and is present in diverse anamniotes like sharks, lungfish, and frogs (Gonzalez

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Abbreviations: BLA, basolateral amygdala; Ctx, cortex; CP, caudate putamen; D, dorsal telencephalon (pallium); Dc, central zone of the dorsal telencephalon; Dd, dorsal zone of the dorsal telencephalon; Dl, lateral zone of the dorsal telencephalon; Dm, medial zone of the dorsal telencephalon; DP, dorsal pallium; Dp, posterior zone of the dorsal telencephalon; EN, entopeduncular nucleus; GP, globus pallidus; Hip, hippocampus; LGE, lateral ganglionic eminence; lot, lateral olfactory tract; LP, lateral pallium; LV, lateral ventricle; MGE, medial ganglionic eminence; MP, medial pallium; NT, nucleus taeniae; OB, olfactory bulb; P, pallium; pirCtx, piriform cortex; PSB, pallial–subpallial boundary; Po, preotic region; S, subpallium; Sep, septum; TV, telencephalic ventricle; V, ventral telencephalon (subpallium); Vd, dorsal nucleus of the ventral telencephalon; Vl, lateral nucleus of the ventral telencephalon; VP, ventral pallium; Vv, ventral nucleus of the ventral telencephalon; Y, sulcus ypsiloniformis

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and Northcutt, 2009; Northcutt, 1981; Northcutt, 2009; Pombal et al., 2009; Rodriguez-Moldes, 2009; Wicht and Northcutt, 1998). Ray-finned fish (actinopterygians) like zebrafish have been denied this privilege. Comparative studies have not established a distinct cortex homologue (Northcutt, 2008). We also lack specific markers that could help identify the cortex region. Molecular markers (*pax6* and reelin) which label the mammalian cortex in a characteristic, stage dependent manner are not expressed in regions qualifying for a cortex homologue in zebrafish (Costagli et al., 2002; Wullimann and Rink, 2001). Also, none of the extensive molecular and gene expression studies on embryonic and larval stages of zebrafish have indicated a cortex homologue (Mueller and Wullimann, 2005; Mueller and Wullimann, 2009).

The main obstacle for identifying pallial divisions in zebrafish is the unusual development of the teleostean telencephalon (Fig. 1). The telencephala of zebrafish and other ray-finned fish develop through a unique process of outward folding called eversion. The exact nature of this eversion process has been a subject of debate for the past 130 years. A number of eversion models have been proposed, ranging from very simple to highly elaborate (Braford, 1995; Braford, 2009; Butler, 2000; Gage, 1883; Nieuwenhuys, 2009; Northcutt and Davis, 1986; Northcutt, 2008; Studnička, 1894; Wullimann and Mueller, 2004; Yamamoto et al., 2007). However, little developmental evidence has validated any of these models. As a result, there is no consensus on the exact anatomical delineation of even well established pallial homologies such as the teleostean pallial amygdala, the hippocampus, and the piriform cortex (Nieuwenhuys, 2009; Northcutt, 2008). Yet, all of the participants in the current debate agree that the exact anatomical delineation of these homologies and the identification of the dorsal pallium depend on a complete topological analysis of the teleostean eversion (Nieuwenhuys, 1962; Nieuwenhuys, 2009).

We chose a comparatively simple yet effective method for deciphering the zebrafish pallium. To determine and map true pallial histogenetic units, we studied consecutive sections of adult zebrafish that were stained against nicotine adenine dinucleotide phosphate diphorase (NADPHd) activity and parvalbumin. The differential staining patterns of both of these markers visualized pallial zones and their topological site of origin. For the first time, we show that the central (Dc) zone reaches the dorsal proliferative zone at the rostral pole of the telencephalon. Dc comprises its own germinative zone of origin and, thus, is a true pallial histogenetic unit. In a subsequent BrdU long-term labeling experiment, we provide additional evidence that the posterior (Dp)-zone, is the result

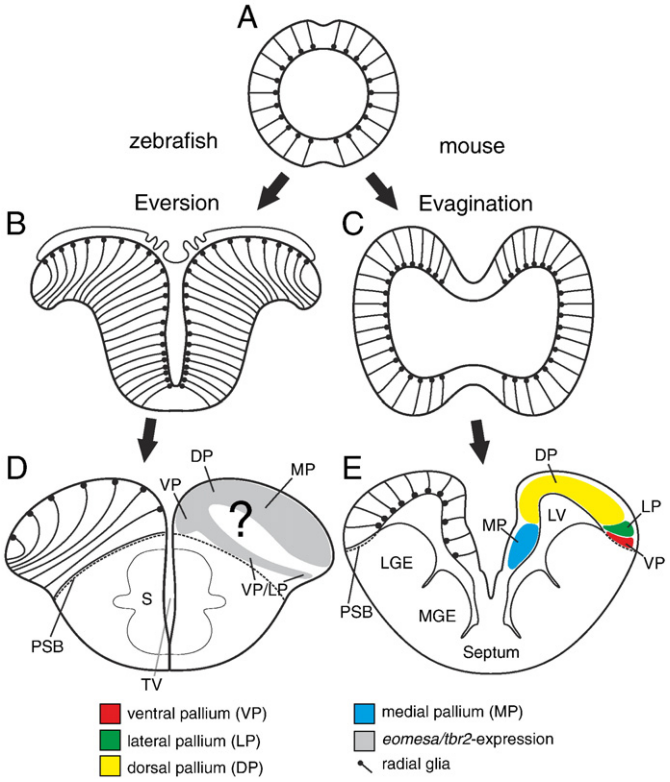

Fig. 1 – Development of the telencephalon in teleosts and mammals. (A) Coronal view of the vertebrate anterior neural tube giving rise to the telencephalon. (B and D) The teleostean telencephalic outward folding (eversion) leads to a dorsal telencephalon (pallium) where proliferative zone and ventricular surface are located on its dorsal most site (indicated by location and orientation of radial glia). The development of the medial (MP), dorsal (DP), lateral (LP), and ventral (VP) pallial divisions which in mammals give rise to the hippocampus, cortex, piriform cortex, and pallial amygdala is poorly understood. Eversion models simplified after (Nieuwenhuys and Meek, 1990) and (Mueller and Wullimann, 2009). (C and D) The mammalian (mouse) telencephalon develops through evagination. Proliferative zones are inwardly oriented towards the ventricle. Pallial divisions in mouse simplified (Puelles et al., 2000).