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The heterogeneity of human Cajal-Retzius neurons

Gundela Meyer*, Miriam González-Gómez

Units of Histology (GM) and Anatomy (MGG), Department of Basic Medical Science, Faculty of Medicine, University of La Laguna, Tenerife, Spain

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ABSTRACT

The definition of a Cajal-Retzius neuron (CRN) is still controversial, in part possibly due to species differences. We review the developmental history of CRN in human neocortex and focus on two main CRN family members, transient (t) and persisting (p) CRN. They share the expression of Reelin andTbr1, complemented by p73, calretinin, CXCR4 and NOS, but differ in their moment of appearance, fate and morphology. The distinctive feature of tCRN is the axon plexus in the lower third of the marginal zone, which innervates the apical dendritic tufts of pyramidal cells and may serve as a migration substrate and waiting compartment for interneurons descending from the subpial granular layer (SGL) into the cortical plate. Around midgestation, the SGL also gives rise to a transient interneuron type, the miniature neuron, that provides the GABAergic innervation of tCRN, which eventually, through diverse signaling pathways involving p73, contribute to the demise of tCRN and the breakdown of their plexus. The pCRN appear in the last trimester of gestation and may derive from committed CRN progenitors which migrate with the SGL from the periolfactory forebrain. They lack the horizontal CR plexus, and may be implicated in cortical folding, distribution of blood vessels, and plasticity of microcircuits in the molecular layer.

Contents

1. Introduction

Cajal [1–3] and Retzius [4–6] discovered the neurons in the outer layer of the developing cortex that are now known as "Cajal-Retzius neurons" (CRN). The original reports already showed that CRN stand out from other cortical neurons due to their unusual and variable morphology. Retzius [4] initially regarded them as

* Corresponding author at: Department of Basic Medical Science, Faculty of Medicine, University of La Laguna, La Laguna, Santa Cruz de Tenerife, 38200, Spain.
E-mail address: gundelam@aol.com (G. Meyer).

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neuroglia, whereas Cajal described them as "special cells" [1,2]. During more than 100 years, the functional significance of CRN remained obscure, and they were rather considered a morphological curiosity interesting only for a few experts in embryonic cortex. This changed in 1995 with the discovery that CRN secrete the large glycoprotein Reelin [7,8], crucial for radial migration and cortical lamination [9,10]. Since that moment, CRN have attracted the attention of many researchers, which led to a plethora of studies mostly in laboratory animals such as rat and mouse, on the molecular profile, origins, and functional properties of CRN. More than 20 years after the cloning of the *Reelin* gene, and the elucidation of the Reelin-Dab1 signaling pathway, as well as of other molecular cascades in which CRN are implicated, there is still uncertainty about how to define a CRN, or the members of the CRN family [11–14]. In our opinion, this confusion is related to the fact that most of the recent experimental work has been done in rodents, whereas the initial descriptions of Retzius were based on observations in human fetuses, later also in dogs and cats [4–6]. Cajal, in turn, studied mice, rabbits and human infants [1–3]. We are thus dealing with two confounding, often neglected factors: species differences, and the existence of age-specific CRN forms in human. It is often stated that CRN are the earliest-born neurons of the cortex, generated only at the onset of corticogenesis, a concept based on the postulate by Marin Padilla [15] that CRN are the first neurons of his primordial plexiform layer (now termed the preplate [16]), together with neurons of the subplate. The arrival of the first neuronal cohorts destined to the cortical plate (CP) would split the preplate into a marginal zone (MZ) above the CP, populated by CRN, which would remain unchanged though diluted in the growing cortex, and the subplate, positioned below the CP. Birthdating studies in rats, mice and cats confirmed the early birth of CRN [17–19]. In monkey, CRN are generated during a somewhat longer period, between embryonic days 38-50 [20].

This review is centered on the human CRN from their first appearance to adulthood. Importantly, human CRN express the human accelerated regions RNA gene *HAR1F* [21], which may be related to human-specific features of CRN not present in other species. We describe the sequential arrival of several populations of human CRN, which arrive at specific time points of corticogenesis, even until rather late developmental stages, in contrast to the rodent situation.

2. Definition of human CRN

The morphology of CRN in human cortex is highly variable and age-specific, with transient CRN preceding in time the persisting CRN, which requires a morphology-independent neurochemical and molecular definition of this cell family [13]. The core requirement for a CRN family member is the co-expression of Reelin and the pallial transcription factor Tbr1, complemented by the more variable expression of the tumor protein p73, calcium binding proteins, most commonly calretinin, the enzymes Acetylcholinesterase (AChE) [22,23] and nitric oxide synthase (NOS)/NADPH diaphorase [23,24], and the cytokine receptor CXCR4 [25–27]. In rodents, CRN co-express a large variety of transcription factors and morphogens (reviewed in [28]), most of which as yet have not been explored in the human cortex. In contrast to the GABAergic Reelin+ interneurons which appear later in development and populate not only the superficial layer I but also deeper layers, CRN are glutamatergic and thus excitatory [17,29–31].

3. Neurochemical and molecular markers of CRN

3.1. The Reelin – Dab1 signaling pathway

Ever since their initial description, the function of CRN remained a mystery, until the discovery that they are the main source of the extracellular matrix protein Reelin [7] shed light on their activity. Reelin is secreted by CRN and crucial for laminar positioning of radially migrating neurons which respond to the Reelin signal in the MZ [32]. The cortex of the *reeler* mouse, a spontaneous mutation deficient in Reelin, shows a disorganized architecture with a roughly inverted lamination, which exemplifies the importance of Reelin in establishing the normal inside-out gradient of the neocortical CP [33]. According to this gradient, early-born CP neurons occupy the deep layers of the cortex, and are by-passed by later generated neurons which, after finishing their radial glia-guided migration from the cortical periventricular proliferation zones, occupy successively more superficial positions, such that the latest-generated neurons form the most superficial layer II [34]. The adult layer 1 is cell-sparse and populated only by interneurons and persisting CRN (discussed in Sections 6 and 7). In the *reeler* mouse, the preplate does not split, and the migration gradient is disturbed. The Reelin signal is transduced via the lipoprotein receptors ApoER2 and VLDLR leading to tyrosine phosphorylation of the adapter protein disabled 1 (Dab1), expressed by the radially migrating pyramidal cells of the CP [32,35–37]. The Reelin/Dab1 signaling pathway specifically acts on somatic translocation at the end of radial migration [38,39]. The integrity of the Reelin-Dab1 pathway is required for normal corticogenesis, since the combined inactivation of both lipoprotein receptors, as well as Dab1 deficiency, result in a *reeler*-like phenotype [37].

Reelin is not exclusive to CRN, but also expressed by interneurons in the CP [40–44]. Reelin+ interneurons migrate by tangential migration from their birthplace in the caudal ganglionic eminence into the cortex, independently of Reelin-Dab1 signaling [45,46]. Importantly, the *reeler* mouse, despite the abnormal organization of the cortex, presents a predominantly cerebellar syndrome, namely ataxia and a "reeling" gait. Mutations of the human *REELIN* gene result in a profoundly abnormal, lissencephalic cortex associated with cerebellar hypoplasia and severe mental deficiency [47]. The severity of Reelin deficiency in human is consistent with an evolutionary amplification of the Reelin signal [9,48], in parallel with an increasing evolutionary complexity of CRN [49,50]. The expression of Dab1 is similarly complex in fetal human cortex [51]. The Dab1 signal is highest in the outer cortical plate adjacent to the Reelin signal; at midgestation, Dab1 mRNA and protein are also present in cells in the intermediate zone and subplate, and even in a subpopulation of CRN [51]. Dab1 and vimentin are partially colocalized in radial glia cells in the ventricular and subventricular zones (SVZ), pointing to a role of Reelin-Dab1 signaling not only in migration but also in neurogenesis. Also in mice, ApoER2, VLDLR and Dab1 are co-expressed in radial glia precursors [52]. In human, expression of VLDLR and ApoER2 is strongest in the upper CP at midgestation, and in pyramidal cells of future layers III and V [53]. In addition, in human, all components of the signaling pathway (Reelin, the two lipoprotein receptors plus Dab1) are co-expressed in a subset of CRN around midgestation, suggesting that Reelin may exert an autocrine and ǫ r paracrine effect on CRN, another possibly significant difference between human and rodent CRN [51,53].

3.2. Tbr1

The T- box transcription factor Tbr1 is expressed by early-born glutamatergic neurons characteristic of the pallium [17,54]. In human cortex, Tbr1 is present in CRN from embryonic stages onward [55], and is thus, together with Reelin, a defining marker of CRN [56]. Glutamatergic, excitatory cortical neurons undergo a developmental program consisting in the sequential expression of transcription factors Pax6 in radial glia, Tbr2 (Eomes) in intermediate progenitor cells, and Tbr1 in postmitotic projection neurons [57]. In the preplate, Tbr1 is expressed in the direct step from radial glia to postmitotic neuron [57].

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