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The heterogeneity of human Cajal-Retzius neurons

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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

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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 / or 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].

3.3. Calcium-binding proteins

The calcium-binding proteins calretinin, parvalbumin, and calbindin are expressed in largely non-overlapping interneuronal populations, and used for categorization of inhibitory interneuronal subpopulations in the cortex [58], even though calbindin and calretinin are also present in distinct pyramidal cell classes. Calretinin is most consistently related with CRN, to the point that is has been used as a marker for this cell type [29,59]. Calretinin plays roles in the cellsí homeostasis of calcium; it undergoes considerable Ca2+-dependent conformational changes, which indicate that calretinin might have "Ca2+ sensor" functions [60]. Nevertheless, the expression of calcium binding proteins in CRN seems to be dependent on species, age and location; calbindin [61] is also expressed in many human CRN, and parvalbumin is observed in late gestational human fetuses [61,62]. In addition, calretinin is expressed in very early appearing non-CRN cell types of the human cortex, including cells of the pioneer plate [55,63], independently of their GABAergic or glutamatergic nature. In human, calretinin is also expressed by most SGL cells [64] (see Section 5.1), and is therefore not an unequivocal marker of CRN. In the adult monkey molecular layer, calretinin is commonly expressed by various interneuron classes [65,66], and thus the distinction between persisting CRN and interneurons calls for additional criteria.

3.4. P73

P73 belongs to the family of the tumor supressor p53, with which it shares structural similarities [67]. It is expressed in two main isoforms under the control of different promoters. P73 is a complex multifunctional protein with a variety of isoforms. Transactivation (TA) competent p73 isoforms are able to transactivate p53 target genes and are thought to have pro-apoptotic activities, whereas the N-truncated DeltaNp73 isoforms are anti-apoptotic and may function as oncogenes [68]. Alternative splicing of both TA and DeltaNp73 isoforms gives rise to multiple C-terminal variants (p73 alpha, beta, etc [69]. P73 has been implicated in survival and death of neurons [70,71]. In the developing brain, antibodies against p73alpha (which may react with TAp73alpha or DeltaNp73alpha) reveal high nuclear expression in few cell classes in the brain: CRN, the choroid plexus epithelium, and later in development, the ependyma [72–75]. This expression pattern is specific and highly restricted. In adult human cortex, low levels of TAp73 and DeltaNp73 isoforms are present in the cytoplasm and/or nucleus of pyramidal cells [73]. The importance of p73 for generation of CRN is illustrated by the fact that CRN do not develop in p73 KO mice [72,76]. The precise p73 isoform in CRN is unknown; TAp73 KO mice [77] and DeltaNp73 KO mice [78] both have decreased numbers of CRN, and thus it appears reasonable to conclude that expression levels of TAp73 and DeltaNp73 in CRN are precisely balanced, allowing survival under some conditions, leading to cell death in others. P73 is expressed in virtually all CRN at midgestation, and may be instrumental in the death of the transient CRN population shortly thereafter [72,79] (see section 5.2). Remarkably, despite the absence of CRN in the total p73 KO mouse, the cortical phenotype is almost normal [75], unlike the dramatic *reeler* cortex, and the most striking malformations are a dysgenesis of the dentate gyrus and hydrocephalus. Reelin in CRN may thus not be strictly necessary for the small simple mouse cortex [75,80], but may be essential for building the human brain [81].

3.5. Additional neurochemical markers of CRN

The enzymes Acetylcholinesterase (AChE), catalyzing the breakdown of Acetylcholine but carrying out also non-catalytic functions, and neuronal nitric oxide synthase (nNOS), responsible for the synthesis of nitric oxide from L-arginine, and which can also be detected with NADPH-diaphorase histochemistry [23], are commonly expressed in CRN [22,23], although they are rarely used to identify this cell type. It may be interesting to elucidate the significance of NOS in CRN [22–24], which via nitric oxide, a gaseous vaso-active transmitter, might influence perfusion of the developing cortex.

In mice, the cytokine receptor CXCR4 controls the tangential migration of CRN in response to its ligand, SDF1 aka CXCL12, which is expressed in the meninges [25–27,82]. CXCR4 is expressed both in the large transient CRN at midgestation and by the small persisting CRN at term [79].

4. The early development of CRN

4.1. The first CRN are generated in the cortical neuroepithelium

CRN are usually referred to as the oldest neurons of the cortex, as originally proposed by Marin Padilla [15,83], and confirmed in birthdating studies in laboratory animals [17–19]. In human embryonic cortex, a few Reelin+ neurons representing the first CRN are detected at Carnegie stage (CS) 16 (5 GW) [84], shortly after the formation of the telencephalic vesicle at CS 14 [85]. (In the embryos, we refer to CS because they are more reliable than gestational weeks, and well characterized [85]). At CS 16, no other postmitotic neurons are present in a very narrow MZ outside the proliferating neuroepithelium [84], and these first CRN thus preceded the appearance of the subplate, or of any other cortical cell population, with the possible exception of the "predecessor neurons" [86], which may appear even earlier. In the following stages, CS 17-19, Reelin+ radial columns appear in the neuroepithelium of the anterior cortex and spread into the MZ (Fig. 1A,B), indicating a massive local birth of CRN [84]. Cells within the columns co-express Reelin and Tbr1, but are p73-negative [55]. They are also positive for doublecortin, a marker of newborn neurons [87]. This local origin of CRN in the form of distinctly spaced columns within the cortical ventricular zone has not been described in any other species, and is a first hint at the heterogeneous origins of CRN.

The transformation of the preplate into CP, MZ and subplate takes place at CS 20/21 (approximately 7-8 postconceptional weeks), and is a complex process involving transient neuronal populations, some of which possibly arrive from the subpallium through tangential migration [55,63]. An example are the GABAergic calretinin+ bipolar neurons which display the bipolar horizontal morphology attributed to CRN but are Reelin-negative [63]. The subsequent condensation of calretinin+/Tbr1+ cells gives rise to the "pioneer plate" [55,63]. During this transformation process, CRN are restricted to a directly subpial position, spatially segregated from the cells in the advanced preplate/pioneer plate. They are still small and immature, and express moderate levels of Reelin [84]. A similar though less complex transition process was described in the rat [88], where calbindin/calretinin+ pioneer cells derived from the cortical neuroepithelium give rise to the first efferent projections of the cortex, whereas Reelin+ CRN migrate tangentially from an extracortical source in the periolfactory forebrain.

4.2. Additional sources of CRN

The dominant molecular profile of CRN at CS 20-23 (positive for Reelin, Tbr1, p73) is slightly different from that observed in the local columns at CS 17-19 (Reelin/Tbr1 +), and points to additional sources of p73+ CRN (Fig. 1 B-D). Already at CS 18, the periolfactory basal forebrain including the septum gives rise to Reelin/p73+ cells which migrate tangentially along the pial surface into the cortex primordium [72]. At CS 21, while the pioneer plate develops from

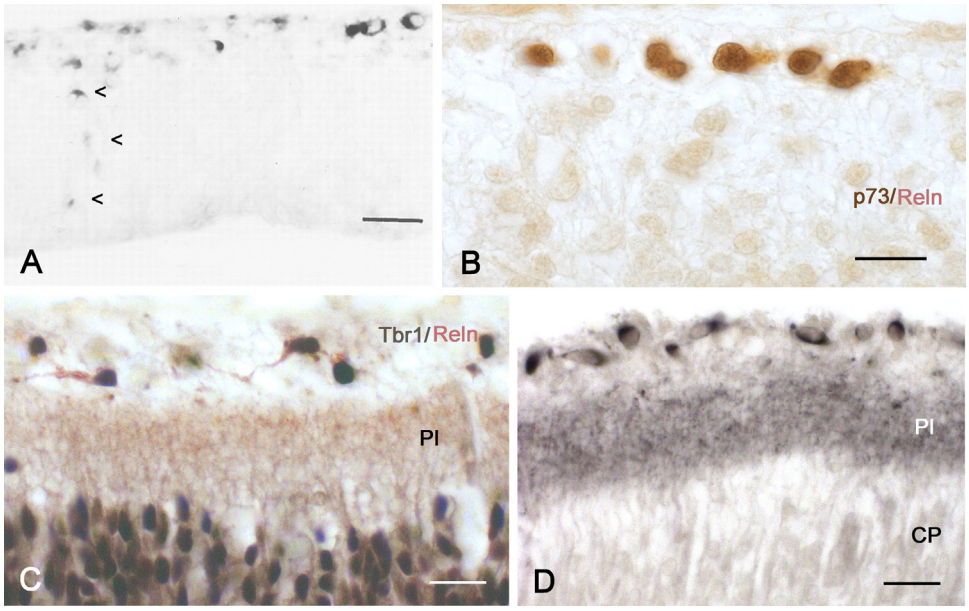

Fig. 1. The early development of CRN. A: At CS16, the first Reelin+ CRN arise from specialized foci in the cortical neuroepithelium (arrowheads) and spread into the narrow marginal zone (MZ). B: In the advanced preplate at CS 19, CRN co-express Reelin (light brown, in the cytoplasm) and p73 (dark brown, in the nucleus). C,D: 11 GW. CRN are still the only neuronal type in the MZ. They co-express Tbr1 (black, in the nucleus) and Reelin (brown, in the cytoplasm), in C. D: Reelin in CRN. At 11 GW, CRN extend a Reelin+ axon plexus (PI) in the deep MZ, at the interface with the cortical plate (CP). At this stage, morphologically they resemble rodent CRN. Bars: in A: 15 μm; in B: 10 μm: in C and D: 10 μm.

lateral to medial, a novel source of Reelin/Tbr1/p73+ CRN appears in the cortical hem, and becomes a massive cell stream at CS 22/23 (8GW), shortly before the appearance of the hippocampus [72]. The cortical hem is a signaling center characterized by the expression of Wingless-related (WNT) and bone morphogenetic proteins (BMP), and implicated in the patterning of arealization of hippocampus and neocortex by regulating transcription factors that control size and position of neocortical areas [89–91]. The massive addition of hem-derived CRN maintains high CRN numbers in the MZ at a time point when the ventricular zone (VZ) and SVZ start an intense proliferation leading to a dramatic growth of the CP. From 9 to 12/13 GW, CRN are the only neuronal elements in the MZ (Fig. 1C,D). Their morphology is that of monopolar horizontal neurons with large somata and a prominent nucleus, and the intensity of the Reelin signal increases [64]. From 11 GW onward, a Reelin+ axonal plexus becomes visible in the deep MZ, indicating that CRN have settled at their final position and extend a horizontal axonal plexus contacting the apical dendrites of the pyramidal cells in the CP. This plexus is the most distinctive feature of transient CRN, and will be discussed in detail in section 7.

Additional, less prominent sources of CRN (Reelin/Tbr1/p73 +) are the thalamic eminence at the interface of thalamus and telencephalic choroid plexus [78,81,92], and the amygdalar hem [81], which would correspond to the structure described as strionuclear neuroepithelium [93]. The amygdalar hem, similarly connected with the choroid plexus, is the source of a stream of CRN toward the amygdala/prospective entorhinal cortex [81]. Even more caudally, a ventral cortical hem generates CRN destined to the ventral hippocampus [94]. The finding that most sources of the CRN are connected to the p73+ choroid plexus gave rise to the hypothesis of a “”hem system” implicated in the coordinated regulation of ventricular size, cell proliferation in the VZ, and the numbers of CRN produced in the p73+ hem sites, necessary for providing Reelin for the growing cortex [81]. In mice, cortical hem, septum, and thalamic eminence form a “forebrain hem system” that requires the transcription factor Lhx2 to delimit its extent; in the absence of Lhx2 function, all 3 structures are greatly expanded, and the CRN population is dramatically increased [95]. The hem system stops to produce CRN once the adjacent structures (hippocampus, corticomedial amygdala) emerge.

The various origins of CRN were confirmed in the rodent [96], where they may function as “mobil units” [97] instructing areal specification via the expression of a variety of transcription factors and morphogens; mice, however, have an additional CRN source at the pallial-subpallial boundary, which was not detected in human.

5. The subpial granular layer and the polymorphic CRN

Cortical growth and surface expansion are much more dramatic in human than in the conventionally studied laboratory animals. After the initial appearance of the CP at CS 21, production of cortical neurons increases massively during the second trimester, and even continues into the third trimester [98]. During this period of intensive growth, the number of CRN increases despite surface expansion [64], which contradicts the rodent situation that CRN are the earliest-born neurons of the cortex, and remain unchanged once the CP has formed. How can the number of CRN increase after the regression of the hem system?

A possible answer may be found in the analysis of the subpial granular layer (SGL), first described by Ranke in 1910 [99]. The SGL is a transient structure in the MZ that has been described only in human and monkey, and is possibly primate specific. The SGL derives from the SVZ of the rhinencephalic ventricle [79,100–102], an extension of the anterior horn of the lateral ventricle that initially reaches into the olfactory bulb [103]. Around midgestation, this ventral extension closes, and the birthplace of the SGL shifts to more dorsal levels near the SVZ of the ganglionic eminences [79]. In the absence of experimental animal models, most of the current knowledge derives on descriptive studies of the human and monkey SGL. The human SGL emerges around 13/14 GW in the periolfactory prosencephalon [100,101], follows the lateral olfactory tract into the primary olfactory cortex and spreads through subpial tangential migration all over the neocortex. This initial migration must proceed very fast, because already at 16 GW the SGL covers the entire cortex (Fig. 2A–C). The components of the SGL are densely packed immature neurons which express molecules characteris-

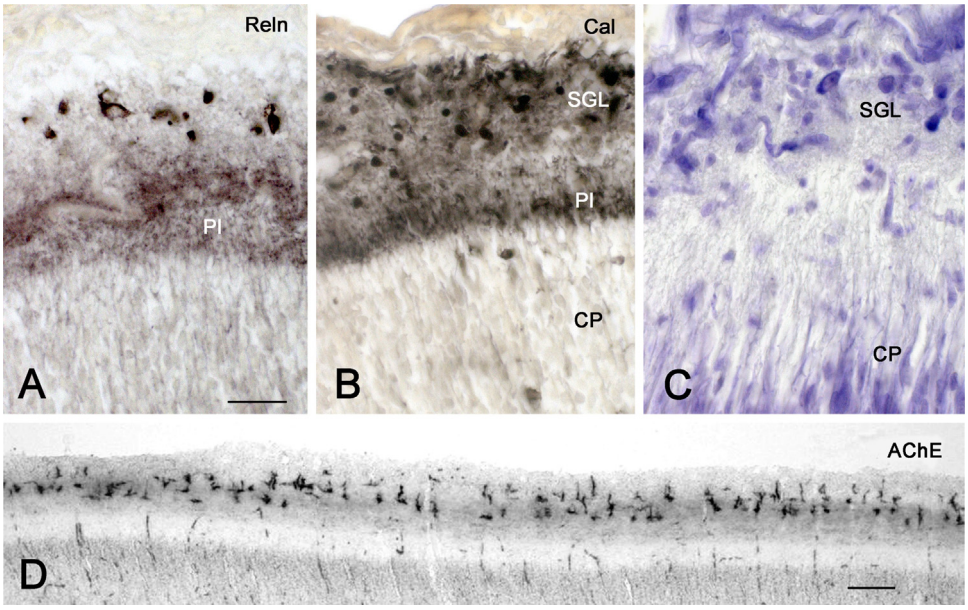

Fig. 2. CRN and the appearance of the SGL. A-C: 16 GW. In A, Reelin+ (Reln) CRN of different sizes are in the upper MZ, while their plexus occupies the lower MZ. In B, calretinin+ (Cal) CRN are surrounded by similarly calretinin+ positive granule cells. The CR axon plexus (PI) is positive for Reelin and calretinin. C: A parallel Nissl-stained section shows the architecture of MZ and upper CP. Notice the intense capillarization of the SGL. D: 21 GW. Acetylcholinesterase (AChE) in large transient CRN. The 80 μm-thick section gives a better impression of the morphology, magnitude, and cell density of this polymorphic CRN population than our usual 10 μm sections. Bars: In A, for A-C: 15 μm. In D: 70 μm.

tic of interneurons: GABA or its synthetizing enzyme glutamate decarboxylase (GAD), calretinin (Fig. 2B), plus the transcription factors Dlx1, indicating an origin from the lateral ganglionic eminence, and to a lesser degree, NKx2.1, a marker of medial ganglionic eminence derivatives [104]. The superficial tiers of the SGL expresse doublecortin, and thus contain the more immature cells [79].

As a consequence of the invasion by the SGL, the CRN become completely immersed within a layer of GABAergic cells, and begin to change morphology. From an initial horizontal orientation and bipolar arrangement of axonal and dendritic processes (Fig. 3), CRN change into the polymorphic forms characteristic of midgestation, with many of them adopting an elongate vertical soma and giving rise to profuse, mostly ascending dendritic processes, while the axons descend to the deep CR plexus (Figs. 2D,4). Simultaneously, CRN descend from their original subpial position to deeper strata of the MZ [23]. In parallel, also part of the SGL granule cells begin to differentiate, and descend to deeper levels of the MZ.

It is possible that the population of CRN within the SGL is not homogeneous. Meyer and Goffinet [64] described the presence of large, morphologically differentiated CRN side by side with smaller, more immature-looking CR-like neurons (see also Fig. 2A), which led to the suggestion that the SGL is an additional origin of CRN. This point may require further studies.

5.1. Cell components of the SGL

SGL and CRN are closely interrelated around migestation [23,79]. At 19/20 GW, somata of GABA and/or calretinin+ granules are closely apposed to CRN somata and processes (Fig. 4). In the following gestational weeks, a subclass of SGL granules differentiates into tiny “miniature” interneurons [79], which extend a varicose GABAergic plexus in the middle tier of the MZ, surrounding CRN somata and establishing vesicle-mediated contacts, visualized by synaptophysin+ terminals. Another subclass of SGL granules descends to the horizontal CR axon plexus at the interface of CP and MZ. While in the early SGL the plexus area is cell-free, during the descent of granules from 16 to 23 GW the plexus area becomes cell-dense, mostly occupied by calretinin+ cells (Fig. 4). Before analyzing the possible significance of this finding, we want to mention the rodent literature pertinent to the migration of interneurons through the MZ.

Cortical interneurons comprise a large variety of local-axon neuronal classes with distinct morphologies and neurochemical profiles, even though all express the inhibitory transmitter GABA [105]. In rodents, interneurons are born in the ganglionic eminences (lateral, medial and caudal GE), from where they take multiple tangential migration routes, including the MZ, toward their target layer in the CP. Interneurons migrating through the MZ may take different orientations and directions, and may even soujourn for a few days before switching to a radial migration mode and descend into the cortical plate [106–110].This migration is controlled by many factors; among them the chemokine receptor CXCR4, which controls tangential migration in response to its ligand, CXCL12 aka SDF1, expressed in the meninges [25,26,111–113]. Interestingly, this chemokine signaling pathway is also involved in the subpial tangential migration of CRN, which are positive for CXCR4 [27,82].

It is still a matter of debate whether the birthplace of interneurons in human is restricted to the ganglionic eminences as it is in rodents. Various studies point to a more widespread generation, including the cortical proliferating zones, as a result of a diversification of interneuron origins in primate evolution [114–119]. In the case of the human MZ, it is reasonable to infer that part of the SGL granule cells are migrating interneurons en route to the CP, which use the CR plexus as a migration substrate to travel to distant target regions. The dimensions of the human cortex are far beyond those of the mouse cortex, a factor that may have contributed to the development of migration modes that are not present in smaller cortices.

5.2. The GABAergic innervation and death of transient CRN

The GABAergic nature of the SGL raises the question of a GABAergic innervation of CRN. While GABAergic neurons are a consistent

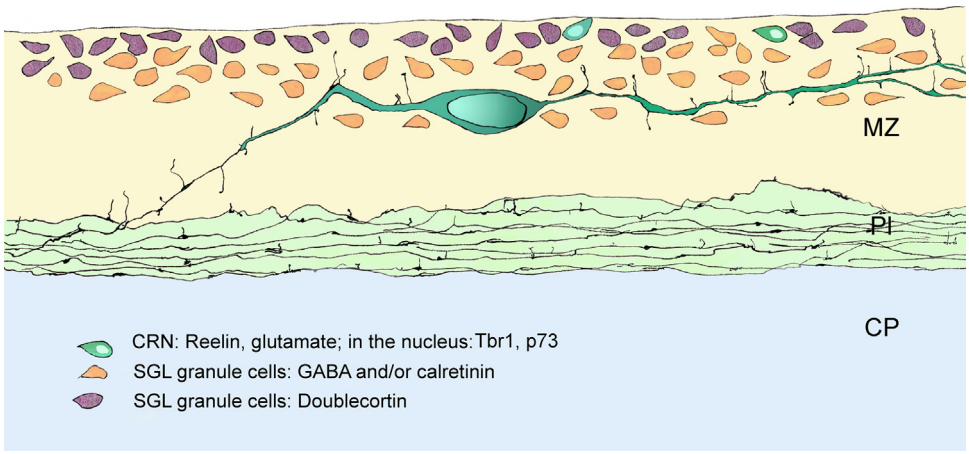

Fig. 3. Semi-diagrammatic representation of the initial SGL and CRN at 14 GW, drawn from DiI-labeled CRN. CRN still display a horizontally oriented soma and give rise to a descending axon that courses in the CR plexus (PI; light green) in the deep MZ. Smaller, more immature CRN lie immersed in the SGL. SGL granule cells express calretinin and/or GAD, with a high degree of colocalization. More immature SGL granule cells express doublecortin and form the most superficial tier of the SGL. The CP is shown in light blue.

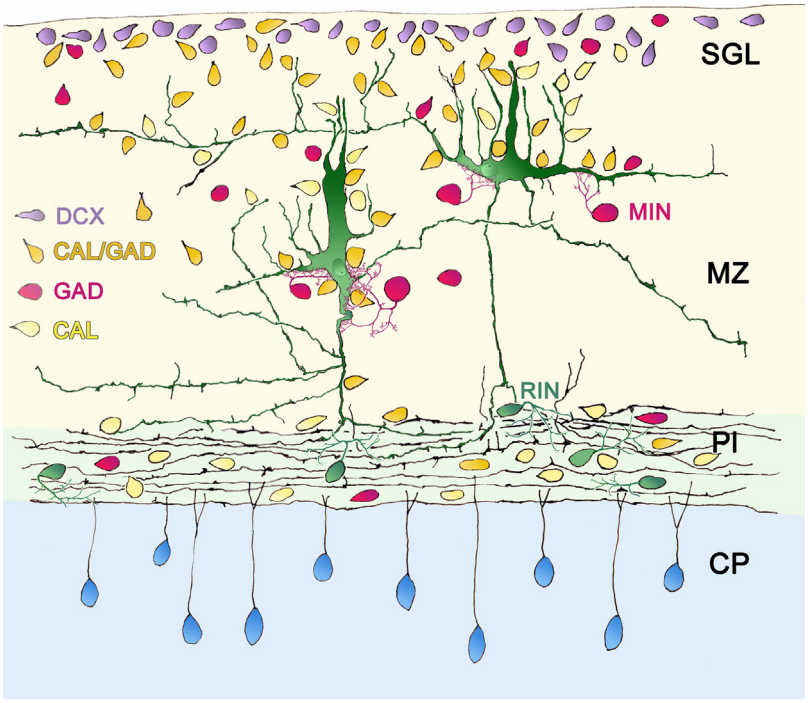

Fig. 4. Semi-diagrammatic representation of the differentiating SGL-derivatives and the transient polymorphic CRN at 25 GW. Two large tCRN are shown extending their axons into the plexus (PI; in light green). Different SGL- derivatives are represented with different colors (color code in the Figure). The tCRN are densely surrounded and contacted by SGL cells. The GABAergic miniature interneurons (MIN) form an axonal plexus that innervates the tCRN somata. In the plexus area, Reelin+ interneurons (RIN) extend processes and contribute to the Reelin signal. The plexus area is now populated by numerous interneurons, most of which are calretinin+ (cal). Calretinin and GAD are expressed in largely overlapping though not identical SGL-populations.

though not numerous component of the cortex from the advanced preplate stage onward [55,84,120], the arrival of the SGL provides a massive GABAergic environment for CRN. In the initial stage, around 14-16 GW, when CRN lie immersed in a GABAergic SGL (Fig. 3), the overall immaturity and probably migratory movements of granule cells make the establishment of permanent synaptic contacts unlikely; in fact, synaptophysin+ vesicles are at this time point restricted to the CR axon plexus innervating CP pyramidal cells [79]. However, GABA in the immature nervous system may act through non-vesicle mediated volume transmission, and the SGL may temporarily exert a trophic influence on CRN [121–123]. The constitutive expression of Reelin in CRN from early stages on is not necessarily a sign of maturity; CRN rather undergo a pronounced morphological differentiation, i.e. profuse outgrowth of processes and changes in orientation, *after* the arrival of the SGL, while they continue to extend more axonal branches into the CR plexus. The maturation of the SGL and of CRN is thus proceeding in concert around midgestation. The maximum development of the miniature GABAergic interneurons at 23-25 GW coincides with the onset of degenerative changes in the polymorphic CRN, which shortly before their death display a massive presence of GABAergic terminals contacting their somata [79] (Fig. 4). While the GABAergic influence on human CRN is basically unexplored, there are numerous studies in rodent cortex addressing this question up to the death of CRN during the second postnatal week [30,31,124,125]. In the late embryonic and early postnatal period, CRN in rats and mice

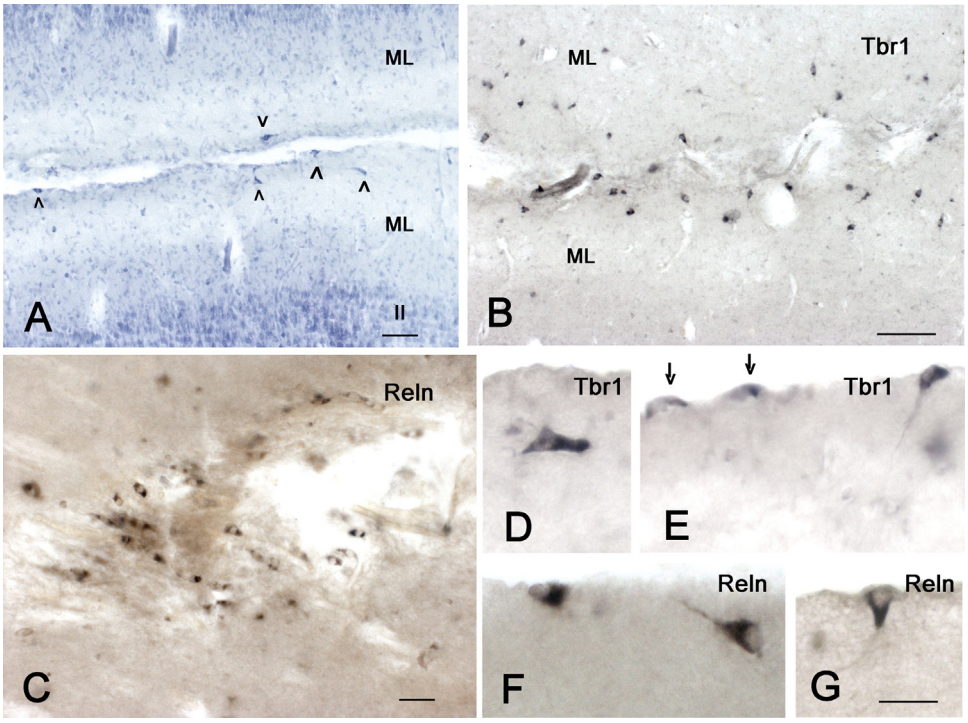

Fig. 5. The persisting CRN in the cortex at term (40GW). A: Nissl-stained section showing the molecular layer of closely adjacent gyri. Presumed pCRN below the pial surface are marked with arrowheads. B: Tbr1+ pCRN at the interface of two closely adjacent gyri, separated by the pia mater and a blood vessel. ML: molecular layer. C: A meningeal blood vessel enters the cortex at the bottom of a sulcus and branches in the molecular layer. Numerous pCRN, in this case stained with a Reelin-antibody, are aggregated around the vessels. D,E: Examples of pCRN immunostained with Tbr1. Notice the extremely superficial position of the pCRN (arrows) in E. In the pCRN, Tbr1 is localized in the cytoplasm, whereas in the tCRN, it is in the nucleus. F,G: Reelin+ pCRN. Bars: in A: 20 μm; in B: 40 μm: in C: 20 μm, in G, for D-G: 10 μm.

receive GABA A-receptor mediated GABAergic input from several sources [126,127]. First, there are the interneurons of the molecular layer [30,31,128], second, Martinotti-type neurons in the CP sending GABAergic axons into layer I [129], third, axons from GABAergic neurons in the subplate [130], and fourth, GABAergic projections from the zona incerta [131,132].

During development, GABA has a different functional significance than in the mature brain, owing to the differential expression of chloride transporters. Immature neurons express high levels of the chloride inward transporter NKCC1 which is downregulated later in development [133]; in turn, the chloride outward transporter KCC2 is developmentally upregulated as cortical neurons mature [134]. This developmental imbalance leads to high intracellular concentrations of Cl^- maintained by an active chloride transport, and renders the GABAergic signal depolarizing [123,131,135,136]. In this context it is important that CRN fail to upregulate KCC2 [137] but permanently express NKCC1. Recent work demonstrated that NKCC1-dependent depolarizing GABAergic signaling activates cell death in CRN mediated by the neurotrophin receptor $p75^{NTR}$, a member of the tumor necrosis factor family [138]. Interestingly, TAp73, expressed in CRN around midgestation, is a direct activator of $p75^{NTR}$ [139]. Expression of p73, a double faced life/death protein, may thus delimit the life span of the transient CRN, and eventually be instrumental in their demise through a signaling cascade involving NKCC1 and $p75^{NTR}$.

There is an important difference between rodents and human regarding the timing of the death of CRN. In rodents, CRN die during the second postnatal week, when the definitive interneurons of the molecular layer are in place and functionally active [31,125,140,141]. The innervation of the transient (t) CRN by equally transient GABAergic SGL-derived miniature neurons takes place around 23-27 GW [79], when the interneuron populations of layer I are not yet present. However, in both species, the signaling cascade leading to the death of CRN may be the same.

6. The appearance of the persisting CRN

The large, polymorphic CRN that dominate the MZ around midgestation disappear between 23 and 28 GW, although solitary remnants may be found also at later stages. Signs of degeneration (cytoplasmic vacuoles, broken processes, breakdown of the axon plexus) are visible at 22/23 GW, and progress rapidly [23,64,72]. At the same time, a new population of CRN appears in the MZ just below the pial surface, often attached to the basal limiting membrane [79] (Fig. 5). These cells persist into postnatal and even adult life, and are thus considered persisting (p)CRN. They are much smaller than the preceding transient population, and have triangular or horizontal bipolar somata. The axons are no longer visible with Reelin or calretinin immunostaining. According to the Golgi study by Retzius [4] in an 8-month fetus (who at that time considered these cells as a variety of neuroglia), the axons initially descend and then give rise to festoon-like bends with ascending branches. Although morphologically they are different from the tCRN, the pCRN have the same molecular and biochemical profile as the tCRN [79]: In addition to Reelin (Fig. 5C, F,G), they express Tbr1 (Fig. 5 B,D,E), initially also p73 (which is possibly downregulated around term), calretinin, CXCR4, and NOS. They are numerous in the newborn [79], and less common in the adult molecular layer, possibly diluted in the growing cortex [15,83]. It is thus not surprising that pCRN were observed in the adult cortex of a variety of mammals including human, where the authors emphasized the prototypical (rodent-like) CRN-like morphology [15,142,143]. The appearance of a new population of pCRN after the demise of the tCRN may be one of the reasons for the difficulty of defining a CRN, already addressed by Retzius and Cajal. Another reason is possibly the resemblance of some human pCRN with the characteristic morphotype of rodent CRN, whereas the large polymorphic, often vertically oriented tCRN are not present in mice and rats.

An important question is the possible birthplace of pCRN. It has been suggested that some subpial granule cells develop into CRN [64]. This seems now unlikely, since SGL cell components are GABAergic and thus Tbr1-negative. However, around migestation, the presence of solitary dividing, PCNA+ cell nuclei surrounded by doublecortin+ immature neurons [79] suggest the possibility of ongoing division of committed CRN progenitor cells, which might migrate within the SGL, and divide when and where Reelin levels descend to critical levels due to the death of tCRN. pCRN are particularly common near the bottom of small sulci, or along the walls of closely adjacent sulcal walls (Fig. 5A,B), often in close vicinity to blood vessels entering through the pial surface (Fig. 5 B,C) [79], and may play a role in shaping the convoluted surface of the perinatal and postnatal cortex, and influence perfusing vessels through the release of vasoactive substances such as NOS.

7. Two main classes of CRN in human cortex: Features of transient and persisting CRN

Two main variants of CRN exist in the developing human cortex: the tCRN, which dominate the early fetal and midgestation cortex, and the pCRN which appear during the last trimester of gestation. The question arises why an entire CRN population should be eliminated by programmed cell death, just to be replaced by another CRN cell population with a similar molecular profile that persists into adult life? To answer this question, three points may be considered. The tCRN express high levels of Reelin, to the extent that the intensity of their immunoreactivity is unequalled by any other cell type in the brain. The Reelin signal in the cytoplasm is further amplified by the CR plexus, which also secretes Reelin [144] and thus forms a Reelin+ sheet covering the entire cortex, being complemented by late-appearing (23-25 GW) Reelin+ interneurons within the plexus (Fig. 4) [79]. The period of 25-27 GW is a critical time point in corticogenesis, because the massive migration of CP neurons is basically finished, and the high Reelin signal in the MZ may no longer be required. The second point regards the CR axon plexus that provides a generalized, excitatory input to all pyramidal cells of all neocortical areas [83]. However, the human neocortex does not mature homogeneously; for instance, association areas develop differently than primary sensory or motor areas [145]. A unifying, homogeneous innervation may no longer be necessary when functional areas are established, or may even be counterproductive for functional and architectonic diversification. The third point also relates to the transient CR plexus. Golgi staining and DiI-labeling in human revealed that individual axons within this plexus are very long; even in the small mouse cortex they could be followed for over 2 mms. The observation that even degenerating CRN still had axonal growth cones [23,140], suggests that tCRN are engaged, until their death, in extending long axonal collaterals destined to innervate the continuously increasing numbers of apical dendrites of pyramidal cells. Taking into account that the formation of primary sulci begins around 27GW and steeply increases until birth [146,147], the CR plexus may not be able to keep pace with the dramatic expansion of the folding cortical surface [145], and breaks down. At the same time, tCRN may be unable to meet the functional requirements placed upon them by the intense GABAergic signaling, and die as described in section 5.2.

The pCRN do not form a massive plexus at the boundary of layers I and II [79]; in keeping with their small size, their axonal field may be more local. They may be adapted to a situation when new sulci are emerging and a close interplay between the cortical gray matter, meninges and perfusing microvessels is required (Fig. 5). In any case, pCRN may be able to fulfill the functions attributed to CRN in postnatal rodent cortex, such as contributing to early cortical circuits and the formation of cortical columns [30,31,135,136]. Reelin in adult cortex has also roles in synaptic plasticity [148–151], and the pCRN are in an ideal position to innervate the apical dendrites of pyramidal cells.

It is important to point out that the human perinatal and adult molecular layer contains interneurons that display similar morphologies, and sometimes share the direct subpial position of pCRN. The decisive difference is in the transmitter identity: pCRN express Tbr1, although now in the cytoplasm and not in the nucleus as during early stages (Fig. 5D,E), and are therefore not GABAergic; vice versa, interneurons express GABA and may co-express Reelin or calretinin [79]. The question of p73 expression in pCRN remains unclear. Initially, around 30 GW, they are p73-immunoreactive [79]; however, this positivity is not detected postnatally, and it is possible that p73 is downregulated in cortical pCRN. By contrast, in the hippocampus low numbers of p73+ CRN are maintained into adulthood [152]. Low expression levels and a perfect balance between the various anti- or pro-apoptotic isoforms of this complex protein [73] may be some of the reasons why pCRN survive into adulthood.

8. Conclusion

In the human cortex, CRN form a heterogeneous cell family with transient and persisting members. The first few members appear at the very onset of corticogenesis, many others are added at distinct time points later in development, and originate from a variety of sources. After midgestation, at the onset of gyration, virtually all transient CRN degenerate and die. They are replaced by a new family member, the persisting CRN. Despite their different morphologies and fate, transient and persisting CRN share a common molecular profile, characterized by the co-expression of Reelin and Tbr1, complemented by other molecules, such as p73 and calretinin. The extraordinary diversification of human CRN may be human-specific, having evolved in parallel to the increasing complexity of cortical architectonics and functions. It remains an open question whether rodent CRN display a similar heterogeneity.

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