Review article

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Cajal-Retzius cells: organizers of cortical development

Introduction

At the end of the 19th century the neuroanatomist Santiago Ramón y Cajal observed in neocortical samples of a human fetus a specific cell type (**Fig. 1a**) that was characterized by its location close to the outer cortical surface and dendritic processes extending toward the pia mater [10]. A few years later neurons with similar properties were observed in the immature neocortex of other species (**Fig. 1b**) and termed "Cajal'sche Zellen" by the Swedish neuroanatomist Gustaf Retzius [62, 78]. Now this cell population, characterized by their mostly transient appearance in the uppermost layer of the developing cerebral cortex, is termed Cajal-Retzius cells (CRc). In addition, CRc were also described in the developing hippocampus [83]. CRc gained a lot of interest after it was discovered that they are a major source of the extracellular matrix protein reelin, which is essential for layer formation in the neocortex [71, 16]. By their location in the superficial layer and by their reelin expression, CRc were recognized in many species, including primates, rodents, carnivores, pigs, chicken, lizards, crocodiles and turtles, indicating that CRc can probably be found in all amniotes (see [1] for a detailed review). In this review we will summarize (1) the current knowledge about identity, origin and fate of CRc, (2) their functional properties and (3) their relevance for neocortical and hippocampal development.

What is a CRc?

The basic question what defines a CRc is difficult to answer regarding the fact that this cell type was classified by heterogeneous morphological criteria [29]. The current view is that CRc most probably encompass several subpopulations of neurons in the superficial layers of the developing cortex, comparable to the term "pyramidal neurons" that also describes various subpopulations of neurons with a clear functional overlap [58].

Essential features of CRc are (1) their location in the uppermost layer of the developing neocortex (the marginal zone, MZ) or in the outer layers of the hippocampus, (2) their axodendritic organization, (3) their expression of reelin, and (4) their early generation. Birthdating studies revealed that CRc are generated within a rather restricted interval between embryonic day (E) E10 and E12 in mice and E12 to E14 in rats [89, 61] and thus belong to the earliest generated neuronal populations in the cortex.

Typical for CRc is their main axodendritic orientation parallel to the pial surface, with a single main dendrite and an axon that appeared mostly at the opposite pole of the soma, and dendritic branchlets reaching the pial surface. Particularly the "tadpole-like" appearance of the ovoid soma with a single, tapered dendrite running parallel to the pial surface [19, 65] has occasionally been considered as sufficient to characterize CRc, because this attribute allows identification of CRc already in living tissue (**Fig. 1c**). However, it should be noted that other neurons located close to the pial surface, e. g. early glutamatergic pioneer neurons or migrating interneurons, may share this purely morphological feature [52, 68, 69, 91]. On the other hand, CRc differ from these neuronal populations by their wide axonal projections (**Fig. 1d**), which are restricted to the uppermost layer [4, 44, 52, 55, 77, 79].

Immunostaining for the extracellular matrix protein reelin (see excurse 1) strongly labels CRc in the neocortex and hippocampus (**Fig. 1e**), which have accordingly been identified as the major source of reelin in the developing cortex [71, 16]. Thus, CRc were formerly defined "as the family of reelin-immunoreactive neurons in the MZ" [62], and expression of the extracellular matrix protein reelin is considered as the most characteristic feature of CRc. However, although reelin is a necessary marker for CRc, it is not sufficient to unequivocally identify these cells because GABAergic neurons in the MZ also express reelin [3, 35, 52, 68, 69, 72].

Expression of the calcium-binding proteins parvalbumin and calretinin was also frequently used to identify CRc. However, recent studies demonstrated that the expression of these calcium-binding proteins depends on the developmental state, the ontogenetic origin of CRc and the species [35, 60, 91]. In addition, a substantial portion of GABAergic interneurons in the MZ express parvalbumin or calretinin during the first postnatal week [52]. Therefore expression of calcium binding-proteins does not allow for an unambiguous identification of CRc.

Recently other proteins have been used as markers to label CRc. Two interesting candidates are the early B-cell

Excurse 1: Reelin

Spontaneous mutation in the reelin gene led to a severely disorganized organization in the cerebellum, neocortex and hippocampus of the reeler mouse [22, 33, 84]. Using a specific antibody against reelin, it was later revealed that CRc are the major source of reelin in the developing neocortex [16]. Reelin is a relatively large, secreted glycoprotein that integrates into the extracellular matrix (see [92] for review). It is most probably released by constitutive, depolarization-independent pathways [87]. The canonical receptors for reelin are VLDLR (very low density lipoprotein receptor) and ApoER2 (apolipoprotein E receptor 2), which activate various molecular downstream targets via the adaptor protein Dab1 [36, 37]. Reelin also interacts with α3β1 integrins expressed in migrating neurons [20]. Besides its important role during development [92], reelin plays also a role for the maintenance of the mature brain [25].

Reelin has been proposed as a stop signal that terminates radial migration and promotes detachment of migrating neurons from radial glial cells [37]. In addition, reelin may be involved in a stabilization of leading processes, thus anchoring the leading process to the MZ and allowing somatic translocation from the ventricular zone (VZ) to the cortical surface [12, 13, 25]. In contrast, radial glia-dependent locomotion, which is more important when the neocortical anlage becomes thicker, is not affected by reelin [24]. This is different in the developing hippocampus, where reelin directly affects radial glial processes [26]. The simple view that reelin provides a stop signal for migrating neurons was challenged by the observation that bath application of reelin or ectopic expression of reelin in the VZ can rescue migration deficits in organotypic slices from reeler mice [40, 54]. However, reelin was found to rescue a compact granule cell layer in the dentate gyrus only when provided in normal topographical position [23, 93]. These findings suggest that reelin is more than a simple stop signal and contributes to radial migration in a complex way.

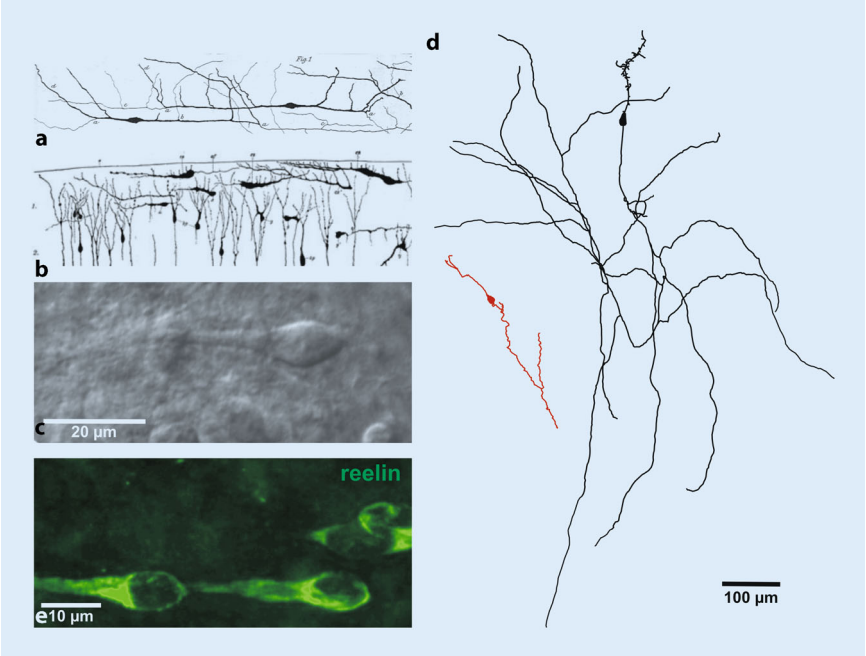

Fig. 1 ▲ Morphological properties of Cajal-Retzius cells (*CRc*). **a** Golgi-impregnation of CRc in an immature rabbit cortex [10]. **b** Golgi impregnation of CRc in a fetal dog brain ([78], taken from [41]). **c** Typical appearance of a CRc in a tangential slice preparation using differential interference contrast optics. **d** Somatodendritic reconstruction of CRc in tangential slices from a E16.5 (*red*) mouse fetus and a P4 (*black*) mouse pup (modified from [46] and [79], respectively). **e** CRc stained with anti-reelin antibody in a tangential slice preparation of a P2 rat

factor2 (Ebf2) and the chemokine receptor CXCR4, which have been utilized to specifically drive GFP or EYFP expression in CRc [5, 14]. However, it is currently unclear whether all or just subpopulations of CRc are labeled in these transgenic animals. Hippocampal CRc have been specifically labeled by expression of EYFP under the control of Wtn3a [75] or CXCR4 [5]. In the MZ of the developing cortex the tumor suppressor gene P73 is found exclusively in CRc [63]. And finally, expression of GFP under a promoter for metabotropic glutamate receptor 2 also led to a specific labeling of CRc in postnatal mice [81].

In summary, a valid definition for CRc are early born, reelin-expressing, glutamatergic neurons in the MZ, with a single tapered dendrite and an axonal compartment restricted to the MZ. However, it is important to consider that most studies on CRc relied only on a restricted set of these criteria, which may explain some of the inconsistent results published.

Origin and fate of CRc

Neocortical CRc are generated at different sites from which they populate the neocortical surface (**Fig. 2a**, b). The earliest CRc that appear during early prenatal stages (E10.5) are most probably generated directly in the ventricular zone of the neocortical *anlage* [56]. The most important source of neocortical and hippocampal CRc is the cortical hem [32, 90], an area which is located at the dorsomedial region of the developing neocortex and is a major organizing center during corticogenesis (**Fig. 2a**). The lateral region of the pallial-subpallial border (sometimes referred as "anti-hem") also gives rise to a subpopulation of CRc [7]. Other sources of CRc have been identified in the retrobulbar area and the pallial septum [7, 63, 91], rostromedial regions at the border between pallium and subpallium. Also subcortical areas such as the thalamic eminence have been suggested as a possible source of CRc [86]. One possible explanation why CRc are generated at so many different locations is that multiple sources are required to provide a sufficient number of CRc during a relatively short developmental period [82]. While the CRc of different origins populate distinct neocortical regions during early developmental periods, at later stages hem-derived CRc dominate most areas of the neocortex [7]. Distinct migratory rates of the different CRc subpopulations contribute to the spatiotemporal profile of CRc distribution (**Fig. 2b**; [6]).

The migration of CRc is restricted to the MZ by an interaction between the chemokine CXCL12 (also referred as

stromal-derived factor 1, SDF-1) released from leptomeninges and its receptors on CRc, CXCR4 [14] and CXCR7 [88]. Interestingly, the interaction between CXCL12 and CXCR4 induces a strong hyperpolarization and reduces the excitability of CRc [53], suggesting that chemical cues and electrical signals can interact during structural development. The migration rate of CRc is enhanced after cell-type selective inactivation of Vamp3, which is required for exocytosis of soluble factors, indicating that autocrine processes may be involved in the regulation of CRc migration [6].

The vast majority of neocortical CRc disappear during the first two postnatal weeks in rodents [14, 19] and during comparable time periods in other species, including humans (62, but see [57]). Only about 3.5% of CRc, which were unequivocally labeled in Ebf2-GFP transgenic animals, survive until P58 in rodents [14]. Interestingly, in the hippocampus a considerably higher portion of CRc (ca. 15–20%) persist until P60 [5]. The loss of CRc is most probably due to apoptotic cell death (**Fig. 2b**; [4, 19]). In particular glutamatergic inputs [67] and depolarizing GABAergic inputs [8] seem to be a trigger for apoptosis. Further downstream mechanisms are currently not completely understood, but regulation by the anti-apoptotic factor P73 [86] and the neurotrophin receptor $p75^{NTR}$ [8] is most probably involved in this process. Although several reports suggest that CRc persist until adulthood in the neocortex of humans or other higher mammals, in most of these studies insufficient criteria for CRc identification, like expression of calbindin, calretinin or reelin, were used. Thus, it is currently unclear whether neocortical CRc can persist in higher mammals.

Functional properties of CRc

CRc show the characteristic physiological properties of immature neurons: a low resting membrane potential, high input resistance, depolarized action potential threshold and action potentials with small amplitude and long duration [34, 51]. A variety of voltage-dependent potassium and calcium channels has been described in pre- and postnatal CRc (e. g. [48, 66]). Neocortical and hippocampal CRc show a prominent hyperpolarization-activated voltage sag, which was mediated by hyperpolarization-activated cyclic-nucleotide dependent channels [43, 31].

CRc express a variety of neurotransmitter receptors, suggesting that they are integrated into immature neuronal networks (**Fig. 3**). $GABA_A$ receptor-mediated currents dominate both spontaneous and evoked synaptic inputs in neocortical [44, 77] and hippocampal CRc [53, 74]. Activation of $GABA_A$ receptors induces depolarizing and often suprathreshold membrane responses in CRc [50, 65], due to intracellular chloride accumulation mediated by the Na^+,K^+-$2Cl^-$-symporter NKCC1 [2]. In contrast to most neocortical neuronal populations, in which functional expression of the neuron specific potassium chloride extruder KCC2 shifts the GABA reversal potential to hyperpolarizing potentials during postnatal development, CRc do not express KCC2 and thus GABAergic responses remain depolarizing [73]. Since GABAergic inputs to CRc showed heterogeneous pre- and postsynaptic properties [49], they may arise from distinct neuronal sources. GABAergic neurons in the subplate and Martinotti-like interneurons have been identified as presynaptic sources of GABAergic inputs in the neocortex [15, 70], while GABAergic fibers from the zona incerta of the thalamus and other neocortical GABAergic interneurons have been suggested as additional sources (**Fig. 3a**). In the hippocampus neurogliaform interneurons of the stratum lacunosum-moleculare and interneurons of the oriens-lacunosum-moleculare subtype have been identified as presynaptic sources [74]. In addition to GABA, glycine receptors elicit depolarizing responses in CRc [45]. However, since no evidence for synaptic glycinergic current has been found, these receptors are most probably activated non-synaptically by the endogeneous glycinergic agonist taurine [76].

Ionotropic glutamate receptors of the NMDA subtype have also been found on CRc, while AMPA receptors are probably not expressed in rodents [21, 67]. Murine CRc also express metabotropic glutamate receptors [59]. Glutamate receptors are most probably not considerably implicated in synaptic transmission, as only in rat CRc sparse glutamatergic excitatory postsynaptic potentials mediated by NMDA receptors have been observed [77]. CRc also receive serotonergic [39] and noradrenergic [80] synaptic inputs, but their physiological functions have not been investigated yet.

While the expression of neurotransmitter receptors and the synaptic inputs clearly indicate that CRc are integrated into immature synaptic networks, the

Abstract

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Abstract
Cajal-Retzius cells (CRc) are a major neuronal population in the marginal zones of the developing neocortex and hippocampus. CRc belong to the earliest born neurons in the cortex and originate from several regions at the pallial-subpallial border. A substantial fraction of CRc disappears during postnatal development. CRc express a variety of neurotransmitter receptors, receive mainly GABAergic synaptic inputs and give rise to glutamatergic synapses. Recent studies identified some modes of how CRc are integrated into immature neuronal circuits, although their exact role for immature information processing remains unknown. As a major source for the extracellular matrix protein reelin, which is critically involved in lamination of the cerebral cortex, CRc are an important factor for the structural development of the neocortex and hippocampus. In addition, CRc contribute to the patterning of cortical areas and shape the development of perforant path connections in the hippocampus. In summary, CRc are a major cellular element in the structural development of the cerebral cortex and may serve as a link between early electrical activity and morphological organization during prenatal und early postnatal development.

Keywords
Cortical development · Neuronal migration · Marginal zone · Reelin · Hippocampus · Neocortex

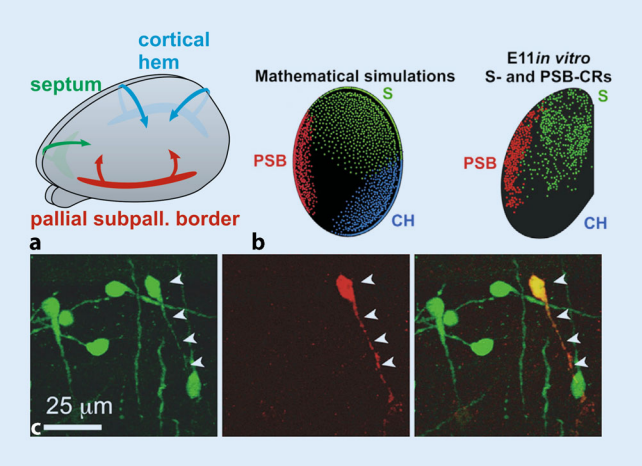

Fig. 2 ▲ Origin and fate of CRc. **a** Schematic diagram of proposed sources and migratory routes of CRc subpopulations originating from the septal anlage (*green*), the cortical hem (*blue*) and the pallilal-subpallial border (*red*). **b** Computer simulation and real distribution of different CRc subpopulations (color code as in **a**) in fetal neocortical flatmount preparations [6]. **c** Expression of activated Caspase 3 (*red* immunostaining) in an Ebf2-GFP labeled CRc, which is showing first signs of degeneration (from [14])

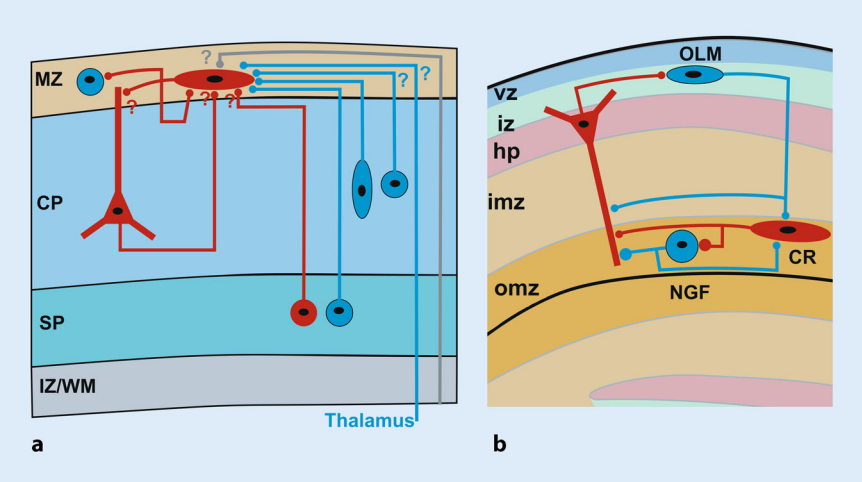

Fig. 3 ▲ Hypothetical circuit diagram illustrating the integration of CRc in immature neocortical (adapted from [47, 28]) and hippocampal networks (adapted from [75]). **a** Neocortical CRc receive mainly GABAergic synaptic inputs (*blue lines*), with identified direct connections from subplate (*SP*) neurons and Martinotti cells (*blue ovoid symbol*) and suggested additional GABAergic inputs from unidentified neocortical interneurons and the thalamic zona incerta. The mostly silent glutamatergic synapses (*red symbols*) on CRc may originate from glutamatergic SP neurons, pyramidal neurons in the cortical plate (*CP*) or other CRc. In addition, CRc are affected by serotonergic or adrenergic inputs from raphe nucleus or locus coeruleus, respectively (*gray line*). The glutamatergic CRc are supposed to synapse on pyramidal neurons and glutamatergic and GABAergic neurons in layer I. **b** Hippocampal CRc receive GABAergic inputs from neurogliaform interneurons (*NGF*) located in later stratum lacunosum-moleculare and from oriens-lacunosum-moleculare (*OLM*) interneurons. CRc make strong glutamatergic synapses on NGF, thus mediating a feed-back of CRc and a feed-forward inhibition of pyramidal neurons, and infrequently contact pyramidal neurons directly (*vz* ventricular zone, *iz* intermediate zone, *hp* hippocampal plate, *imz/omz* outer/inner marginal zone)

output of neocortical CRc has only cursorily been identified (◘ **Fig. 3**). Studies using immunohistochemical markers indicate that CRc are glutamatergic [17, 35]. The glutamatergic nature of CRc was corroborated by the expression of vesicular glutamate transporters [38] and functional glutamatergic outputs [75]. Is has been suggested that neocortical CRc provide an excitatory input to the apical tufts of cortical pyramidal cells [56], in accordance with the observation that they form asymmetric, putatively glutamatergic synaptic contacts on terminal tuft dendrites of non-GABAergic neurons [4, 77]. In addition, CRc make synaptic contacts on other glutamatergic targets, most probably other CRc, and on GABAergic cells in the neocortical MZ [4]. However, functional evidence for synaptic transmission to postsynaptic targets of neocortical CRc is missing [81]. In contrast, in the hippocampus functional glutamatergic synapses from CRc to pyramidal cells and neurogliaform interneurons have been identified (◘ **Fig. 3b**; [5, 75]).

Role of CRc during corticogenesis

One of the major functions proposed for CRc is their direct involvement in neocortical and hippocampal development. The extracellular matrix protein reelin released from CRc is supposed to play a major role in the lamination of the six-layered neocortex, acting mainly as a stop signal for migrating neurons that reach the CP-MZ border (see Excurse 1 for details). In addition, reelin is probably also a permissive factor that is required for adequate radial migration [40, 54].

On the other hand, the central role of CRc in organizing cortical lamination has been questioned by the observation that absence of the majority of CRc in P73-depleted mice [64] or hem-ablated mice [90] affect neither the formation of the cortical plate nor neocortical lamination, respectively. Although the result of these experiments seems to suggest that CRc-derived reelin is not essential for cortical lamination, reelin released by reelin-expressing interneurons or a compensation by transient CRc subpopulations of different ontogenetic origin may be sufficient for adequate reelin supply to the MZ [90]. Recently, it has been shown that nectin1, an integral membrane protein expressed in CRc, interacts directly with nectin3 in radially migrating neurons, which provides the first evidence that CRc can influence radial migration also by direct cell–cell interactions [28].

Moreover, recent results indicate that the different subpopulations of CRc are involved in the patterning of neocor-

tical areas. Selective ablation of septum-derived CRc at early developmental stages (E10–11), although compensated for by other CRc subpopulations originating from the hem or the pallial-subpallial border, results in an increased area of motor cortex, while the somatosensory cortex is slightly shifted toward caudolateral directions [30]. These effects were most probably caused by a direct effect of this CRc subpopulation on neuroblasts in the ventricular zone via secreted molecules, putatively fibroblast growth factors [30]. In line with this, the redistribution of different CRc subpopulations after selective alteration of migratory rates in Vamp3-inactivated CRc shifts the localization of primary and secondary sensory areas in the mouse neocortex [6], further emphasizing that CRc can impose regionalization cues to the immature neocortical anlage.

In addition to this morphogenic function of CRc in the cerebral cortex, hippocampal CRc are also required for establishing proper connectivity in the hippocampus. In the developing hippocampus CRc axons projecting towards the entorhinal cortex [11] most probably serve as guiding cues for ingrowing entorhinal afferents [18, 85]. In contrast, CRc seem to limit the ingrowth of commissural axons in the hippocampus [9].

Conclusion and summary

CRc have been described for more than 100 years, but it was only after the application of modern methods that detailed insights into their physiological properties and molecular functions were archived. These experiments clearly identified Cajal-Retzius cells as an integral part of immature neuronal circuits and as a major cellular organizer of structural development in the neocortex and hippocampus. Intriguing questions concerning the functional properties that remained to be addressed are the following: (1) Can a concise definition of CRc according to either molecular markers and/or functional roles be maintained or do CRc just represent an arbitrary compilation of neurons with similar appearance, but different origins and functional roles during development? (2) Can CRc serve as integrators between electrical activity and cortical development by an activity-modulated release of reelin or growth factors? (3) What is the exact role of neocortical and hippocampal CRc for transient neuronal circuits? While the role of early born subplate neurons for neonatal network activity and the formation of mature connectivity has been established [42], only sketchy information about the exact integration of CRc into neuronal circuits is currently available.

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Werner Kilb studied biology at the Heinrich-Heine University in Duesseldorf. After his PhD work on the electrophysiological properties of Retzius neurons in the medicinal leech, he changed his focus to Cajal-Retzius neurons in the rodent brain. In addition, he is interested in the development of GABAergic inhibition and chloride homeostasis as well as in the role of taurine as neuromodulator during early brain development.

Michael Frotscher studied medicine at the Humboldt-University in Berlin. After his medical thesis on development and regeneration of neocortical neurons, he turned his attention to studies on the differentiation and plasticity of hippocampal neurons and their connections. Currently he is Hertie Professor for Neuroscience at the Center for Molecular Neurobiology Hamburg (ZMNH).

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