PRDM12 in Health and Diseases

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PRDM12 is a member of the PRDI-BF1 (positive regulatory domain I-binding factor 1) homologous domain (PRDM)-containing protein family, a subfamily of Kruppel-like zinc finger proteins, controlling key processes in the development of cancer. PRDM12 is expressed in a spatio-temporal manner in neuronal systems where it exerts multiple functions. PRDM12 is essential for the neurogenesis initiation and activation of a cascade of downstream pro-neuronal transcription factors in the nociceptive lineage.

cancer | cell metabolism | neurogenesis | pain perception | PRD-BF1 and RIZ homology domain containing gene family

1. PRDM12 is a member of PRDM gene family

The human PRDM gene family consists of 19 members that encode for Kruppel-like zinc finger proteins, which share a conserved N-terminal PR domain, followed by several zinc finger domains [1][2]. The PR domain is endowed with lysine methyltransferases (KMTs) activity; however, enzymatic activity is established only for a few family members [1][3][4][5]. PRDMs regulate gene expression, the transduction of many cell signals and participate in many developmental processes, including the proliferation/differentiation switch, inflammation and metabolism control. Recently, several reports indicated a pivotal role of multiple PRDMs in neuronal cell fate establishment [6]. PRDMs can also regulate the proliferation and differentiation of neuronal progenitors through epigenetic modifications. The dysregulation of PRDMs is also involved in the onset and progression of several human cancers. Most PRDM genes express two main molecular variants, with one lacking the PR domain. These two isoforms, which can be generated by either alternative splicing or the alternative use of different promoters, play opposite roles in cancer [1][7][8]. Specifically, the full-length product (PR-plus) usually acts as a tumor suppressor, whereas the short isoform (PR-minus) functions as an oncogene [7][9]. This duality is termed the ‘Yin and Yang’ mechanism [1][8][9][10].

2. Established PRDM12 Functions: Neurogenesis

In P19 embryonal carcinoma cells, an in in vitro mouse model systems for neurogenesis, retinoic acid (RA) that prompted neural differentiation into neurons and glial cells, induced Prdm12 expression, possibly through the regulation of a putative RA receptor (RAR)-beta response element. Additionally, Prdm12 overexpression impaired P19 cell proliferation and increased the percentage of cells in the G1 phase accompanied by p27 upregulation. Furthermore, both the PR domain and zinc finger domains were required for the anti-proliferative activity of

PRDM12. In contrast, Prdm12 knockdown and Prdm12 mutants resulted in an increased number of cells in a suspension culture of RA-induced neural differentiation [11]. Altogether, these results suggested that Prdm12 was induced by the RA signaling and might control neural differentiation during development through p27 expression level regulation.

During the early neurula stage of Xenopus embryos, prdm12 expression was also revealed in the lateral pre-placodal ectoderm after the late gastrula stage (st. 13), where it was regulated by both BMP and Wnt signaling (**Figure 1** B) [12]. Several gain- and loss-of-function experiments were approached to clarify the role of Prdm12 in early Xenopus development. prdm12 overexpression through mRNA injection inhibited the expression of neural crest markers (Foxd3, Slug, Sox8, -9, -10 and Twist) via H3K9 trimethylation (H3K9me3) (**Figure 2** B). Otherwise, prdm12 knockdown through an antisense morpholino oligomer (MO) inhibited the expression of presumptive trigeminal placode markers and expanded the neural crest region through a H3K9me3 level decrease in the Foxd3 gene promoter (**Figure 2** B). Notably, the histone demethylase, Kdm4a, inhibited the expression of presumptive trigeminal placode markers producing a similar effect of prdm12 knockdown. Accordingly, ChIP-qPCR analyses revealed that the expression of H3K9me3 on the Foxd3, Slug, and Sox8 promoters was inhibited by Kdm4a overexpression. Altogether, the mutual relationship between Prdm12 and Kdm4a indicated that the modification of the H3K9 methylation levels on the neural crest gene promoters by these two proteins would determine a demarcation line between the pre-placodal ectoderm and the neural crest region [12]. Interestingly, a recent analysis, performed to screen for zic1 targets in the midbrain region of Xenopus , revealed that prdm12 was a downstream target of zic1 [13]. Zic1 is a highly conserved zinc finger transcription factor playing a critical role in the establishment of the nervous system; it is expressed on the lateral edge of the neural plate and in the dorsal neural tube [13]. Here, prdm12 was expressed in the caudal forebrain, midbrain and hindbrain. Moreover, during embryonic development, zic1 and prdm12 were co-expressed in the same cell, with Zic1 controlling the expression of prdm12 mediated by Wnt signaling during brain cell differentiation. Additionally, gain- and loss-of-function experiments revealed that prdm12 was both necessary and sufficient to promote midbrain formation in the embryo [13].

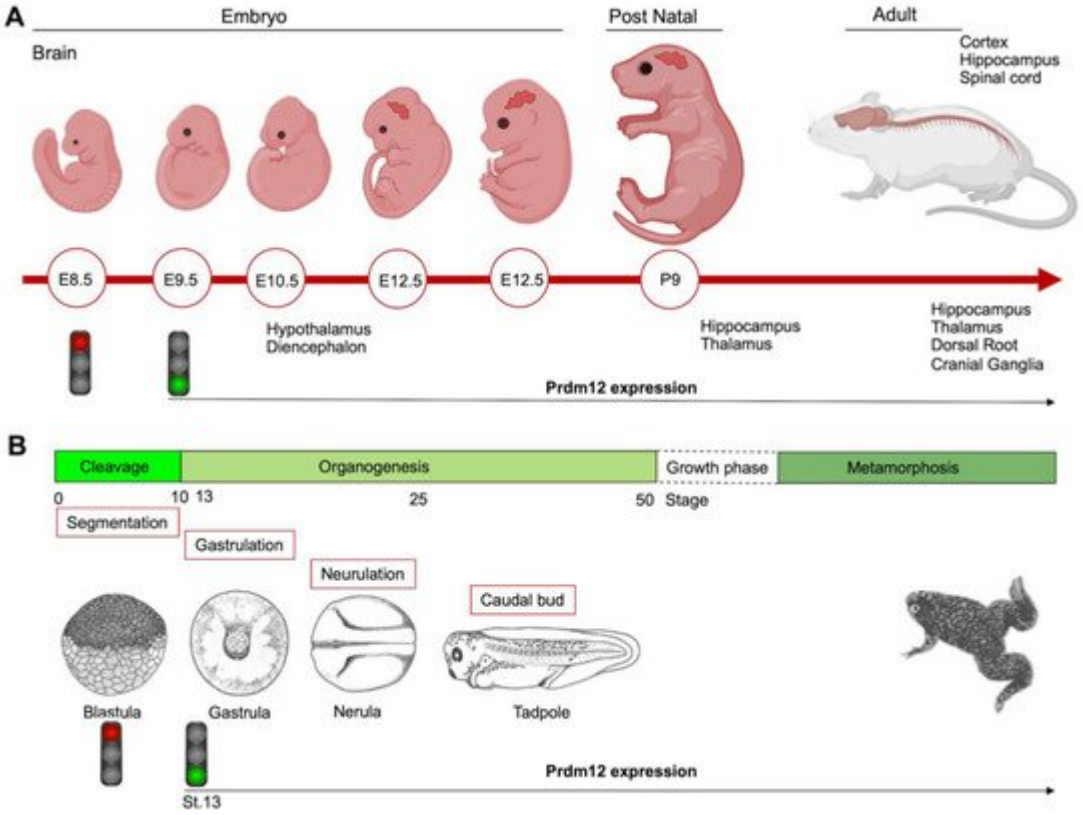

Figure 1. Schematics showing the Prdm12 expression data collected throughout mouse brain development and in different embryonal stages of *Xenopus*. (**A**) *Prdm12* was expressed from early neurogenesis (E9.5) in the developing spinal cord. Additionally, *Prdm12* can be detected weakly in the caudal forebrain and midbrain where it increases at E10.5 in precise neuronal progenitor areas. (**B**) *prdm12* expression was revealed during the early neurula stage of *Xenopus* embryos, specifically in the lateral pre-placodal ectoderm after the late gastrula stage (St.13).

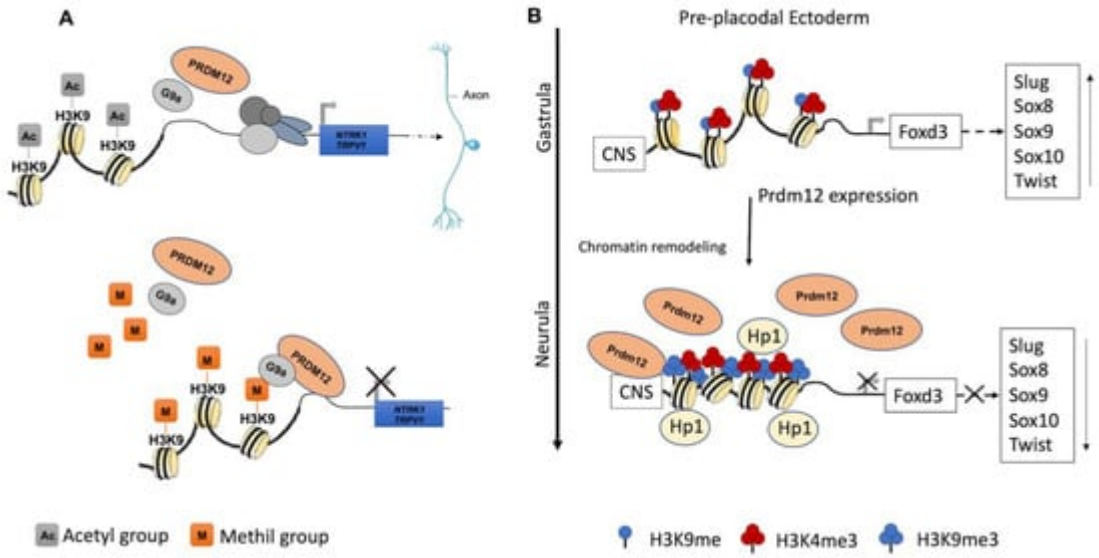

Figure 2. Recognized PRDM12 functions in neurogenesis. (**A**) PRDM12 lacks an intrinsic HKMTase activity, and it recruits, through its second zinc finger domain, the H3K9 methyltransferase G9a to dimethylate histone H3 at lysine 9 (H3K9me2), a repressive transcriptional mark. Particularly, PRDM12 regulates a nociceptor-specific transcriptional program, such as NTRK1/TRPV1. (**B**) In the pre-placodal ectoderm, *PRDM12* is expressed and specifically stimulates the trimethylation of histone H3 at lysine 9 (H3K9me3) on the *Foxd3* promoter to bind a conserved noncoding sequence (CNS). Additionally, Prdm12 inhibited the expression of different neural crest markers (Slug, Sox8, -9, -10 and Twist). A chromatin remodeling factor, HP1, recognizes the trimethylation of H3K9me3 and recruits other factors to convert euchromatin to heterochromatin.

In addition to the central nervous system, prdm12 expression was also detected in the peripheral nervous system. The V1 interneurons are a class of inhibitory glycinergic neurons playing a conserved role in vertebrate locomotion; they originate from the spinal cord p1 domain and are characterized by the expression of Engrailed-1 (En1/Eng1). prdm12b , the zebrafish prdm12 homolog, was expressed in the p1 domain of the neural tube at least partially in response to Sonic Hedgehog (Shh) signaling. Interestingly, prdm12b disruption led to the inappropriate dorsoventral patterning of the neural tube, depletion of the V1 interneurons and an impaired escape response in zebrafish. These data suggest that prdm12b is a key component of the genetic program required for motor circuit formation [14]. Likewise, in the frog embryos, prdm12 was selectively expressed in p1 progenitors of the hindbrain and spinal cord; this restricted expression profile was also observed in the neural tube of chick embryos and in the ventral nerve cord of the larvae of the basal chordate amphioxus. Moreover, in frog, chicken and mice, Prdm12 expression in the p1 domain progenitors of the caudal neural tube was dependent on RA signaling and Pax6 and it was repressed by Dbx1 and Nkx6-1/2 expressed in the adjacent p0 and p2 domains [15]. Functional studies in Xenopus and the genome-wide identification of molecular targets by RNA-seq and ChIP-Seq, revealed that the vertebrate Prdm12 acted as a general determinant of V1 cell fate, at least in part, by directly repressing Dbx1 and Nkx6 genes. Both the PR and zinc-finger domains of Prdm12 were required to exert this function; specifically, Prdm12 may act as a G9a-dependent repressor to induce En1. However, this activity was not found in the amphioxus, and differences in the C-terminal region of the protein, including the zinc-finger domains, may account for the differential functions of the amphioxus and vertebrate proteins. Overall, these findings indicated that Prdm12 could promote V1 interneurons through cross-repressive interactions with Dbx1 and Nkx6 genes. Interestingly, this function could be acquired after the split between the vertebrate and cephalochordate lineages [15]. Recently, the analysis of CRISPR/Cas9 prdm12 mutants, recapitulating the phenotypes observed by MO-based approaches, has demonstrated that prdm12b acts as transcriptional repressor in zebrafish, and that it can interact with both EHMT2/G9a and Bhlhe22, a member of the basic Helix-Loop-Helix (bHLH) family, through its zinc-finger domain. However, bhlhe22 function is not required for eng1b expression in vivo, suggesting that other bhlh genes could be involved during embryogenesis. This study also suggested that prdm12b is not only required to repress non-p1 fates, but also to promote p1 fates [16]. Additionally, a study in a mouse model revealed strong evidence that Dbx1 and Prdm12 expression was inhibited by both Pax3 and Pax7, two highly related transcription factors controlling the spatial organization of spinal differentiation [17]. Notably, another member of the Prdm family, PRDM13, was recently shown to be required for the restriction of Prdm12 expression to the ventral neural tube during mouse embryogenesis [18]. In mouse Prdm13 mutants, Prdm12 was aberrantly expressed in the dorsal region, altering the

identity of these neurons. Mechanistically, PRDM13 interacted with the genomic regions, overlapping those bound by neural bHLH factors and functions, by limiting the ability of these bHLH factors to activate enhancer-driven reporters. Specifically, PRDM13 repressed Prdm12 in the dorsal neural tube via the inhibition of NEUROG1 and NEUROG2, which were likely to activate mouse Prdm12 transcription through one enhancer localized more than 25 kb upstream of the ATG starting site [18].

PRDM12 could also function in the vagal sensory nervous system, to maintain visceral homeostasis. Indeed, transcriptome profiling performed to reveal differentially expressed genes between nodose and jugular C-fiber neurons detected Prdm12 as preferentially expressed in mouse jugular vagal neurons [19].

3. Established PRDM12 Functions: Pain Perception

Initially, 10 different homozygous mutations in PRDM12 were identified in subjects from 11 families with a congenital insensitivity to pain (CIP), a type of hereditary sensory and autonomic neuropathy (HSAN), which is a clinically and genetically heterogeneous group of inherited neuropathies predominantly affecting peripheral sensory and autonomic neurons [20]. Most of the variants were missense mutations, despite the revelation of a splice-site mutation, a frame-shift mutation and an 18-alanine-repeat mutation (general population contains a maximum of 14-alanine in this polymorphic site; **Figure 3** and Table S1). Heterozygote carriers were asymptomatic with a normal pain perception. To determine whether these mutations could cause developmental defects in the sensory neurons, committed to becoming nociceptors, the expression of PRDM12 during embryogenesis and the differentiation in various in vivo models (mouse, Xenopus and human iPSC derived sensory neurons) was explored. Prdm12 was expressed in nociceptors and their progenitors and participated in the development of sensory neurons [20]. Moreover, the CIP-associated PRDM12 mutations impaired the histone-methylation capacity [20]. In an independent study, Prdm12 was also investigated as a key regulator of sensory neuronal specification in *Xenopus* [20]. In this case, the modeling analysis of human PRDM12 mutations causing HSAN revealed a remarkable conservation of the mutated residues during evolution. As shown by RNAseq analyses, the expression of wild-type human PRDM12 in Xenopus induced the expression of several sensory neuronal markers including Islet1 and Tlx3; in contrast, embryos treated with PRDM12 MO or PRDM12 mutants displayed reduced levels of these markers [21]. In *Drosophila* , the Hamlet gene was identified as the functional PRDM12 homolog that controls nociceptive behavior in sensory neurons. Interestingly, the ectopic expression of human PRDM12 mutants in Drosophila nociceptor neurons impaired pain perception, thus supporting the idea that PRDM12 was an evolutionary, conserved, master regulator of sensory neuronal specification that played a critical role in pain perception [21]. In addition to that, RNAseq analyses of human patient fibroblasts with PRDM12 mutations disclosed the possible downstream target genes. Among them, the gene-encoding, thyrotropin-releasing, hormone-degrading enzyme (TRHDE) was revealed; its substrate, TRH, was previously found to affect pain in human and rodents. TRHDE knockdown in Drosophila sensory neurons resulted in an altered cellular morphology and impaired nociception. These findings also added to our knowledge that novel molecules and pathways controlled evolutionary, conserved nociception [21].

The upstream genes and signals controlling PRDM12 expression in developing sensory ganglia still remain to be addressed. It could be speculated that PRDM12, essential for TrkA initiation, is also a target of NGF-TrkA signaling, considering that, in adult mice and humans, NGF signaling induces nociceptor sensitization leading to chronic pain states [22] and *PRDM12* is highly expressed in mature nociceptors. Interestingly, PRDM12 expression increased significantly (by 1000 times) when skin-derived precursor cells (a subtype of neural crest stem cells that persist in certain adult tissues such as the skin) were induced in vitro to differentiate into sensory neurons by several molecules, including NGF, which prompted the upregulation of neurogenins [23].

Moreover, both other partners of PRDM12 constituting the transcriptional complex, which epigenetically regulated gene expression in developing nociceptors, as well as the PRDM12 transcriptional targets need to be identified. Overall, these studies suggest that pharmacotherapies targeting this pathway, or the epigenetic mechanisms controlled by PRDM12, and could be a promising strategy in the treatment of chronic pain conditions.

The supplementary understandings of the identity of the potential PRDM12 interactors and the transcriptional, and epigenomic changes in the sensory neuron progenitors upon PRDM12 manipulation, will be relevant in understanding the PRDM12 gene regulation during the generation of the nociceptive lineage. The further comprehension of the involved molecular mechanisms will provide key insights into how sensory neuron diversity is generated and may provide genetic tools to induce a desired neuronal lineage in stem cell engineering.

4. Exploring Novel *PRDM12* Functions: Cancer

Although little is known about the function of PRDM12 in oncogenesis, previous studies showed that *PRDM12* might act as a tumor suppressor gene in human chronic myeloid leukemia (CML) [24][25][26]. In approximately 15% of CML patients, deletions occur on the derivative chromosome 9 [der(9)] within a region containing the PRDM12 gene. The *PRMD12* disruption could prompt the aggressive phenotype and the observed short survival [25]. However, further investigation is warranted to elucidate its role in the CML pathogenesis.

Our pan-cancer meta-analysis based on The Cancer Genome Atlas (TCGA) data showed that *PRDM12* was upregulated in several cancer types: colon, breast, kidney, colon, lung, liver, thyroid, ovary and prostate cancers, suggesting that it could represent a putative tumor marker [7]. These findings indicate that *PRDM12* is not expressed in adult normal tissues. Accordingly, *PRDM12* expression was described only in dorsal root ganglia but not in other adult tissues [7]. Additionally, the integrated analysis of abnormalities of HMTs encoding genes in prostate cancer from TCGA, identified a role for *PRDM12* in the pathogenesis of this cancer type [7]. *PRDM12* gene amplification induced an mRNA expression level increase in cancer cells compared to adjacent normal ones. Moreover, *PRDM12* gene expression showed a significantly positive correlation with the Gleason's score. These findings indicated that *PRDM12* expression level alterations in prostate cancer tissue samples could have a prognostic value [27]. Similarly, in a recent study, somatic copy number alterations were also found for *PRDM12* in stomach adenocarcinoma samples [27]. However, currently, no studies have identified the mechanism by which PRDM12 could participate in oncogenesis. Moreover, unlike the other PRDM family members, a unique

transcript is known for *PRDM12* gene signifying, that the well-known “Yin and Yang” mechanism could not function [10].

The mutational profiling analyses of *PRDM12* gene across human cancers revealed 72 mutations, 30 of which were detrimental somatic mutations (frameshift, in-frame deletions, stop gained and start lost mutations; splice site, UTR, and intron variants). Interestingly, those mutations were significantly enriched in the PR domain of PRDM12 [7]. In particular, PRDM12 was frequently mutated in a splice donor site in a region coding for the PR domain in different tumor types (breast cancer; colon adenocarcinoma; kidney renal clear cell carcinoma; lung adenocarcinoma; pancreatic adenocarcinoma; prostate adenocarcinoma; skin cutaneous melanoma; thyroid carcinoma; uterine corpus endometrial carcinoma) indicating this position as a possible mutational hotspot site (**Figure 3**) [7].

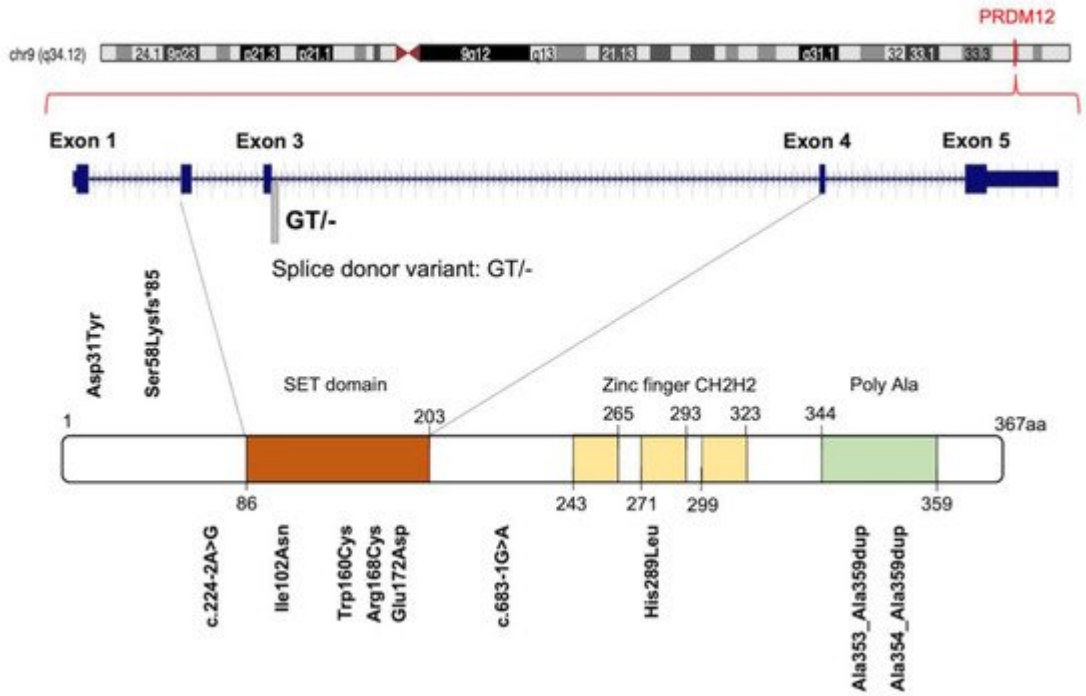

Figure 3. Graphic illustration of human *PRDM12* gene, protein and distribution of known congenital insensitivity to pain (CIP)-causing mutations. Figure shows a schematic representation of PRDM12 architecture: Su(var)3-9, Enhancer-of-zeste and Trithorax (SET) domain, three ‘classical’ zinc fingers (ZnF_C2H2), and a Poly Ala region. Amino acid numbering is reported. See text for details.

Although preliminary lines of evidence suggest that PRDM12 is endowed with a tumor-promoting function, several aspects should be investigated to define the role of PRDM12 in cancer. Cancer tissue specimen analysis by immunohistochemistry could be useful to establish if a correlation among PRDM12 expression, with grading, tumor size, biomarkers serum levels, tumor vascular invasion, overall survival and prognosis, exists. Additionally, in vitro studies should be carried out to investigate the functional role of PRDM12. Overexpression and silencing experiments should be performed to assess its role in cell viability, cell death and proliferation, and cell migration and invasion. Finally, a transcriptome profiling analysis of both PRDM12 overexpressing and silenced cells could

reveal PRDM12 target genes and the involved regulated pathways, thus clarifying its mechanism of action. The PRDM12 function elucidation could provide new insights useful for the discovery of novel therapeutic approaches.

5. Exploring Novel *PRDM12* Functions: Cell Metabolism

An interesting and unexpected PRDM12 role in metabolism was recently demonstrated [28]. Food intake and energy balance regulation depends on the arcuate nucleus of the hypothalamus (ARH), consisting of two distinct neuronal populations: the pro-opiomelanocortin (POMC)-expressing neurons and the neuropeptide Y/agouti-related peptide (NPY/AgRP)-expressing neurons. POMC and NPY/AgRP expressing neurons derive from the same hypothalamic progenitor but have opposing effects on food intake, being the first anorexigenic (POMC) and the last orexigenic (NPY/AgRP). The cell-type-specific transcriptome profiles of developing POMC and NPY/AgRP neurons in mice revealed that POMC and NPY/AgRP cell fates are specified and maintained by distinct intrinsic factors. The transcription regulator PRDM12 was selectively enriched in POMC neurons but absent in NPY/AgRP neurons (**Figure 4**A) [28]. PRDM12 plays an essential role in the early establishment of hypothalamic melanocortin neuron identity and function. PRDM12, indeed, is co-expressed with POMC in mouse neurons of the ARH from the onset of *Pomc* expression at E10.5 and throughout the lifespan [29]. The selective ablation of *Prdm12* from ISL1 neurons greatly reduced *Pomc* expression in the developing hypothalamus, demonstrating that it was essential for the onset and later maintenance of *Pomc* expression. PRDM12 integrates a distinctive set of transcriptional regulators, including NKX2.1 and ISL1, to dictate the neuronal-specific expression of ARH *Pomc*. Moreover, PRDM12 acts to program bodyweight homeostasis, maintaining the hypothalamic *Pomc* mRNA expression level. Adult mice of both sexes selectively lacking *Prdm12* from POMC neurons, showed a considerable reduction in *Pomc* mRNA levels that led to an amplified food intake, adiposity and bodyweight gain, as well as early-onset obesity that recapitulated symptoms of human POMC deficiency (**Figure 4**B) [29][28].

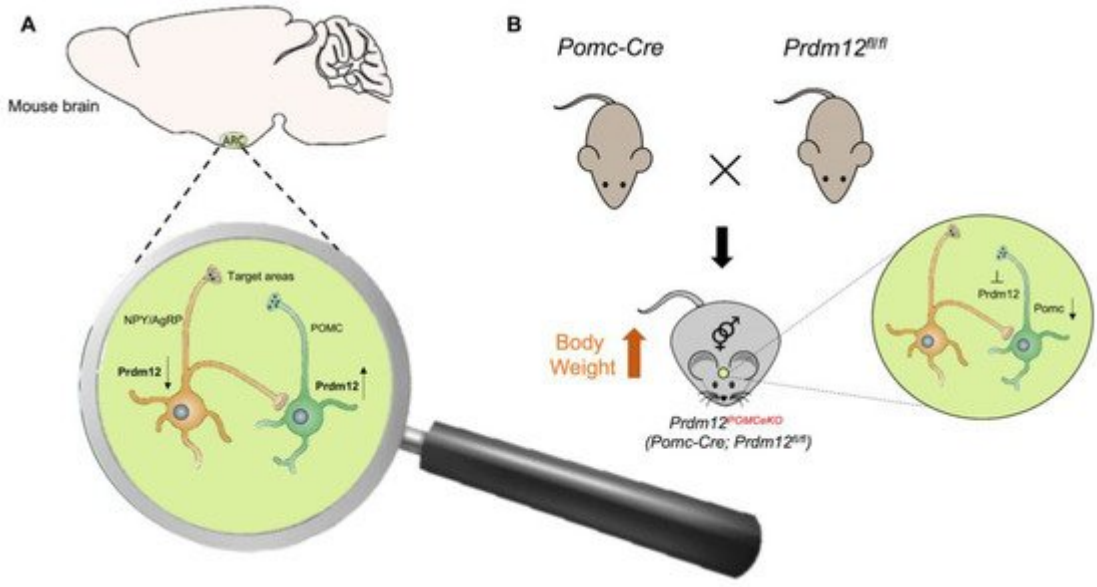

Figure 4. Possible mechanism of PRDM12 in POMC neurons. (**A**) PRDM12 expression level in POMC and NPY/AgRP neurons in the arcuate nucleus of the hypothalamus (ARH) in mouse brain. (**B**) To study the role of

PRDM12 specifically in postmitotic POMC neurons, *Pomc-Cre* mice were bred with *Prdm12fl/fl* mice to generate *Pomc-Cre*; in *Prdm12fl/fl* mice *Prdm12* was selectively deleted in embryonic POMC neurons (designated as Prdm12POMCeKO mice). The expression of Npy and Agrp remained unaffected. Prdm12POMCeKO mice lacking Prdm12 selectively from POMC neurons showed a considerable reduction in *Pomc* mRNA levels that led to severe obesity.

Additional studies should be performed to define the PRDM12 role in human metabolic diseases. The study population could be useful to define whether *PRDM12* polymorphisms represent a risk factor for obesity under permissive environmental conditions. It is conceivable that *PRDM12* polymorphisms generating hypomorphic alleles could impair ARH *Pomc* expression, and thus compromise food intake and energy balance control. Moreover, the disclosure of the PRDM12 mechanism of action in food intake and energy balance could have a relevant impact for the identification of new strategies to counteract obesity.

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