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Review

The Cajal body

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ABSTRACT

The Cajal body, originally identified over 100 years ago as a nucleolar accessory body in neurons, has come to be identified with nucleoplasmic structures, often quite tiny, that contain coiled threads of the marker protein, coilin. The interaction of coilin with other proteins appears to increase the efficiency of several nuclear processes by concentrating their components in the Cajal body. The best-known of these processes is the modification and assembly of U snRNPs, some of which eventually form the RNA splicing machinery, or spliceosome. Over the last 10 years, research into the function of Cajal bodies has been greatly stimulated by the discovery that SMN, the protein deficient in the inherited neuromuscular disease, spinal muscular atrophy, is a Cajal body component and has an essential role in the assembly of spliceosomal U snRNPs in the cytoplasm and their delivery to the Cajal body in the nucleus.

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1. Introduction

The Cajal body is the site of initial modification and assembly of several U snRNPs, newly-imported from the cytoplasm by the SMN complex [1] or re-cycled within the nucleus [2]. The U snRNPs then receive additional proteins from the splicing speckles (interchromatin granules) [3], while the final assembly of the spliceosome from its component U snRNPs (and other proteins) takes place *in situ* on nascent pre-mRNAs at the site of transcription (perichromatin fibrils) [4] (Figs. 1 and 2).

The Cajal body, or coiled body, was first described by Ramon y Cajal [5] in neuronal cell nuclei, where the structure is often larger than in other cells. It was originally described as a nucleolar accessory body, because of its frequent appearance as a nucleolar cap in neurons, and the name "coiled body" was given after ultrastructural studies revealed coiled threads within it [6–8]. Structures closely-related, though not identical, to Cajal bodies have been described as "sphere organelles" and "Binnenkörper (endobody)" in germinal vesicles of amphibians and insects respectively [9], as well as "nucleolar bodies" in yeast [10]. The name of Cajal body was adopted only recently,

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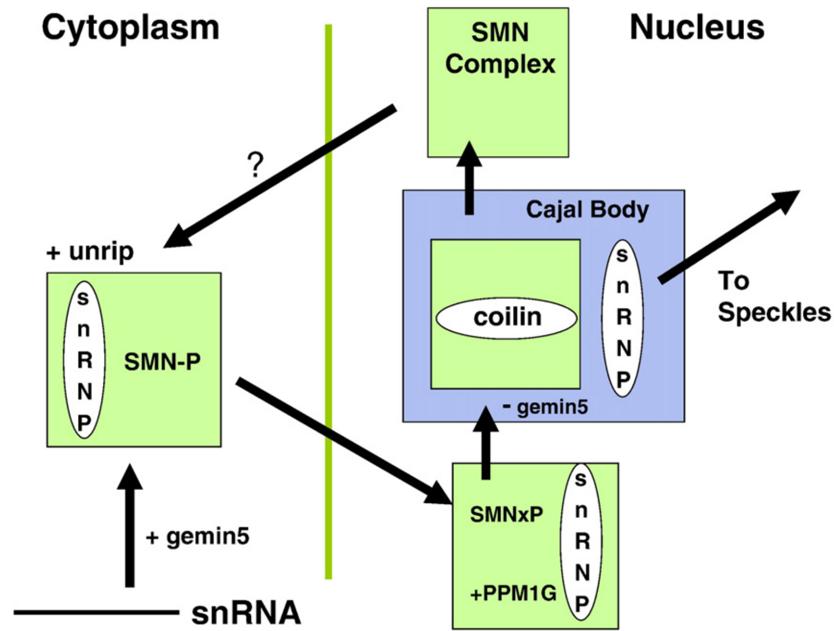

Fig. 1. The Spliceosomal U snRNP Cycle. Newly-synthesized spliceosomal U snRNAs (pink squares) are exported to the cytoplasm where they are assembled into U snRNPs (red squares) by the SMN complex, which also transports them into the nucleus and delivers them to the Cajal body. Further modifications of U snRNPs and assembly of the tri-snRNP occurs in the Cajal body before the snRNPs are assembled into the spliceosome *in situ* on newly-transcribed pre-mRNA in the perichromatin fibrils (PF) at the chromatin periphery. Essential splicing factors are supplied by the splicing speckle, or interchromatin granule (ICG). After each splicing step, UsnRNPs are re-cycled to the Cajal body for re-assembly and the spliced mRNA with attached proteins (mRNP) is exported to the cytoplasm. See text for references. Inset A: This model of the SMN complex is based on data in Ref. [121]. The balls represent SMN ("1" = gemin1), gemins 2–8 and unrip. The Sm ring is the U snRNA with seven Sm core proteins attached.

following a proposal by Gall et al. [11], nearly 100 years after its first description. The marker protein, coilin, was identified using human auto-antibodies [12] and antibodies against this protein have since been used almost exclusively to define the Cajal body (CB) in mammalian cells (Fig. 3). All U snRNPs involved in splicing contain another set of human auto-antigens, the Smith or Sm antigens, and a

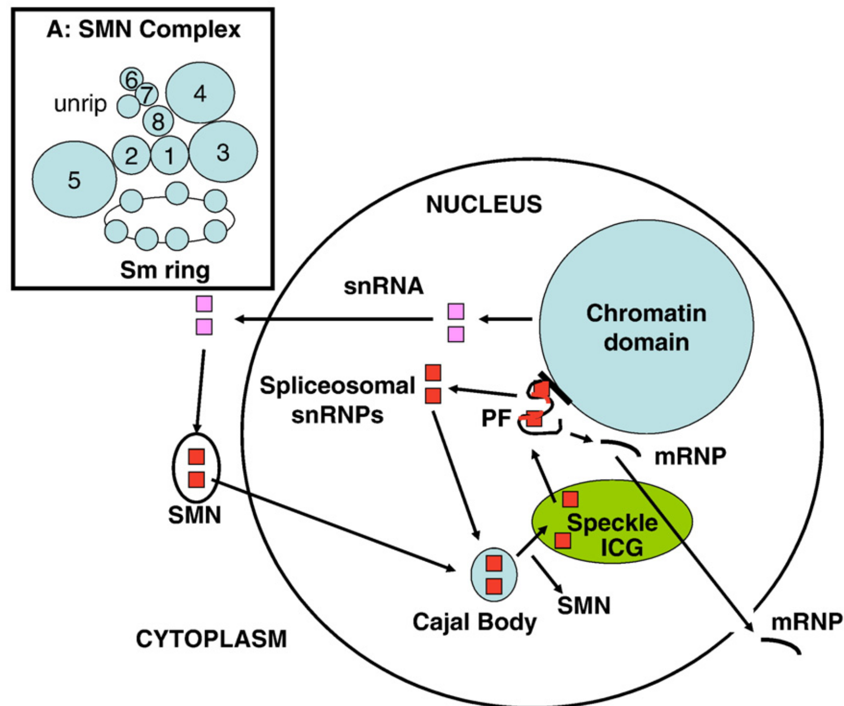

Fig. 2. The SMN complex cycle. In the cytoplasm, the U snRNP core is assembled by the SMN complex, which includes the WD-repeat proteins, gemin5 and unrip. Gemin5 delivers the snRNA and SMN is maintained in a highly-phosphorylated state (SMN-P). Methylation of the snRNA by the TGS1/PIMT methylase enables its transport to the nucleus, where SMN is dephosphorylated by PPM1G before it binds to coilin in the Cajal body. SMN complexes without gemin5 or snRNPs remain in the Cajal body and the U snRNPs undergo further modification and assembly before they are released to transcription sites for spliceosome assembly, picking up splicing factors from the "speckles" on the way. See text for references.

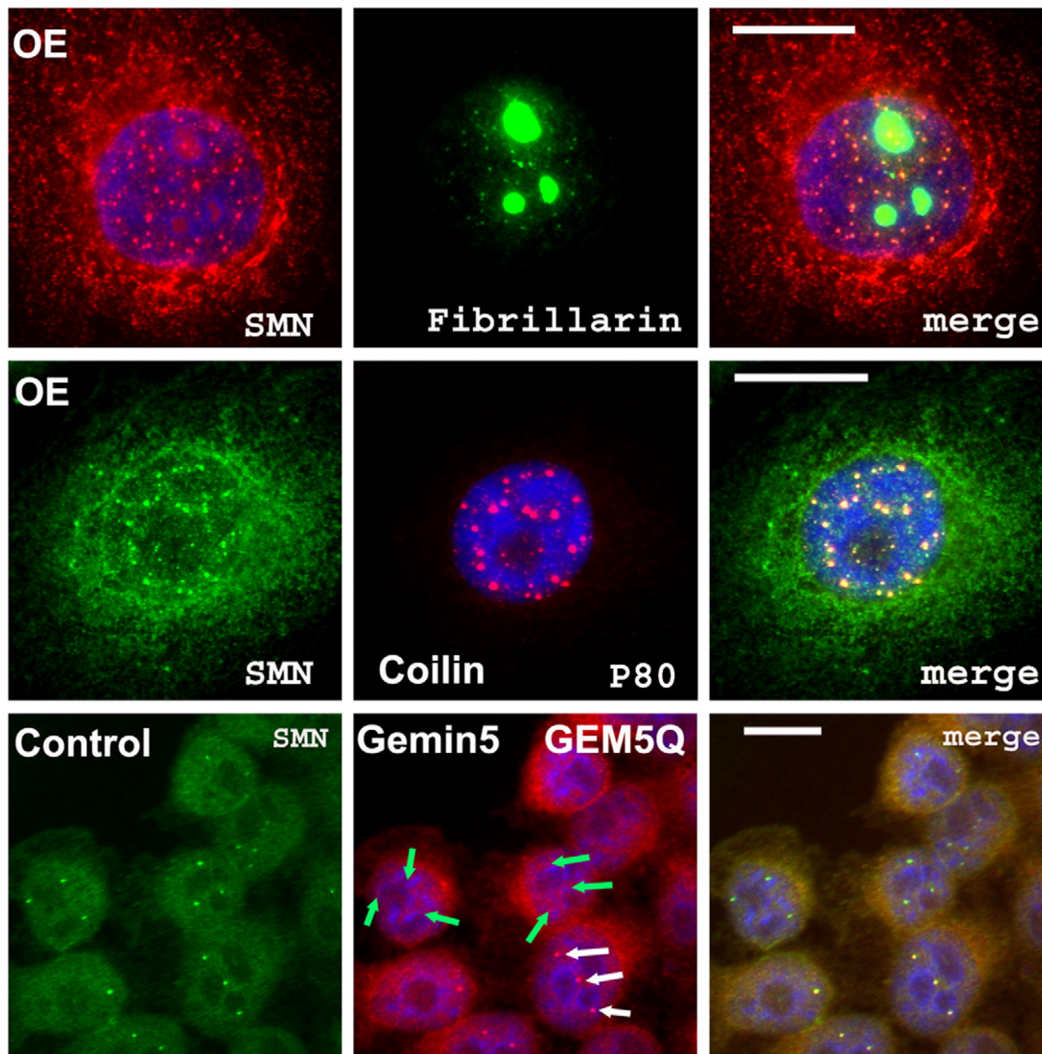

Fig. 3. The relationship of SMN to fibrillarin, coilin and gemin5 in HeLa cells. HeLa cells normally have 2–3 Cajal bodies per nucleus, but they increase dramatically in both size and number when SMN is over-expressed. The presence of SMN in HeLa nucleoli and of fibrillarin in Cajal bodies becomes apparent only when SMN is over-expressed. Coilin is dramatically upregulated by SMN overexpression and is found only in the nucleus, whereas SMN occurs in both nucleus and cytoplasm. In untransfected HeLa cells, gemin5 colocalizes with SMN in Cajal bodies in a few cells (white arrows), but is absent from all CBs in most cells (green arrows). OE = SMN-overexpressor HeLa cells, control = untransfected HeLa cells. Bar = 10 μm. Data from Ref. [19].

mouse monoclonal antibody, Y12, against one specific Sm epitope [13] has been widely used as a marker for U snRNPs, both in Cajal bodies and elsewhere.

Coilin appears to be essential for CB integrity and function. CBs without coilin [14], also known as "residual CBs" [15], do remain when coilin is removed experimentally, but are unable to recruit splicing snRNPs, some of which become located with scaRNAs in separate nuclear bodies [16]. Surprisingly, however, neither coilin nor CBs appear to be essential for splicing, since the coilin−/− mouse can survive, although with reduced viability [15]. This is consistent with a view of the Cajal body as a means of increasing efficiency of snRNP assembly by concentrating enzymes and substrates in one region of the nucleoplasm [17]; in the absence of CBs, the same reactions proceed with lower efficiency in the nucleoplasm [18].

The Cajal body is a dynamic structure in many ways. First of all, it does not exist as a "visible" structure in all cells; even in rapidly-growing HeLa cells, a small proportion (5–10%) may lack CBs at any point in time [19]. Furthermore, all nuclei of certain cell types in adult tissues completely lack visible CBs, including smooth and cardiac muscle cells, skin cells (dermal and epidermal) and spleen parenchymal cells [20]. It has been suggested that the abundance of CBs is determined by snRNP levels and RNA processing rates in the nucleus [1,21,22] and, even *in vivo*, Cajal body numbers can respond quickly to changes in transcription rates [23]. CBs increase in both size and number when SMN is over-expressed in HeLa cells (Fig. 3), possibly in response in increased snRNP production. Secondly, in cultured cells, time-lapse filming shows that many CBs move freely in the nucleoplasm [24–26]. CBs disassemble during mitosis [27], but they do not appear to dissolve and reform on a regular basis during interphase, although they may split into two or fuse with each other [25]. They are not normally associated with nucleoli, but nucleoplasmic CBs can be induced to form a nucleolar cap by treatments such as reduced temperature or actinomycin D [28]. They can also become associated with specific gene loci, such as histone genes or the U2 snRNA gene [29]. Thirdly, photobleaching experiments suggest a continuous traffic and quite rapid exchange of proteins between CBs and the nucleoplasm [30]. Even coilin and SMN had a retention time of just a few minutes, while that for snRNPs was shorter still with a half-time of about 30 s [31]. This is consistent with the fact that most of the coilin and SMN in the nucleus is found in the nucleoplasm outside CBs [32].

How should we regard a structure that appears to be non-essential and to lack enclosing membranes or unique proteins? The Cajal body might be regarded as a transient, entropy-driven assembly of macromolecules in an overcrowded nuclear environment [17], but this view is hardly consistent with a structure that can be biochemically purified as a nuclear subfraction [33]. Admirably, the Cajal body displays a resolute stability in the face of its own transience.

To understand the main known function of CBs, we should consider first the assembly of U snRNPs in the cytoplasm, then their transport into the nucleus for delivery to the Cajal body and finally production of modified snRNPs within the Cajal body. We'll begin with a very brief review of the splicing process, extensively reviewed in great detail elsewhere [4,34] to understand why assembled U snRNPs are required.

2. Splicing in a nutshell

Of the seven U snRNPs, only five are involved in the spliceosome (U1, U2, U5 and the U4/U6 complex), one is involved in ribosomal RNA processing (U3 snRNP; [10]) and one is involved in histone 3′-end processing (U7 snRNP; [35,36]). The five spliceosomal snRNPs vary enormously in their complexity and protein composition [reviewed in 37]. The U2 snRNP is much more complex than the U1 snRNP and many of its additional protein components are added in the CB after delivery of the core U2 snRNP by the SMN complex [37].

To assemble the spliceosome, the U1 snRNP attaches to its target sequence at the 5′-end of each intron in the RNA transcript, assisted by splicing factors, such as ASF/AS2. The 3′-target sequence in the intron is recognized by the U2AF (U2 snRNP auxiliary factor) complex. Other SR-type splicing factors then bridge the two splice sites to form the E complex. This enables binding of the U2 snRNP and other splicing factors to form the A complex, or "pre-spliceosome". The "tri-snRNP" is assembled in the Cajal body from the U4, U5 and U6 snRNPs [37]. The U6 snRNP is unusual in being produced by RNA polymerase III, assembled using Lsm proteins instead of Sm core proteins and targeted to the CB by the protein SART3 rather than by SMN, so it does not need to pass through the cytoplasm [37]. The addition of the tri-snRNP to the spliceosome to form the B complex appears to require the splicing factor, SPF30, a protein with some homology to SMN [38]. A structural rearrangement of snRNPs, after loss of U1 and U4, brings together the 5′ and 3′ splice sites in the C complex and the intron "lariat" is excised with the U2, U5 and U6 snRNPs still attached. Over 150 proteins are involved in the spliceosome at some stage and alternative splicing is controlled by the SR and SR-like protein factors [4,34]. This complexity is further increased by the fact that a minority of pre-mRNAs are spliced by an alternative system in which U1, 2, 4 and 6 snRNPs are replaced by U11, 12, 4atac and 6atac snRNPs [39].

To produce the spliceosomal U snRNPs *de novo*, newly-synthesized U snRNAs have to leave the nucleus to be modified and assembled into core U snRNPs in the cytoplasm.

3. The SMN complex assembles snRNPs in the cytoplasm

After synthesis in the nucleus, U1, U2, U4 and U5 snRNAs are m^7G-capped and exported to the cytoplasm where each is assembled with the same ring complex of seven different Sm core proteins (SmB/B′, SmD1, SmD2, SmD3, SmE, SmF and SmG) to form the U snRNP core [40]. Studies with purified Sm proteins *in vitro* show an ordered assembly of three Sm sub-complexes, B/B′–D3, D1–D2 and E–F–G, onto the "Sm sequence" of U snRNAs [41]. This assembly is promoted by another complex of at least 9 proteins, the SMN complex. This complex is named after one of its components, SMN or the Survival of Motor Neurons protein. SMN is the protein affected by mutation in Spinal Muscular Atrophy (SMA), a neuromuscular disorder characterized by loss of motor neurons, and the severity of SMA is inversely related to functional SMN levels [42,43]. Assembly of snRNPs by the SMN complex is promoted by symmetrical arginine methylation of some of the Sm core proteins by cytoplasmic methylases, notably PRMT5 [44].

It appears that newly-synthesized spliceosomal U snRNAs pass only once in their lifespan through the cytoplasm for assembly by the SMN complex. U snRNPs are recycled after each round of splicing and, since the components of the tri-snRNPs in particular are disassembled after each round of splicing, these must pass again through the Cajal body for re-assembly before they can take part in a further round of splicing [2]. Thus, experimental inhibition of release of U5 snRNP from the intron lariat leads to accumulation of U4 and U6 snRNPs in the CB.

Apart from the U snRNP, the SMN core complex consists of SMN (gemin1) with 8 additional "gemins", gemin2–8 and unrip (unr interacting protein). The manner in which these proteins assemble into a complex is emerging slowly. One model in use for some time had SMN at its centre interacting directly with gemin2, gemin3, gemin5 and gemin7 [45]. The binding of gemin6 was mediated by gemin7 and that of gemin4 by gemin3 in this model. The discovery of gemin8 placed this protein between gemin7 and SMN [46], while unrip was found to bind to gemin7 also. A more recent study resulted in a similar model except that gemin5 was found to bind indirectly to SMN via gemin2, and the indirect binding of gemin4 to SMN was mediated by gemin8, as well as by gemin3 [47; see Fig. 2A]. Another study, however, found a sub-complex of gemins 3, 4 and 5 [48], so it is difficult to say that there is a general "consensus" at the present time.

So far, there are only clues about the precise function of each SMN complex component. SMN is able to bind snRNAs, as well as actin mRNA in the neuronal cell cytoplasm, while gemin2 appears to have a close relationship with SMN, giving some justification for regarding SMN-gemin2 as a heterodimer [48,49]. The gemin3–gemin4 sub-complex may also function independently of SMN as a major component of microRNPs (miRNPs), though its exact role is unclear [50]. Gemin3 is a predicted DEAD-box RNA helicase and these are generally involved in enabling structural changes in RNA, presumably snRNA in the present case, and in controlling RNA–protein interactions. The size and structural similarities between Sm core proteins and the gemin6–gemin7 pair have lead to the suggestion that these gemins might act as a template for assembly of Sm core proteins onto the snRNA [51], although there is no evidence that such a template is required. Gemin5 is a member of the WD-repeat family of assembly proteins [52] and binds snRNA to the SMN complex in the cytoplasm by recognizing specific sequences [53]. It is an interesting feature of the model from the Fischer laboratory (Fig. 2A) that the three proteins likely to interact functionally with snRNPs (SMN, gemin3 and gemin5) form one face of the SMN complex. Although essential for snRNP assembly in the cytoplasm, gemin5 appears to detach from the SMN complex when it reaches the Cajal body in the nucleus [19], since it is detectable biochemically in nucleoplasmic SMN complexes [19,48], but is absent from all Cajal bodies in most HeLa cells ([19]; see Fig. 3). Unlike coilin and all other gemins, gemin5 is not increased in CBs after SMN overexpression [19]. Unrip is another WD-repeat protein that may no longer be required after the snRNP is assembled by the SMN complex in the cytoplasm [54,55]. Both gemin5 and unrip may function more widely as assembly proteins, since unrip is also involved in the assembly and export of mRNP particles in neuronal cells [56]. There has also been a suggestion that unrip may also be involved in the cytoplasmic SMN phosphorylation that is subsequently reversed by a dephosphorylation step inside the nucleus ([57]; see Fig. 1). There is still a long way to go in elucidating the catalytic reactions within the SMN complex and the question of what happens to SMN and gemins after they have delivered snRNPs to the Cajal body remains largely unanswered, but there are indications that the composition of the SMN complex may change according to its immediate function.

SMN also binds the TGS1/PIMT methylase [58], which is responsible for the U snRNA tri-methylated "m_3G cap" required for snRNP transport back into the nucleus.

4. The SMN complex delivers snRNPs to the Cajal body in the nucleus

The SMN complex accompanies the snRNP into the nucleus [59,60], and finds its way to Cajal bodies before U snRNPs are transferred into splicing speckles (interchromatin granules) for assembly into the spliceosome [61]. Targeting of SMN complexes to the Cajal body appears to require the direct interaction of SMN with coilin, via a symmetrically dimethylated arginine in the coilin RG domain [62]. Consistent with this, SMN in CBs is found in close association with the coilin thread structure [63,64].

The Cajal body may also be the site where the SMN complex is released from the snRNP for cycling back into the cytoplasm. SMN interacts with a similar dimethylarginine residue on some of the Sm core proteins in the core snRNP [65]. Coilin could theoretically release the snRNP from the SMN complex, since coilin and Sm protein RG domains are known to compete for SMN binding [62], while coilin binds to a different site on Sm proteins. Stanek et al. [2] found that the close proximity of SMN and snRNPs observed by FRET in the cytoplasm no longer exists in the CB, although both SMN and snRNPs are present. This is consistent with a model in which the SMN complex releases the U snRNP when it interacts with coilin (Fig. 2), though other explanations are possible. The observed loss of gemin5 from the SMN complex when it reaches the CB [19] might also promote release of the U snRNP, since gemin5 is involved in the initial binding of snRNA to the SMN complex in the cytoplasm [54]. Although it is often assumed that SMN complexes are recycled into the cytoplasm after snRNP delivery (Fig. 1), this has not been rigorously proven.

SMN is multimeric as a result of strong self-interaction at its C-terminus (exon 7-encoded: [66]) and a weaker interaction nearer the N-terminus (exon 2b-encoded: [67]), so that SMN complexes may interact simultaneously with more than one RG domain partner. Many RG domain proteins have indeed been found in SMN complexes (reviewed in [68,69]), including fibrillarin, nucleolin, hnRNPs U, R and Q and GAR1, all of which have arginines asymmetrically dimethylated (aDMA) by the *nuclear* methylase, PRMT1) and Sm core proteins B(B′), D1 and D3 (symmetrically dimethylated by PRMT5 and other methylases in the *cytoplasmic* methylosome [65,70,71]), plus EWS [72] and RNA helicase A [73]. Unlike the symmetrical dimethylation of Sm core proteins and coilin, asymmetrical arginine methylation of fibrillarin and GAR1 does not enhance their binding to SMN [68]. There is evidence that RG domain proteins, like Sm core proteins, bind to the "tudor domain" of SMN encoded by exon 3 [74,75] and perhaps also to the C-terminus of SMN [76,50]. The relative importance of these two SMN regions for binding RG domain proteins has not yet been fully resolved, though the importance of the latter for self-association is undisputed [67] and self-association is vital for SMN function.

Phosphorylation of SMN and gemin3 may be needed to disengage the SMN complexes from coilin and the Cajal body for recycling, since they are normally kept in a dephosphorylated state in the Cajal body by an associated phosphatase, PPM1G [57]. Consistent with this, PPM1G knockdown caused loss of SMN complexes from CBs but left U snRNPs in the CB [57]. Since PPM1G (also known as PP2Cgamma) is an exclusively nuclear enzyme and cytoplasmic SMN is phosphorylated, dephosphorylation of SMN complexes to enable association with CBs must occur after their nuclear import (Fig. 1).

Developmental regulation of phosphorylation or methylation events [64] may explain why SMN forms separate bodies called "gems" in most fetal tissues, instead of co-localizing with the Cajal body [77]. When gems and CBs are separate (e.g. fetal nuclei or HeLa PV cells), the snRNPs are found with the CB marker (coilin) and not with the gem marker (SMN). Since the SMN complexes appear to have performed their function of transferring core snRNPs to CBs, the phosphorylation promoting release of SMN from the CB may be more efficient in this situation. The separate gems are just an accumulation of SMN complexes ready for recycling into the cytoplasm or for turnover, since immunogold labelling shows that SMN has a granular ultrastructure when present in separate gems, whereas, in CBs, both SMN and coilin labelling follow the typical coiled thread ultrastructure [67]. It should be noted that most cultured cells (e.g. COS-7 and skin fibroblasts) have about 10% of separate gems and CBs [21]. In skin fibroblasts from SMA patients with SMN depleted to about 30% of control [78], the number of coilin-positive CBs was little changed, although the great majority lacked SMN [20]. In contrast, when SMN was reduced to 13% of control by RNAi, CBs were dramatically reduced in number and snRNPs did not reach the remaining CBs [79]. In fact, 13% is closer to the expected SMN level in severe SMA patients and it seems likely that SMN levels in cultured fibroblasts have drifted upwards to 30%, even at low passage number, because of natural selection. If so, this would imply that rapidly-dividing cells are compromised by SMN levels below 30%, which is higher than that expected in very mild forms of the disease (about 20% SMN).

These considerations suggest that we should use the term Cajal body when coilin and SMN are present (the normal situation), Cajal body or "Cajal body without SMN" when only coilin is present and "gem" for SMN only. The term "gems/CBs" is sometimes used for structures detected by SMN antibody only, when the presence of coilin is likely or possible, but not necessarily proven. Association is clearly not essential for basic nuclear functions, since HeLa PV cells appear normal (inasmuch as HeLa cells can be called "normal"), even though their gems and CBs are always separate, and there is no evidence that fetal tissues with separate gems and CBs [77] are processing their nuclear RNPs in any different way. In cultured neuronal cells, CBs appear as larger "ring-like" CBs and nucleolar "caps", as well as normal nucleoplasmic CBs. The term "caps" has been used to describe both a group of CBs in contact with the nucleolus and a more diffuse area of coilin staining around the nucleolus, though the latter may be unreactive with anti-Sm, indicating lack of snRNPs [80]. There is evidence that nerve growth factor-induced differentiation of the rat PC12 neuronal cell line causes a shift from regular CBs to snRNP-less nucleolar caps [80], while snRNPs move to the nuclear periphery [81].

It should also be noted that coilin can occur inside the nucleolus, either diffusely under some conditions [82] or as CBs in fetal tissues [77]. The presence of CBs within nucleoli was also reported earlier in breast carcinoma cells [83] and in specialized cell types in hibernating dormice [84]. Changing phosphorylation using okadaic acid [82] or serine mutants [85] promotes nucleolar localization of coilin and CBs. SMN also occurs diffusely inside nucleoli in many nuclei of fetal tissues [77]. SMN and the nucleolar marker protein, fibrillarin, are established binding partners in biochemical studies [86], offering a potential mechanism for targeting SMN complexes to nucleoli, though normally only a fraction of the fibrillarin colocalizes with SMN in Cajal bodies (Fig. 3) [19].

5. What does the Cajal body do?

The viability (although reduced) of the coilin−/− mouse without CBs shows that the essential stages in spliceosome formation can still take place in the absence of both coilin and CBs [15]. This suggests that the normal function of CBs may be to increase the efficiency of processes that otherwise occur at a reduced rate in the nucleoplasm [37]. Even under normal conditions, it has been pointed out that, at any given time, only a small fraction of the coilin, or snRNPs, or indeed SMN complexes, in the nucleoplasm are located in CBs [32]. In contrast to the coilin knockout, the SMN−/− mouse is embryonic lethal [87] consistent with its essential role in getting modified snRNPs into the nucleoplasm.

Specific assembly events shown to occur within CBs so far include (a) assembly of the U2 snRNP, including addition of the SF3a and SF3b oligomeric complexes of splicing factors [88] and (b) the assembly of the U5-snRNP with the U4/U6 snRNP after each round of splicing to reform “the tri-snRNP” [37,89,90].

The Cajal body is also the site for further modification of U snRNA, including 2′-*O*-ribose-methylation and pseudouridylation [16]. Modification of snRNAs in Cajal bodies requires the presence of scaRNAs (small Cajal body RNAs), which guide the modifying enzymes to the correct target sequences [1] and are analogous to the snoRNAs (small nucleolar RNAs) involved in guiding modifying enzymes to the correct ribosomal RNA sequence in the nucleolus. In the nucleolus, the “box C/D” snoRNAs guide a methylase, one component of which is fibrillarin, while “box H/ACA” snoRNAs guide the pseudouridine synthase complex that includes GAR1 (reviewed by [91]).

The snoRNAs themselves must also pass through the CB for 2′-*O*-ribose-methylation and pseudouridylation before they can reach the nucleolus [10,92]. Qiu et al. [91] have recently identified three proteins required to get the U3 snoRNA into yeast CBs and two more proteins needed to get it out again and into the nucleolus. Unlike the spliceosomal U snRNAs, newly-synthesized snoRNAs and scaRNAs do not have to leave the nucleus for modification in the cytoplasm. Specific sequences within the scaRNAs target them to the Cajal body [93]. The telomerase RNA is related to the scaRNAs and also passes through Cajal bodies, possibly to have its RNA component modified by methylation [94,95]. This process appears to promote the ability of the telomerase to associate with telomeres [96].

Cajal bodies are also involved in the processing of replication-dependent histone mRNAs. Intronless histone mRNAs do not require splicing but their 3′-end processing is carried by the U7 snRNP, which is present mainly in CBs and in which Lsm10 and Lsm11 replace D1 and D2 Sm core proteins [36]. It has recently been shown that this processing is enhanced by another CB component, the U2 snRNP, [97]. CBs are sometimes associated with histone gene clusters in both *Xenopus* oocytes [98] and mammalian cells [29]. In *Drosophila* cells, the U7 snRNP is found in a separate body from coilin and CBs and this body is always associated with histone gene clusters [99]. It seems that CBs, or the related *Drosophila* bodies, play a key role in ensuring that histones are maximally expressed when they are required during S phase. A protein called p220-NPAT is located in CBs associated with histone gene clusters. Cyclin E arrives at these CBs during the G1/S transition and p220 is phosphorylated at 5 sites by the cyclinE/CDK2 kinase, enabling p220 to interact with and activate the histone H4 transcription factor, HiNF-P, in CBs [100,101]. The SMN-binding protein, ZPR1, also binds to these CBs in S phase and may play an essential, but as yet undefined, role [102,103].

CBs can also associate with U2 sRNA genes in a quite different way from the histone gene association. The link is transcription-dependent in this case and the CBs associate with new RNA transcripts from the U2 snRNA gene [104] though why they associate with U2 snRNA before, as well as after, assembly of the U2 snRNP in the cytoplasm is still unclear. CBs associated with a snRNA gene locus are often also linked to PML bodies, which are rich in transcription factors, and this link is mediated by an interaction between coilin and the PML protein, PIASy [105].

Cajal bodies may also be involved in the assembly of the transcription machinery in *Xenopus* [106]. Factors involved in transcription, capping, splicing, polyadenylation and cleavage of pre-mRNAs are initially targeted to CBs in the oocyte, suggesting that the RNA polymerase II machinery may be pre-assembled in CBs as “transcriptosomes” [11]. Pellizzoni et al. [107] suggested that the SMN complex may be involved, because gemins interact with the C-terminal domain of RNA polymerase II through RNA helicase A, and dominant negative mutants of SMN inhibit polymerase II and cause it to accumulate in coilin-containing structures.

In plants, CBs have an additional role in the biogenesis of micro-RNAs and small-interfering RNAs [108], including the assembly of an ARGONAUTE4-siRNA complex involved in RNA-directed gene silencing at target loci by the DNA methyltransferase [109].

FLASH (FLICE-associated huge protein) has recently been identified as a component of both CBs [110] and PML bodies [111] that is translocated to mitochondria after activation of the death receptor but the link, if any, with other CB functions is still unclear.

6. Cajal bodies and spinal muscular atrophy

SMN has attracted much attention because its depletion causes the inherited neuromuscular disorder, spinal muscular atrophy (SMA). The effects of SMN depletion in SMA are highly-specific, not just for neurons as opposed to other cell types, but for the large anterior horn alpha-neurons that originate in the spinal cord and innervate skeletal muscles. Cognitive functions and tissues outside the neuromuscular system are unaffected, except in extremely severe cases. How can the role of SMN in a process as fundamental to all cells as RNA splicing be related to such extreme tissue-specificity? The answer seemed to come with the discovery that SMN or SMN complexes are present in the axons of motor neurons, without snRNPs and far from any possible nuclear function [112–114]. There is evidence that axonal SMN binds hnRNP-R [115] and is involved in the transport of actin mRNA [114]. Actin polymerization is important in axonal sprouting and pathfinding to muscle, processes that are defective in SMN-depleted zebrafish [116]. In a mouse model of SMA, post-natal maturation and survival of the newly-formed neuromuscular junction was affected and pre-synaptic neurofilaments were disrupted [117]. Strong evidence for the actin hypothesis has come recently from overexpression of the actin-bundling protein, plastin 3, which corrects SMA defects in the human disease, as well as in mouse and zebrafish models of SMA, and also increases axonal actin levels [118]. Although the circumstantial evidence seems very strong, a clear demonstration of the precise molecular role of axonal SMN in these processes is still lacking, which leaves the possibility that splicing changes caused by reduced SMN levels contribute indirectly to the observed cellular and molecular changes [119,120].

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