

Cajal bodies and coilin—moving towards function

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Many nuclear factors are concentrated within nonmembrane-bound subnuclear bodies. The Cajal body is an example of a conserved nuclear compartment that has been linked to molecular disease. Recent studies have shown Cajal bodies to be surprisingly mobile and offer clues about their function in the cell.

The subnuclear domains now known as Cajal bodies were first reported in 1903 by the eponymous Spanish cytologist Ramón y Cajal, who christened them “nucleolar accessory bodies,” because of their prominent association with nucleoli in neuronal cells (Cajal, 1903). They were subsequently rediscovered by numerous researchers and given a variety of names in different cell types (Gall, 2000). The name “coiled body” was coined by electron microscopists, in reference to their morphology in EM sections. The recent interest in coiled/accessory bodies developed when it was realized that they were enriched in the snRNP spliceosome subunits and when the molecular marker coilin was discovered and could be used to detect them in the fluorescence microscope as bright foci (Fig. 1). Recently, their renaming as “Cajal bodies” (CBs),* in honor of their discoverer, has been widely adopted.

CBs are found in the nuclei of plant and animal cells. This strong conservation suggests that they may play an important role, although it has proved difficult to pin down what function(s) they perform. The number and size of CBs varies among cell types (in mammalian cells typically 0–10 CBs per nucleus, ranging 0.1–2 μm in diameter) and also shows cell cycle variation within cell types. CBs are prominent in cells showing high levels of transcriptional activity, including rapidly dividing cells, but are less abundant or absent in some primary cells and tissues. They are dynamic structures, responding to the cellular environment and to changes in levels of RNA synthesis and RNP assembly.

A surprising range of nuclear factors, including some nucleolar proteins and polymerase II transcription factors, as well as splicing snRNPs and nucleolar snoRNPs, colocalize

in CBs. However, CBs do not contain either DNA (Thiry, 1994) or non-snRNP protein splicing factors (Raska et al., 1991; Carmo-Fonseca et al., 1992) and are therefore unlikely to be sites of transcription or pre-mRNA splicing. Recent evidence suggests that they may be involved in coordinating the assembly and maturation of nuclear RNPs and possibly other macromolecular complexes. Here, we will consider recent data concerning the properties of CBs and discuss their possible cellular role. Due to space limitations, we are unable to cite all key primary data. For additional information describing the structure and prevalence of CBs and their known components, as well as a discussion of previous literature, we recommend the reviews by Matera (1999) and Gall (2000).

Coilin—the CB marker protein

Coilin was discovered using human autoimmune sera that stained bright foci in mammalian cell nuclei when analyzed by immunofluorescence and labeled CBs in EM sections (Raska et al., 1991). The autoantigen was christened coilin to reflect its specific localization in CBs. However, only a minor fraction of coilin is present in CBs at any one time, whereas most is in a diffuse nucleoplasmic pool in dynamic equilibrium with the CB fraction (Carmo-Fonseca et al., 1993; Platani et al., 2000). Transient overexpression of coilin increases the diffuse pool but does not increase the number or size of CBs, indicating that coilin concentration is not a limiting factor for CB assembly. Coilin self-interaction is mediated by signals within its amino terminal 93 amino acids (aa) and is required for targeting to CBs (Hebert and Matera, 2000). Consistent with this, an amino terminal 102-aa fragment of human coilin is sufficient for CB localization in *Xenopus* oocytes (Wu et al., 1994). A recent study showed that a motif within coilin is modified in vivo to form symmetrical dimethyl arginines (sDMA), which affects its binding to the survival of motor neurons (SMN) protein complex and assembly into CBs (Hebert et al., 2002). The sDMA modification on Sm snRNP proteins also enhances binding to the SMN complex (Paushkin et al., 2002).

CBs are detected frequently at the nucleolar periphery and even within nucleoli. Molecular evidence now implicates coilin in this link. Transient expression in mammalian cells of a mutant coilin (ser-to-asp point mutation) caused CB-like structures to form inside nucleoli (Sleeman et al., 1998). The protein phosphatase inhibitor okadaic acid also caused CBs to form inside nucleoli (Lyon et al., 1997). Coilin is a

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*Abbreviations used in this paper: aa, amino acid(s); CB, Cajal body; FP, fluorescent protein; SMN, survival of motor neurons.

Key words: Cajal bodies; nucleoli; coilin; nucleus; guide RNAs

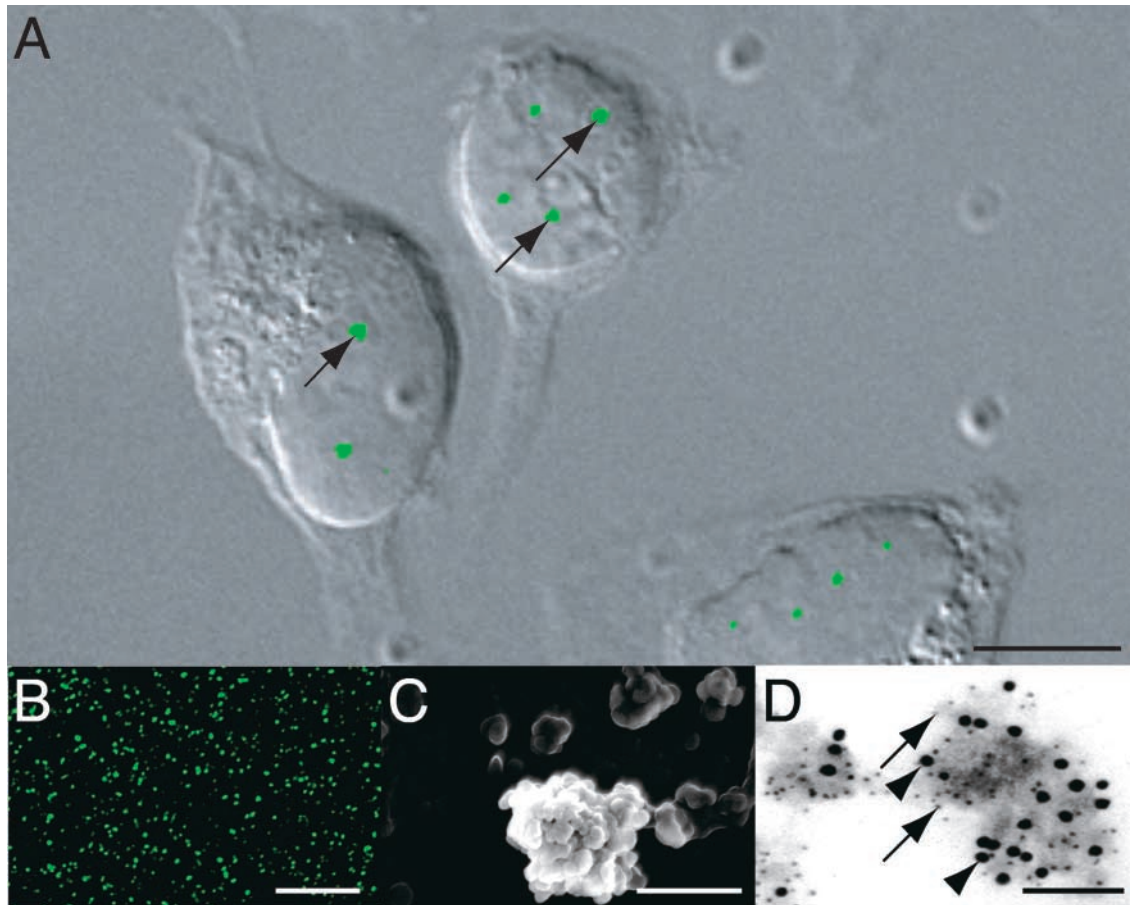


Figure 1. **Cajal bodies.** (A) HeLa cells expressing an FP-coilin fusion protein (arrows indicate Cajal bodies). (B) Fluorescence micrograph of purified CBs immunolabeled with anticoilin antibodies. (C) Field emission scanning electron micrograph of a purified CB. (D) Transmission electron micrograph of a purified CB. Coilin is immunolabeled with 5 nm gold (arrows) and SMN is immunolabeled with 10 nm gold (arrowheads). Bars: (A and B) 10 μm ; (C) 500 nm; (D) 200 nm.

phosphoprotein *in vivo* and its phosphorylation may be involved in the interaction of CBs with nucleoli.

Dominant inhibitory effects on CB assembly and nucleolar interactions are caused by expression of truncated coilin molecules. Upon transient expression in HeLa cells of coilin aa 1–293, “pseudo-CBs” formed, which lacked snRNPs and endogenous wild-type coilin, but sequestered the nucleolar protein Nopp140 (Bohmann et al., 1995b). Smaller fragments of coilin associated with the nucleolar periphery and did not form bodies. Similar studies with deletion mutants of Nopp140 also showed effects on both CBs and nucleoli and indicated that coilin and Nopp140 can interact with one another (Isaac et al., 1998). Expression of a carboxy-terminal Nopp140 fragment disrupted CBs, dispersing coilin throughout the nucleoplasm, and also excluded endogenous Nopp140 from nucleoli and CBs. Nopp140, a predominantly nucleolar protein, localizes in CBs only after initial accumulation within the nucleolus, suggesting a trafficking pathway from the nucleolus to the CB. Collectively, these studies suggest that molecular interactions between coilin and specific nucleolar proteins may help to mediate the morphological association of CBs with nucleoli originally observed by Cajal.

A knockout of the murine coilin orthologue has been generated (Tucker et al., 2001). Mouse embryos homozygous

for the coilin deletion show reduced viability, suggesting a possible developmental defect, although mutant animals that do develop to birth appear normal. Cell lines derived from the mutant embryos show residual nuclear foci, resembling CBs in size and shape, that contain some CB components, e.g., fibrillarin and Nopp140, but not other CB factors, such as splicing snRNPs or the SMN complex (Hebert et al., 2001; Tucker et al., 2001). Future experiments should reveal whether a coilin null genotype has any long-term consequences for the phenotype of adult mice.

Movement of Cajal bodies

The advent of fluorescent protein (FP) tagging, used in conjunction with new methods of digital time-lapse fluorescence microscopy studies on live cells, has added a temporal dimension to the analysis of CBs and has shown that they are dynamic. CB movement in plant cells was detected using a GFP-U2 snRNP B’ fusion, and in animal cells both fibrillarin-GFP, and GFP-coilin have been used (Boudonck et al., 1999; Platani et al., 2000; Snaar et al., 2000). Rates of CB movement varied from <0.1 to ~ 1 $\mu\text{m}/\text{min}$, slower than most of the ATP-dependent, motor driven processes involved in cytoplasmic transport mechanisms. At present, there is no evidence for the involvement of motor proteins in CB movement.

CBs can separate into two daughter bodies and join to form larger bodies. CB-joining events appear to be common and can involve CBs translocating large distances through the nucleoplasm. Separation of CBs into smaller structures can result in the asymmetric segregation of resident CB proteins between the respective daughter CBs. For example, in some cases coilin appears to be equally distributed, whereas fibrillarin is predominantly segregated to one daughter (Platani et al., 2000). CBs may thus be involved in nuclear sorting and/or transport events. Given the link between the CB and the nucleolus, it is notable that CBs can move to and from the nucleolar periphery, indicating that nucleolar-associated CBs need not assemble within the nucleolus, as previously suggested.

Simple diffusion appears to be the predominant mechanism when CBs move (Platani et al., 2002). However, CB movement is heterogeneous, differing both among the CB population in a nucleus and for a single CB over time. Many CBs appear restricted in their movement, suggesting some form of tethering to other subnuclear components. Analysis in HeLa cells coexpressing an FP-tagged histone H2B shows constrained CBs localize to sites of dense chromatin. Conversely, when the same CBs translocate through the nucleoplasm, their most rapid movement is observed in regions with low chromatin density, suggesting that the constrained CBs may be tethered, either directly or indirectly, to chromatin. Interestingly, previous studies using fixed cells showed that CBs can colocalize with specific gene loci, including snRNA and histone gene clusters (Jacobs et al., 1999; Shopland et al., 2001). Analysis of CB colocalization with artificial arrays of either wild-type or mutant U2 snRNA genes in stable cell lines showed that this interaction was dependent on U2 snRNA expression, rather than the presence of specific DNA sequences per se (Frey et al., 1999; Frey and Matera, 2001). The mobility of CBs and their potential dynamic interactions with chromatin and specific gene loci is consistent with their having a possible transport role and underlines the importance of taking into account temporal information for future attempts to characterize CB function in vivo. The same may be true for other nuclear bodies considering that a recent study indicates that PML bodies show similar dynamic properties (Muratani et al., 2002).

A role for Cajal bodies in RNP maturation

Apart from their connection with nucleoli, an important clue to the function of CBs is that they are only formed when RNA synthesis and gene expression are active. Drugs that inhibit RNA polymerase II transcription result in loss of nucleoplasmic CBs and a concomitant accumulation of coilin in perinucleolar caps. Drugs that inhibit protein synthesis decrease the number of nucleoplasmic CBs and generate large numbers of microfoci that contain coilin and fibrillarin, but not snRNPs (Rebelo et al., 1996). The dependence of CB formation on gene expression is also observed after cell division when CBs reform only after transcription has started in daughter nuclei. If activation of RNA polymerase II transcription in the daughter nuclei is prevented, CBs do not assemble (Ferreira et al., 1994). CB function may thus be related to one or more steps connected with gene expression. They were predicted to play a role in the

maturation of snRNPs and nuclear RNP complexes (Bohmann et al., 1995a), and recent studies provide evidence to support this view.

Biogenesis of many nuclear snRNPs and snoRNPs (i.e., small nucleolar RNA-protein complexes) involves cytoplasmic assembly steps followed by nuclear import and further maturation. CBs contain a minor fraction of the total nuclear snRNPs and snoRNPs, and recent temporal studies have shown that both these fractions correspond to newly assembled RNP particles that later accumulate, respectively, in speckles and nucleoli (Carvalho et al., 1999; Gall et al., 1999; Narayanan et al., 1999; Sleeman and Lamond, 1999; Sleeman et al., 2001) (Fig. 2). In the nucleolus, snoRNPs function in the rRNA maturation pathway. They contain "guide RNAs" complementary to rRNA that target modification sites on maturing rRNA by base pairing and thereby align the snoRNP-associated modifying enzymes with their RNA substrate (Fatica and Tollervey, 2002; Filipowicz and Pogacic, 2002). Recently, guide RNAs have been characterized in CBs that are predicted to direct sites of 2'-O-methylation and pseudouridine formation on snRNAs (Jady and Kiss, 2001; Kiss, 2001; Darzacq et al., 2002). RNA modification is important for stable RNA function, and modification sites in snRNA and rRNA are conserved. The modification of snRNAs, at least in some cases, has been shown to occur after their reimport into the nucleus. The discovery of CB-specific guide RNAs, complementary to modification sites in snRNAs, now strongly supports the proposal that the CB is a site where snRNA modification takes place. Furthermore, fibrillarin, a protein component of multiple snoRNPs found in CBs and nucleoli, is structurally similar to methyltransferases (Wang et al., 2000), and mutations in the yeast fibrillarin orthologue, Nop1p, result in accumulation of unmethylated pre-rRNA and concomitant loss of cytoplasmic ribosomes (Tollervey et al., 1991). Therefore, fibrillarin is likely to be a methyl transferase involved in guide RNA-directed 2'-O-ribose methylation.

A role for the CB in nuclear RNP maturation accounts both for the observed linkage of CB formation with gene expression and the fact that they are more common in rapidly dividing cells, because the CB will only form when high levels of RNP synthesis result in a high flux of newly assembled, immature RNPs into the nucleus. In this regard, it is interesting that primary fibroblasts are induced to form CBs in response to overexpression of snRNP Sm proteins (Sleeman et al., 2001). This model can account for the puzzling connection between the nucleolus and CBs, because both structures have roles in RNP maturation and share certain common components involved in RNA modification.

Future perspectives

We have reviewed here recent studies on CBs and coilin that identify the dynamic behavior of CBs and provide experimental support for the CB being involved in RNP maturation and snRNA modification. It is also possible that CBs have additional functions in the nucleus. For example, it has been proposed that they may also coordinate a broad range of macromolecular assembly reactions, including the pre-assembly of transcription factors, based on the immunolocalization of multiple RNA polymerase II transcription factors in *Xenopus* CBs (Gall, 2000). Another suggestion is that CBs

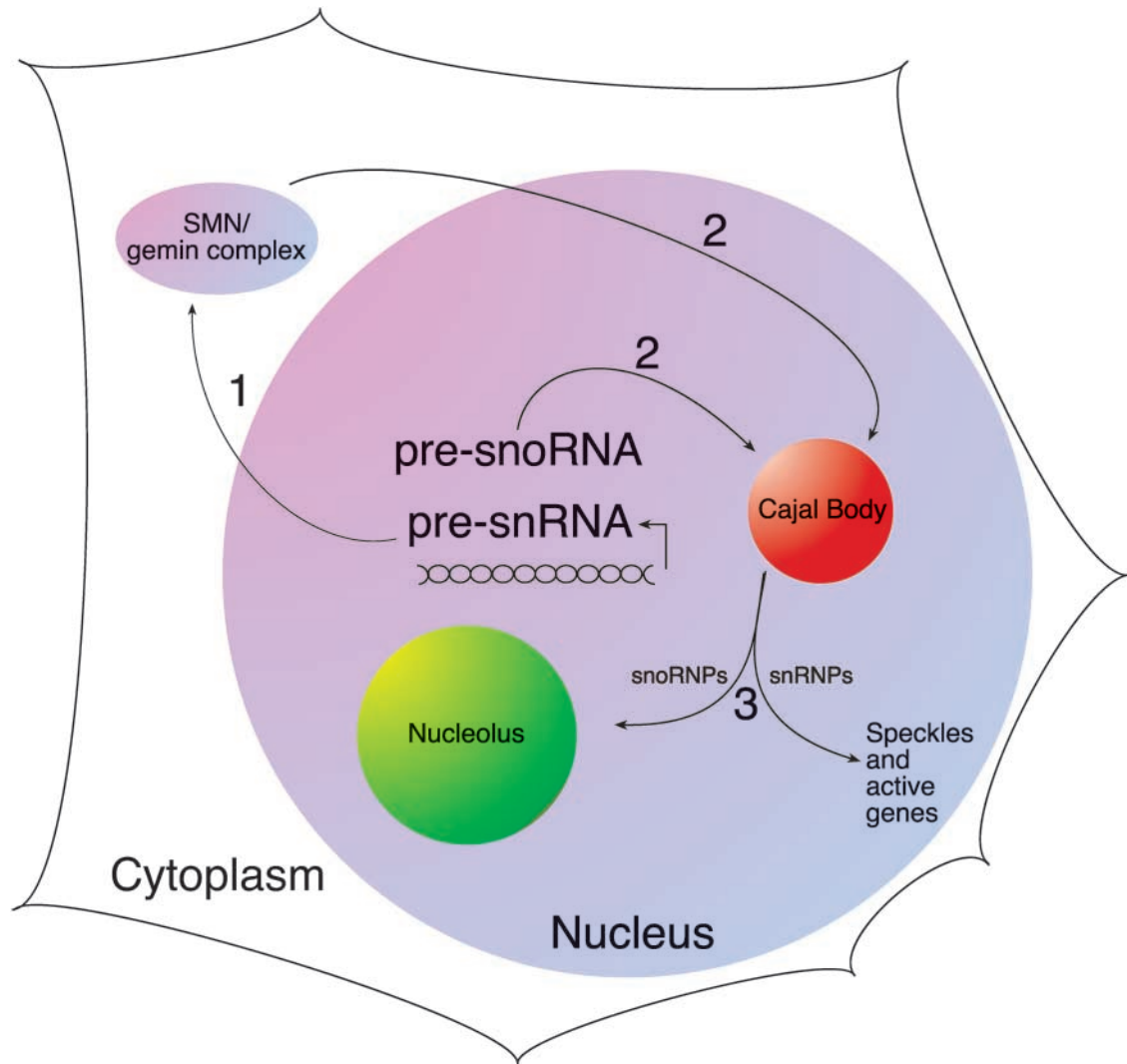


Figure 2. **Model of Cajal body function in snRNP/snoRNP biogenesis.** (1) U1, U2, U4, and U5 snRNAs are transcribed by RNA polymerase II and exported to the cytoplasm where the trimethyl cap is formed and assembly with the core Sm proteins occurs in the SMN-gemin complex. (2) Partially assembled snRNPs or snoRNPs transit initially through the Cajal body on their maturation pathway, where further RNA modification (2'-O-methylation and pseudouridylation) occurs. (3) Mature snRNPs or snoRNPs exit the Cajal body and move to their site of action. SnoRNPs move to the nucleolus to participate in rRNA modification and ribosome assembly, while snRNPs accumulate in nuclear speckles, and at sites of gene transcription where they function in splicing of premRNA.

may play a role in feedback regulation of gene expression (Matera, 1998). A regulatory function could explain the observation that CBs can interact *in vivo* with specific gene loci, including snRNA and histone genes. Just as the nucleolus is now being considered as a plurifunctional structure, we suggest that an analogous multifunctional view of the CB may be appropriate. An important step toward identifying the full range of CB functions will be a systematic and detailed characterization of its protein and RNA components. The recent development of a procedure to purify intact CBs from cultured mammalian cells should facilitate these requisite proteomic studies (Lam et al., 2002).

Another important perspective for future studies on the functional roles of both CBs and other classes of subnuclear bodies is the insight that such studies may provide into a range of human diseases. An example is the finding that CBs may be associated with the Huntington's disease phenotype and other related disorders caused by expansions of poly-

glutamate repeats within genes (Yamada et al., 2001). Analyses of diseased human and mouse brain cells shows a striking association of CBs with the nuclear neuronal inclusions that are characteristic of these polyglutamate disorders.

CBs are related to, and often overlap with, another class of nuclear bodies called "gems" that contain the SMN protein complex. The wild-type SMN protein has been shown to play a key role in coordinating the assembly of Sm proteins onto snRNAs in the cytoplasm and is also proposed to have a more general function in promoting assembly of other classes of RNPs (Paushkin et al., 2002). Loss-of-function mutations in the SMN gene are predominantly responsible for the severe inherited disorder spinal muscular atrophy (SMA), which causes the degeneration of motor neurons and is currently the major genetic cause of human infant mortality. In the nucleus, SMN accumulates specifically in CBs/gems, providing further evidence for the emerging role for CBs in RNP maturation.

The recent studies on CBs provide a good example of progress in understanding the *in vivo* roles played by nuclear bodies and their contribution to nuclear structure and function. We anticipate that further studies during the next few years will see major advances in understanding the molecular interactions involved in the formation and function of CBs and other classes of nuclear bodies, which should help to clarify their respective roles *in vivo*.

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