Drosophila Cajal bodies: accessories not included

A. Gregory Matera

Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, OH 44106

Cajal bodies are nuclear sites of small ribonucleoprotein (RNP) remodeling and maturation. A recent study describes the discovery of the *Drosophila* Cajal body, revealing some interesting insights into the subnuclear organization of RNA processing machineries among different species.

You've just bought that complicated new toy for your child and he or she is waiting anxiously for you to assemble it. After an hour or so, it's ready. Your child runs off, ecstatic, but soon returns, asking why it does not perform all of the miraculous transformations they show in the advertisements. You look on the box it came in and note the fine print: "some accessories not included", it says. You tell your child that the hovercraft and hyperspace modules cost extra and s/he will just have to make do for now without them. Both your pet and your spouse breathe huge sighs of relief. Meanwhile, back at the laboratory, a similar scene appears to be playing out within the nuclei of higher eukaryotes. In this issue, Gall and colleagues (p. 875) have characterized the *Drosophila* Cajal body, finally laying to rest nagging questions about the evolution of this nuclear suborganelle and opening the way for forward genetic approaches to study its function (Liu et al. 2006).

Cajal bodies were discovered over 100 years ago by Santiago Ramón y Cajal, who originally called them nucleolar "accessory" bodies (Cajal, 1903). Like their larger cousin the nucleolus, accessory bodies are prominently stained by the silver chromate impregnation method that was developed by Camillo Golgi and later modified by Cajal. During the intervening century, accessory bodies were rediscovered numerous times in various organisms and cell types but were seldom recognized as the structures described by Cajal. Thus, they were variously termed: endobodies (Binnenkörper), knobs, dots, spheres, snurposomes and, most commonly, coiled bodies (Gall, 2003). In 1999, the structures were renamed "Cajal bodies" in honor of their discoverer. One of the reasons that Cajal bodies and nucleoli stain so well with silver is undoubtedly because they contain high concentrations of RNPs, which are argyrophilic. However, unlike nucleoli, Cajal bodies do not accumulate ribosomal RNPs (rRNPs). Instead, they contain high concentrations of small nuclear RNPs (snRNPs) and a host of other factors, most of which are thought to be involved in RNA processing (Cioce and Lamond, 2005; Stanek and Neugebauer, 2006).

Recent evidence supports the view that Cajal bodies are nuclear sites of RNP assembly and remodeling (Matera and Shpargel, 2006). The maturation of Sm-class RNPs is a multistep process that takes place in several subcellular compartments. The initial steps in snRNP maturation occur in the cytoplasm, whereas later steps take place in the nucleus. A number of RNP remodeling factors concentrate in Cajal bodies, including the survival motor neuron (SMN) protein complex and a class of small Cajal body–specific RNPs (scaRNPs) that guide modification of other snRNAs (Gall, 2003; Matera and Shpargel, 2006). Thus, Cajal bodies appear to be nuclear waystations along the snRNP maturation pathway.

In addition to high concentrations of small RNPs and the SMN complex, vertebrate Cajal bodies are most often identified by the presence of a protein called coilin (Gall, 2003). Although coilin knock-out mice display significant viability and fertility defects, a fraction of the homozygous mutant animals survive (Tucker et al., 2001). Studies of cells derived from these animals reveal that coilin is required not only for the integrity of the Cajal body, but for recruitment of the SMN complex to these structures as well (Matera and Shpargel, 2006). In the absence of coilin, the various factors that normally accumulate in Cajal bodies instead self-assemble into at least three distinct "residual" structures (Tucker et al., 2001; Jady et al., 2003). These findings raised questions about cells derived from species that lack an identifiable coilin orthologue.

Is the Cajal body a universal structure? When grown under certain conditions, budding yeast nucleoli contain domains that resemble Cajal bodies in several details (Verheggen et al., 2002). Plant cells typically display very prominent Cajal bodies (Shaw and Brown, 2004), and a distant coilin homologue can be detected in several plant genomes (Tucker and Matera, 2005). However, the genomes of both *Drosophila* and *Caenorhabditis elegans* apparently do not contain coilin, and histological studies of the nuclei of these organisms have not revealed clear morphological candidates. The Gall laboratory therefore set out to answer the question of whether or not *Drosophila* contain Cajal bodies (Liu et al., 2006).

Using markers diagnostic for these structures in vertebrates, Liu et al. (2006) found that *Drosophila* cells contain several distinct nuclear bodies, one of which contains the U2 spliceosomal snRNP, the U85 scaRNP, as well as the SMN protein. The authors argue

Correspondence to A. Gregory Matera: a.matera@case.edu

Abbreviations used in this paper: scaRNP, small Cajal body–specific RNP; SMN, survival motor neuron; snoRNP, small nucleolar RNP; snRNP, small nuclear RNP.

The Journal of Cell Biology Vol. 172, No. 6, March 13, 2006 791–793
http://www.jcb.org/cgi/doi/10.1083/jcb.200602002

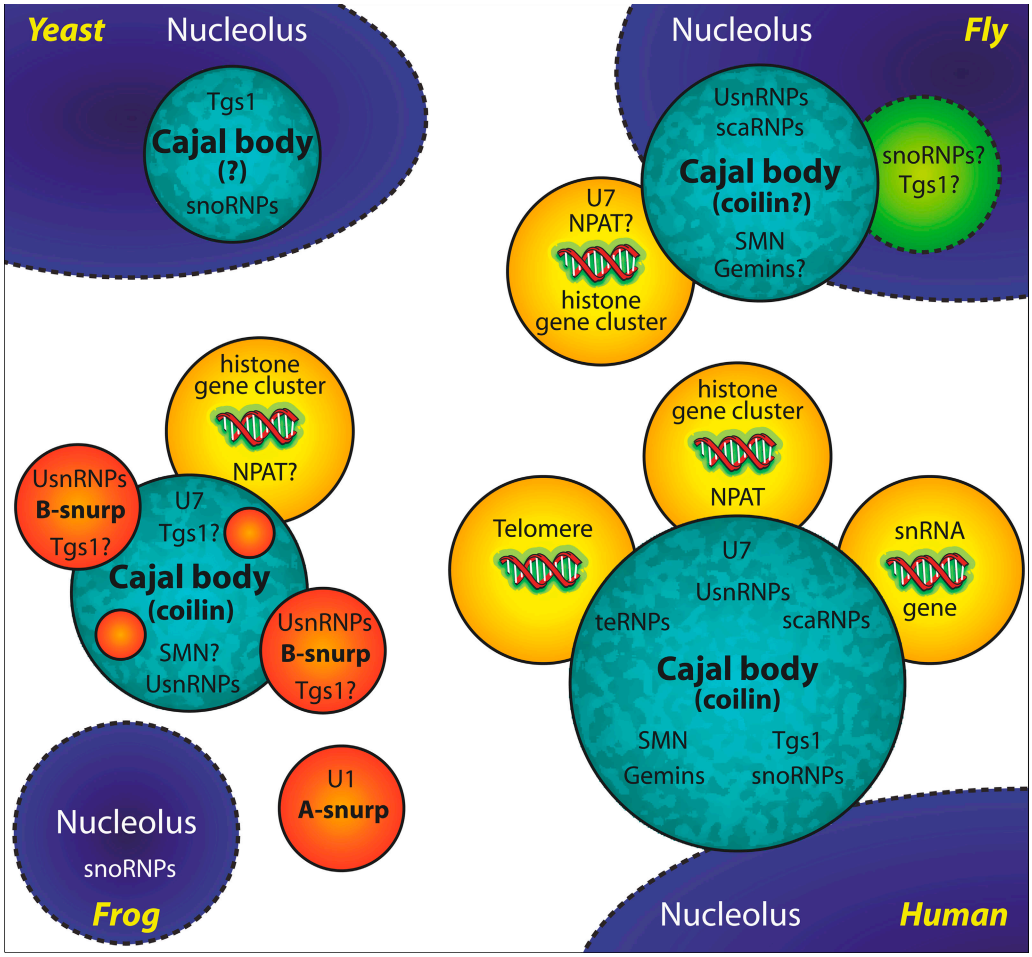

Figure 1. **A schematic of Cajal bodies and their relationship to nucleoli in yeast, fly, frog, and human.** The various components that are known to accumulate in these structures are shown; question marks denote those that have not be experimentally demonstrated. The yeast nucleolar body (herein referred to as a Cajal body) is the least well studied of the four. Only two endogenous factors are known to accumulate in this structure, snoRNPs and the trimethylguanosine synthase protein, Tgs1. Interestingly, when human SMN is ectopically expressed (budding yeast do not encode a recognizable homologue) it accumulates in the Cajal body. Amphibian oocyte nucleoli are extrachromosomal. In the oocyte germinal vesicle, the Cajal body has a modular structure composed of B-type "snurposomes" and a Cajal body matrix that contains, among many other factors, coilin and the U7 snRNP. B-type inclusions are shown within the matrix of the frog Cajal body; A-type snurposomes are thought to accumulate only U1 snRNPs. Somatic Cajal bodies have not been well studied in the frog. A conserved feature among Cajal bodies in humans, flies, and frogs is a frequent association with the cell cycle–dependent histone gene clusters. Human Cajal bodies additionally associate with snRNA genes and telomeres. Moreover, a class of small Cajal body–specific RNPs (scaRNPs), including telomerase, accumulate in human Cajal bodies. Thus, human Cajal bodies appear to have more accessories hanging in and around them than do the respective structures in other eukaryotes. Now that the Cajal body has been identified in the fly, a clearer evolutionary picture is sure to emerge.

convincingly that this domain is the *Drosophila* Cajal body equivalent. However, the distribution of the U7 snRNP, which is a major Cajal body constituent in vertebrates, differed in the fly. The U7 snRNP was found to accumulate in a separate nuclear subdomain that is constitutively associated with the major histone gene cluster on chromosome 2L. Although *Drosophila* U7 snRNPs are displaced from the Cajal body proper, the U7-containing body is typically located adjacent to the Cajal body (Liu et al., 2006). Similarly, vertebrate Cajal bodies also associate with the U7-dependent (i.e., cell cycle–dependent) histone gene clusters (Matera and Shpargel, 2006). The organization of various Cajal body components in yeast, fly, frog, and human is outlined in Fig. 1. Several themes emerge from this comparison: Cajal bodies contain high concentrations of RNPs, they are typically located in or around nucleoli, and they often associate with the major histone gene clusters.

Several differences are also apparent, raising a number of questions with regard to the localization of Cajal body components among the various species (Fig. 1). For example, do yeast spliceosomal snRNAs accumulate in the nucleolar/Cajal body? Human Cajal bodies associate with telomeres and snRNA genes; do *Drosophila* Cajal bodies associate with other genomic loci? Where are the small nucleolar RNPs (snoRNPs) assembled and what factors tether the SMN protein to Cajal bodies in *Drosophila*? In coilin knockout mice, the snoRNPs and SMN complexes localize to distinct nuclear bodies (Tucker et al., 2001). Do fruit flies contain a snoRNP-specific nuclear body?

Originally termed the "U7 nuclear body," the discovery of this structure in *Drosophila* raised some nomenclature issues. In vertebrates, the U7 snRNP does not accumulate within a

separate nuclear body, but localizes in the Cajal body itself (Fig. 1). Because Cajal bodies are often adjacent to the histone gene clusters in interphase nuclei, this arrangement suggests a flux of materials between the two locations. In mammals, the histone gene clusters are constitutively marked by nuclear foci that contain high concentrations of histone-specific transcription factors, called HiNF-P and NPAT (Miele et al., 2005). Although the homologous factors have yet to be discovered in the fly, the prediction is that they exist and will colocalize with the histone gene clusters. Because the U7 snRNP is not constitutively associated with the histone gene clusters, and given that we don't presently know whether the U7-rich structures in the fly are morphologically distinct at the ultrastructural level, the original nomenclature did not stress the conserved features of the system. In light of these issues, Gall and colleagues have decided to call these structures "histone locus bodies" (Liu et al., 2006). The discovery of the novel foci in the fly suggests that, in the absence of coilin, mammalian U7 snRNPs would localize to the histone locus body.

Nomenclature aside, we are left with the question as to why the machineries that carry out diverse (but related) RNP assembly activities are clustered together in a single nuclear locale in mammals but are separated in flies. Coilin appears to be the "glue" that holds together the various nuclear bodies and could thus be viewed as an efficiency factor that facilitates Cajal body function. Or perhaps there may be a common Cajal body organizer that has yet to be discovered. Is there an evolutionary advantage to having all of the RNP assembly modules together in one place? Such an advantage would, necessarily, be a species-specific one, as human Cajal bodies are presumably no better than those of the fly. After all, why would you need that hovercraft module when you already have a great pair of wings?

I would like to thank Karl Shpargel for assistance in preparing the figure and the entire laboratory for lively discussions of Cajal bodies and diverse other subjects.

This work was supported by grants from the National Institutes of Health (GM53034 and NS41617) and the Muscular Dystrophy Association.

Submitted: 1 February 2006
Accepted: 10 February 2006

References

Cajal, S.R.y. 1903. Un sencillo método de coloracíon selectiva del retículo protoplasmico y sus efectos en los diversos organos nerviosos de vertebrados y invertebrados. *Trab. Lab. Invest. Biol. (Madrid).* 2:129–221.

Cioce, M., and A.I. Lamond. 2005. Cajal bodies: A long history of discovery. *Annu. Rev. Cell Dev. Biol.* 21:105–131.

Gall, J.G. 2003. The centennial of the Cajal body. *Nat. Rev. Mol. Cell Biol.* 4:975–980.

Jady, B.E., X. Darzacq, K.E. Tucker, A.G. Matera, E. Bertrand, and T. Kiss. 2003. Modification of Sm small nuclear RNAs occurs in the nucleoplasmic Cajal body following import from the cytoplasm. *EMBO J.* 22:1878–1888.

Liu, J.-L., C. Murphy, M. Buszczak, S. Clatterbuck, R. Goodman, and J.G. Gall. 2006. The *Drosophila* Cajal body. *J. Cell Biol.* 172:875–884.

Matera, A.G., and K.B. Shpargel. 2006. Pumping RNA: Nuclear bodybuilding along the RNP pipeline. *Curr. Opin. Cell Biol.* In press.

Miele, A., C.D. Braastad, W.F. Holmes, P. Mitra, R. Medina, R. Xie, S.K. Zaidi, X. Ye, Y. Wei, J.W. Harper, et al. 2005. HiNF-P directly links the cyclin E/CDK2/p220NPAT pathway to histone H4 gene regulation at the G1/S phase cell cycle transition. *Mol. Cell. Biol.* 25:6140–6153.

Shaw, P.J., and J.W. Brown. 2004. Plant nuclear bodies. *Curr. Opin. Plant Biol.* 7:614–620.

Stanek, D., and K.M. Neugebauer. 2006. The Cajal body: a meeting place for spliceosomal snRNPs in the nuclear maze. *Chromosoma.* In press.

Tucker, K.E., and A.G. Matera. 2005. The Cajal body: A nuclear gathering place. *In* Visions of the Cell Nucleus. P. Hemmerich and S. Diekmann, editors. American Scientific Publishers, Stevenson Ranch, CA. 159–171.

Tucker, K.E., M.T. Berciano, E.Y. Jacobs, D.F. LePage, K.B. Shpargel, J.J. Rossire, E.K. Chan, M. Lafarga, R.A. Conlon, and A.G. Matera. 2001. Residual Cajal bodies in coilin knockout mice fail to recruit Sm snRNPs and SMN, the spinal muscular atrophy gene product. *J. Cell Biol.* 154:293–307.

Verheggen, C., D.L. Lafontaine, D. Samarsky, J. Mouaikel, J.M. Blanchard, R. Bordonne, and E. Bertrand. 2002. Mammalian and yeast U3 snoRNPs are matured in specific and related nuclear compartments. *EMBO J.* 21:2736–2745.