

The human nucleolus organizer regions

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Although the nucleolus was first described in the early 19th century from both animal and plant cells, human nucleoli and particularly the five human nucleolus organizers have not been well characterized. In this issue of *Genes & Development*, van Sluis and colleagues (pp. 1688–1701) present a detailed molecular analysis of these organizers, which occur on the short arms of five human chromosomes. The near identity of these arms suggests extensive interchromosomal exchange during evolutionary history.

The nucleolus is the most obvious component of the interphase nucleus. It is evident without staining or phase contrast and so was described in the early 19th century, decades before the discovery of chromosomes. A lengthy review published in 1898 (Montgomery 1898) listed over 300 references! Nevertheless, the fact that the nucleolus is attached at a specific locus on a chromosome was not recognized until Barbara McClintock's (1934) seminal paper describing the maize nucleolus organizer (NO). Ordinarily, the nucleolus disappears from early prophase nuclei before the chromosomes become evident, but during meiotic prophase in maize (and other organisms), the nucleolus remains intact and is clearly attached at a specific locus on one chromosome. Still more decades passed before it was shown that the organizer contains the genes coding for ribosomal RNA and that the nucleolus is the site for storage and processing of the ribosomal RNA that eventually ends up in the cytoplasm (National Cancer Institute 1965). Many of these important insights came from cytological and molecular studies on *Drosophila* and the frog *Xenopus*, each of which has a single NO. Humans, by contrast, have five NOs on five separate chromosomes, complicating both the genetic and cytological analysis of the human ribosomal genes.

The five chromosomes with NOs are similar in one respect: The NOs are on the short arm, which is essentially identical in overall organization on all five chromosomes. This identity makes it difficult or impossible to study the NO in cells with the normal or near normal chromosome complement. Accordingly, McStay and colleagues (van

Sluis et al. 2019) studied each of the five chromosomes after they had been introduced separately into the mouse A9 cell line. Although the human chromosomes were transcriptionally silent in the hybrid cell lines, they could be reactivated by transfecting the cells with an expression plasmid that encodes human TAF1A–D. With this system, the authors could thus examine the structure and activity of each NO separately.

In the region next to the centromere, each short arm consists of a short proximal junction sequence, a long rDNA array containing up to 6 Mb of repeated sequences, a short distal junction sequence, and a block of satellite DNA consisting of a 48-bp repeat (see Fig. 1A in van Sluis et al. 2019). Their sequencing results confirm the near identity of the short arms of these five chromosomes. The simplest interpretation of these data is that numerous interchromosomal exchanges have taken place in the past and undoubtedly continue to do so.

The distal junction region is of special interest. Several years ago, the McStay group (Floutsakou et al. 2013) demonstrated the existence of a long noncoding transcript whose sequence corresponded to sequences in the distal junction region of the five acrocentric arms. However, because of sequence identity in these regions, it was not possible to know which chromosomes produced the transcripts. They now demonstrate that distal junction (DJ) transcripts are produced by each of the five acrocentric chromosomes contained in the separate mouse A9 cell lines. The data include both molecular analysis and *in situ* hybridization images of very high quality. An interesting feature of the hybridization images is the localization of the DJ transcripts in a few discrete foci near the nucleoli. These transcripts are noncoding, and so their functional significance remains to be determined.

This manuscript also includes molecular information on the homologous regions of the chimpanzee. The overall organization of the short arms is quite similar to that of the human, with the exception that the rDNA repeats are oriented in the opposite direction; that is, the rDNA is transcribed toward the telomere in the chimpanzee but toward the centromere in the human.

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This study is important for several reasons. First, it supplies detailed sequence analysis for the short arms of the five chromosomes that contain rDNA, sequence data that have been missing for a long time from the human genome annotation. As suspected, these arms are essentially identical to each other, presumably because they are subject to frequent interchromosomal exchanges. Second, it provides convincing evidence that a long noncoding transcript is produced from these short arms. The function of this transcript is not known, but its close physical association with the nucleolus raises the interesting prospect that it plays some role related to the transcription and/or processing of the rDNA itself. Finally, by including comparable data from the chimpanzee, this study confirms that the detailed organization of the rDNA has remained stable over a relatively long evolutionary time scale. In summary, this study from van Sluis et al. (2019) provides an important overview of the human nucleolus organizer regions and a starting point for future investigations of their central role in cell metabolism.

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