

Opinion

Satellite DNA: Intragenomic and Extracellular Dispersion

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Abstract

Satellite DNA has traditionally been described as a chromosomal tandem-repeat fraction, mainly associated with the formation of constitutive heterochromatin. However, this description, although correct, does not fully capture interpretations that view satellite sequences as dynamic components of genome architecture, especially in response to stress and instability associated with pathological states such as cancer. In this article, satellite DNA is presented in its full biological dynamism, from chromosomal arrays to extracellular release, with a proposed intermediate extrachromosomal state. Rolling-circle-mediated replacement-repair offers a coherent molecular route capable of explaining not only the turnover of tandem arrays but also the extrachromosomal and extracellular phases. The demonstration of extracellular human alpha-satellite DNA in plasma strongly supports the concept that satellite DNA release is closely connected to the idea of a circulating indicator of cancer-associated genomic instability. This framework links satellite DNA evolution to liquid biopsy and suggests a broader role for repetitive DNA in translating genome dynamics into measurable disease signals.

Keywords: satellite DNA; heterochromatin; extrachromosomal DNA; cell-free nucleic acids; genomic instability; liquid biopsy

1. Introduction: The Biological Problem of Satellite DNA

Satellite DNA is one of the most paradoxical components of eukaryotic genomes. It consists of highly repeated sequences organized in long tandem arrays and accumulates especially in chromosomal domains that are essential for genome architecture, including centromeric, pericentromeric, and subtelomeric regions. This classical definition remains correct, but incomplete: Satellite DNA is not merely a mass of constitutive heterochromatin; it is a dynamic genome fraction involved in chromatin organization, chromosomal stability, stress response, and disease-associated remodeling [1,2,3,4].

The key question is not whether satellite DNA is simply junk or functional, but how its arrays are maintained and reorganized. The more important question is how such extensive, homologous, unstable, and potentially recombinogenic sequences can be maintained, renewed, and reorganized without compromising chromosome integrity. Satellite DNA must satisfy two opposite requirements: it must preserve species-specific chromosomal organization and, at the same time, evolve rapidly in copy number, sequence composition and genomic distribution to contribute to the emergence of new species [5,6].

Classical molecular-drive models, including unequal crossing-over and gene conversion, have historically been used to explain repeat homogenization [7]. However, they do not fully explain how rapid, directional, and structured turnover of large tandem arrays can occur. Rolling-circle-mediated replacement-repair was proposed, on an experimental basis, to address precisely this problem [6,8]. Re-

cent methodological approaches based on long-read sequencing and modern repeat-resolved analyses have substantially reinforced the view that satellite DNA variability and turnover are structured genome processes rather than random background noise [9]. This article aims to present a personal perspective, based on long-term research on the molecular evolution of satellite DNA, with particular emphasis on rolling-circle-mediated replacement-repair as a mechanism linking array stability and rapid evolution to the intragenomic and extracellular dispersion of satellite DNA.

2. Replacement-Repair and Structured Turnover of Satellite Arrays

The replacement-repair model arose from the study of the S1 satellite DNA family in western Palearctic brown frogs. In that system, repeat-unit variability was limited, non-random, and remarkably stable within species. Importantly, the discriminating experimental observation was not simply the existence of sequence variation, but its restricted and structured distribution among repeat units. This pattern was difficult to reconcile with a simple stochastic accumulation of repeat variants followed by homogenization through unequal crossing-over or gene conversion and provided the experimental rationale for proposing replacement-repair. A mechanism was therefore proposed in which damaged or unstable satellite arrays generate intra- and/or extrachromosomal circular intermediates able to undergo rolling-circle amplification and produce tandem DNA that can repair, replace, or expand chromosomal arrays [6,8].



The molecular relevance of rolling-circle amplification is direct: satellite DNA is tandem DNA, and rolling-circle amplification naturally generates and preserves the tandem organization from circular templates. A circular satellite molecule should therefore not be interpreted only as a degradation product; it may represent a physical intermediate in array renewal. In this perspective, replacement-repair connects array damage, circularization, amplification, and chromosomal reintegration in a process capable of producing rapid variation without necessarily generating genomic chaos.

This model does not need to deny the existence of other processes contributing to repeat variation. Its specific value is different: it identifies a molecular route capable of regenerating tandem DNA through an extrachromosomal phase. For this reason, replacement-repair is not a marginal detail of satellite DNA biology, but a possible solution to the fundamental paradox of tandem arrays: they are unstable and yet organized.

3. From the Chromosomal Phase to the Extrachromosomal Phase

The most important conceptual consequence of the model is that satellite DNA may alternate between a chromosomal phase and an extrachromosomal phase. The chromosomal phase corresponds to tandem arrays embedded in chromatin and associated with centromeric, pericentromeric, or subtelomeric organization. The extrachromosomal phase corresponds to satellite-derived molecules, circular or linear, generated during instability, repair, or chromatin remodeling [10,11].

This does not mean that satellite DNA must be compared with a canonical transposable element. The point is not to assign to satellite DNA an enzymatic mobility identical to that of transposons, but to recognize that a class of tandemly repeated sequences can cross distinct biological states. The chromosomal state provides structural organization; the extrachromosomal state provides amplification potential, redistribution and renewal.

Once satellite DNA enters an extrachromosomal phase, several fates become possible: degradation, reintegration into the original array, insertion into new genomic sites, persistence as extrachromosomal circular DNA (ecDNA), or release into the extracellular space. In this framework, chromosomal satellite arrays, satellite-derived extrachromosomal molecules, dispersed satellite-derived sequences, and extracellular satellite DNA represent different topological and compartmental states of DNA sharing a common satellite-sequence origin. The existence of these different states is experimentally documented, whereas the molecular transitions proposed to connect them are supported to different degrees. Intragenomic and extracellular dispersion of satellite DNA can therefore be interpreted as expressions of the same biological property: the capacity of repeated arrays to leave, at least transiently, their

canonical chromosomal configuration. The documented occurrence of satellite-derived sequences at euchromatic loci, discussed in section 4, demonstrates that satellite DNA can become redistributed within the genome. If extrachromosomal satellite-derived molecules participate in this redistribution, their extensive sequence homology with heterochromatic satellite arrays provides an obvious molecular substrate for homologous reintegration into the original or related arrays. In mechanistic terms, such reintegration is at least as plausible as insertion into less homologous euchromatic regions and represents a central prediction of the replacement-repair model.

4. Intragenomic Dispersion and Regulatory Consequences

The presence of satellite sequences dispersed outside large heterochromatic arrays indicates that satellite DNA can contribute to intragenomic plasticity. In several systems, satellite-derived elements are located near or within genes, where they may acquire regulatory potential. One of the earliest lines of evidence for this phenomenon was obtained in the beetle *Tribolium castaneum*, where dispersed satellite sequences have been associated with modulation of gene expression after heat stress through mechanisms involving satellite transcription, RNA interference, and local heterochromatin formation [12]. Similar results have also been observed in the human genome: alpha-satellite-derived sequences, although mainly associated with centromeres, are also present in euchromatic and intragenic regions. These sequences should not necessarily be considered neutral residues; they may represent traces of previous dispersion events and, in some contexts, substrates for epigenetic or transcriptional regulation [13,14].

The central point is that satellite DNA can retain a dual identity. As a chromosomal array, it contributes to genome architecture; as a dispersed element, it may participate in regulatory remodeling. Intragenomic dispersion is therefore not a marginal phenomenon, but a possible functional extension of satellite turnover.

5. Extracellular Alpha-Satellite DNA: From Genome Dynamics to Liquid Biopsy

The extracellular dimension of satellite DNA has gained direct experimental support with the demonstration of extracellular human alpha-satellite DNA in plasma. In a preliminary study of 46 plasma samples, extracellular human alpha-satellite DNA measured by digital polymerase chain reaction (PCR) was increased in patients with bladder cancer compared with bladder-cancer-negative individuals, yielding an exploratory receiver operating characteristic (ROC) area under the curve (AUC) of 0.944 [15]. Full analytical performance, cohort characteristics, and pre-analytical procedures are reported in the original study.

This observation changes the conceptual framework. Satellite DNA is not only a repeat family involved in

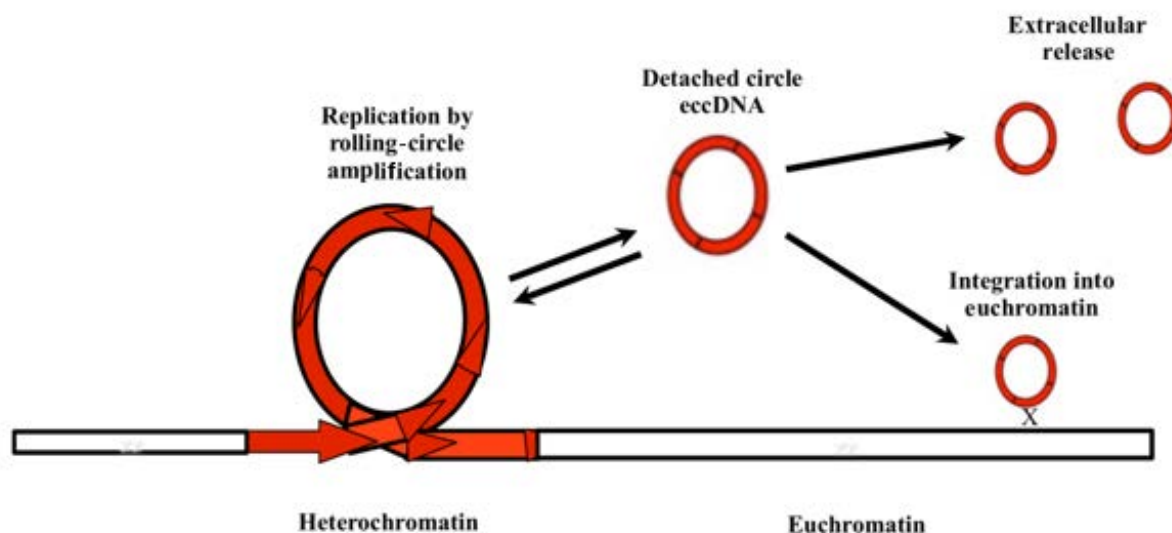


Fig. 1. Conceptual model of satellite DNA intragenomic and extracellular dispersion. The illustrated structures represent different topological and compartmental states of DNA sharing a common satellite-sequence origin. These molecular states have been described experimentally, whereas arrows indicate mechanistic transitions proposed within the rolling-circle-mediated replacement-repair framework and do not imply that every transition has been directly demonstrated. Red segments represent satellite DNA sequences, and the “X” symbol marks the site of satellite-derived DNA integration within euchromatin. Extrachromosomal circular DNA (eccDNA). Created with Keynote '09 (version 5.0.3 (791); Apple Inc., Cupertino, CA, USA).

genome evolution and chromosomal organization; it can also become a circulating molecular signal. Extracellular release of alpha-satellite DNA may reflect genomic instability, disruption of chromatin organization, cell death, release in DNA-protein complexes, extracellular-vesicle-associated secretion, or other pathological processes of tissue remodeling [15,16,17,18,19].

The biological value of this signal does not necessarily coincide with absolute specificity for a single organ or a single mutation. Unlike liquid-biopsy markers based on point mutations, extracellular satellite DNA may indicate a broader state: instability of repetitive chromatin, alteration of heterochromatin, and pathological DNA release. Because of its abundance and tandem organization, alpha-satellite DNA may provide a high-copy signal of genome destabilization.

6. Connecting Evolution, Stress and Cancer

The same properties that make satellite DNA important in evolution also make it informative in disease. Satellite DNA is abundant, repeated, organized in chromatin domains, and sensitive to epigenetic states. These features allow the formation of stable chromosomal architectures, but they also make arrays vulnerable to replication stress, DNA damage, and chromosomal instability.

In cancer, heterochromatin is frequently altered, repeat transcription may become deregulated, and satellite sequences may participate in chromosomal instability. Increased alpha-satellite RNA levels in the blood of patients with metastatic castration-resistant prostate cancer,

together with the effects of heat stress and antibiotic exposure on alpha-satellite chromatin, support the connection between satellite DNA, cellular stress and pathological states [20,21,22].

The release of alpha-satellite DNA into plasma may therefore represent the extracellular trace of a deeper nuclear process: the destabilization of repetitive chromatin domains. In this sense, satellite DNA evolution and its relevance as a biomarker are not separate topics; both depend on the capacity of repeated arrays to undergo reorganization, amplification, dispersion, and release.

7. Evolutionary Implications

Darwinian evolution explains how heritable variation is filtered by natural selection [23]. However, evolutionary theory also requires molecular mechanisms capable of generating variation at different scales, from point mutations to large genomic reorganizations. Satellite DNA turnover belongs to this second category: it can rapidly modify copy number, array composition, chromosomal distribution, and heterochromatin state.

This point is also relevant to models of discontinuous evolutionary change, such as the punctuated equilibria proposed by Eldredge and Gould [24]. Such models describe rapid or episodic evolutionary patterns, but they require molecular substrates capable of producing relatively rapid and structured genomic reorganizations. Satellite DNA replacement-repair provides a possible molecular basis for this level of genome dynamics.

The model does not replace natural selection. On the contrary, it proposes a mechanism through which an abundant and structurally important fraction of the genome can generate variation on which selection may act. In this perspective, satellite DNA does not only record genome history; it actively contributes to the production of genomic plasticity.

8. Conclusions

Satellite DNA should not be considered only a tandemly repeated fraction of constitutive heterochromatin. It is a dynamic genomic system capable of intragenomic and extracellular dispersion. Rolling-circle-mediated replacement-repair offers a coherent molecular mechanism linking chromosomal array renewal, extrachromosomal intermediates, and redistribution of repeated sequences. The demonstration of extracellular human alpha-satellite DNA in plasma extends this framework to translational biology. Satellite DNA can be released from cells and measured as a circulating signal associated with genomic instability, a common but heterogeneous feature of many cancers. This connects molecular evolution to liquid biopsy and suggests that repetitive DNA can translate genome dynamics into measurable disease information. A unified representation of these pathways is shown in Fig. 1. Conditions associated with increased satellite-DNA instability should also be accompanied by increased extrachromosomal and/or extracellular satellite-derived DNA. Testing this relationship will determine whether these molecular states represent connected manifestations of the same satellite-DNA turnover process.

Author Contributions

IF conceptualized, wrote, reviewed and edited the manuscript. The author read and approved the final manuscript and agrees to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author declares no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During preparation of this version, AI-assisted tools (ChatGPT) were used for linguistic support. The author reviewed and edited the content and takes full scientific responsibility for the manuscript.

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