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On the edge: how nuclear pore complexes rule genome stability

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Nuclear organization has emerged as a critical layer in the coordination of DNA repair activities. Distinct types of DNA lesions have notably been shown to relocate at the vicinity of nuclear pore complexes (NPCs), where specific repair pathways are favored, ultimately safeguarding genome integrity. Here, we review the most recent progress in this field, notably highlighting the increasingly diverse types of DNA structures undergoing repositioning, and the signaling pathways involved. We further discuss our growing knowledge of the molecular mechanisms underlying the choice of repair pathways at NPCs, and their conservation — or divergences. Intriguingly, a series of recent findings suggest that DNA metabolism may be coupled to NPC biogenesis and specialization, challenging our initial vision of these processes.

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Introduction

Among the cellular components that contribute to nuclear architecture and genome organization are the nuclear pore complexes (NPCs), which are megadalton-sized proteinaceous assemblies inserted into the nuclear

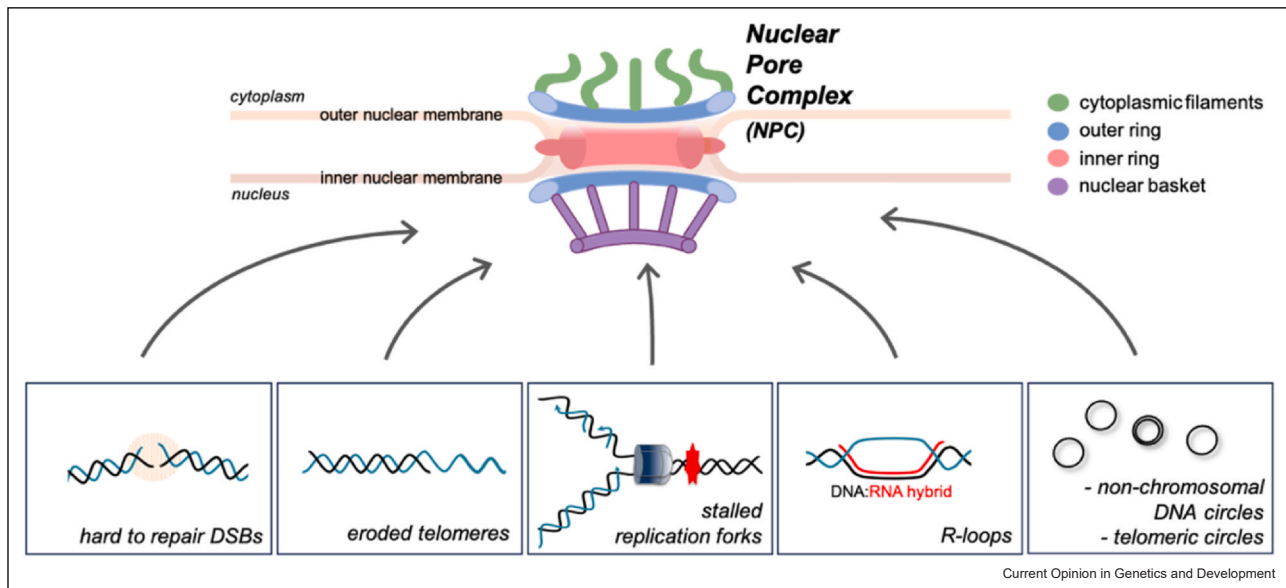
envelope at the points of fusion of the inner and outer nuclear membranes. NPCs are composed of repeated copies of ~30 polypeptides called nucleoporins (Nups) and assembled into structural modules, delineating a three-ring symmetric scaffold flanked by peripheral appendages, namely the cytoplasmic filaments and the nuclear basket (Figure 1). In addition to their well-characterized interactions with transport receptors, which are instrumental for the nucleocytoplasmic exchanges of macromolecules, NPCs and their components also establish contacts with the genome, influencing virtually all DNA-based transactions, thus impacting the maintenance of genetic integrity [1].

Genome stability critically relies on the DNA damage response (DDR), a series of pathways that sense genotoxic insults or impediments to DNA metabolism, and respond through the establishment of dedicated signaling and DNA repair mechanisms. Several layers of spatiotemporal regulations control the activation and outcome of the DDR, from epigenetic modifications and chromatin organization, to chromosome structure and nuclear compartmentalization (reviewed in Refs. [2,3]). Here, we will focus specifically on the increasingly multifaceted role exerted by NPCs in the control of genetic stability, as first observed in yeast and now expanded to several model organisms.

Multiple damages on the way to the nuclear periphery

Following the observation that mutations in several Nups confer sensitivity to various DNA-damaging agents and lead to DNA damage accumulation [4], the groundbreaking discovery of a function of NPCs in the DDR was the demonstration of the robust recruitment of hard-to-repair double-strand breaks (DSBs) to the nuclear pores in yeast [5]. This observation hinted at the potential for NPCs to serve as a hub for specific molecular transactions at damaged DNA sites, a function independent of the trafficking of repair factors in and out of the nucleus. Together with the subsequent establishment of a role of NPCs in anchoring eroded telomeres in the absence of telomerase and in regulating telomere recombination [6,7], this led to the notion that NPCs could help resolve ‘congested’ DNA intermediates by promoting noncanonical error-prone repair pathways [8]. However, this initial model faced challenges as increasing evidence pointed to various

Figure 1



An overview of the various DNA structures relocating to NPCs. The different structural modules of the NPC are represented according to the indicated color code. See text for details.

DNA structures relocating to NPCs with distinct consequences (Figure 1). Notably, replication forks stalled at several natural or model replication barriers were shown to relocate to the nuclear pores. These include structures such as triplet-nucleotide repeats (TNR) [9], tightly DNA-bound proteins at telomeres [10,11], rDNA [12], or a site-specific model barrier [13]. Beyond DNA replication, recent research also unveiled the role of NPCs in responding to R-loops, which are genotoxic structures formed when nascent RNAs hybridize back to their DNA templates. R-loops also act as a trigger for relocation to NPCs, yet independently of damage formation [14]. Importantly, DNA–NPC interactions extend beyond chromosomes. Extrachromosomal DNA circles (ecDNA), which are by-products of recombination events between repeated sequences (e.g. at ribosomal DNA or telomeres), also relocate to yeast NPCs [15,16]. Given their relevance in cancer cells and potential involvement in mutagenesis [17], ecDNA relocation to NPCs represents an intriguing avenue of exploration. In line with this, anchoring of telomeric C-circles to NPCs in yeast potentially contributes to recombination-based alternative telomere lengthening, driving survival in the absence of telomerase [16]. Thus, the relocation to the NPCs concerns a wide variety of chromatin and DNA structures and is not restricted to pathological situations (Figure 1).

Despite these significant findings, the shared features dictating the relocation of various DNA structures to NPCs remain unclear (Table 1). The detection of damaged DNA is largely associated with a wave of post-

translational modifications (PTMs) targeting several DNA-binding proteins and repair factors, notably through SUMOylation, which relies on the covalent coupling of the small ubiquitin-like modifier (SUMO) polypeptide to its targets. Although the specific SUMOylated proteins might vary depending on the type of damage, the common thread is their recognition by NPC-associated SUMO-targeted ubiquitin ligases (STUBLs), driving the relocation to nuclear pores (reviewed in Ref. [18]). Extensive accumulation of RPA (replication protein A)-bound single-stranded DNA is the critical signal for the SUMOylation wave [19] and RPA interacts with the STUBL component Slx5 in yeast [7]. Accordingly, RPA appears as a key factor in NPC relocation [14,20] although its poly-SUMOylation might be instrumental only when resection is limited [21]. Of note, ecDNA seems to use a distinct and less-understood pathway relying on factors involved in the coupling between transcription and mRNA export [15,16].

Among the intriguing facets of DNA damage relocation to NPCs is the role of the cytoskeleton and motor proteins. Nuclear actin filaments participate in DNA damage relocation to the nuclear periphery and/or NPCs, with Arp2/3 actin nucleators having been shown to mediate repositioning of heterochromatic DSBs in *Drosophila* [22] and replication-stressed telomeres in human cells [11]. Accordingly, F-actin promotes the mobility of stressed replication foci and DNA breaks [23,24]. Increased mobility of damaged DNA also involves changes in nuclear microtubule dynamics and

Table 1

Factors involved in repositioning at NPCs and associated DNA repair events, as inferred in yeast models.

DNA structures	Factors involved			Functional consequences				
	DDR	Chromatin	SUMO pathway	NPC	Repair pathway affected	[Effect]	Loss-of-function assessed	Gain-of-function assessed
DSBs [4,5,25,32-34]	Checkpoint: Mec1 [5]	SWR1/Htz1 [33]	<i>Poly-SUMOylation</i> : SUMO E3 ligases: Siz2, Mms21 [32]; STUbLs: Six5-Six8 [32]	Nup84 complex [5]	NHEJ [4,25,32]	[+]	Nup84 complex ^(a) , Nup60, and Ulp1	-
Stalled replication forks [5,9,13,20,55]	Resection: Sgs1, Exo1, and Mre11 [20]; fork remodeling: Rad51 [13] ^(b) , PCNA loading: Ctf18-RFC? [55]	Smc5/6 complex [20]	<i>Mono-SUMOylation</i> : Rad52, Rad59, and RPA [20]; SUMO E3 ligases: ScMms21 [20], SpPli1 [13]; STUbLs: ScSix5-Six8 [20], SpRfp1-Rfp2/Six8 [13]	Nup84 complex [9,13], Nup1 [10]	Homologous recombination (HR) [5] BIR [25,32]	[+]	Nup84 complex, Nup84 complex, Nup60, and Six8	LexA-Nup84
Eroded telomeres [7,10]	Checkpoint: Rad9, Rad24 [7]	?	<i>SUMOylation</i> : SUMO E3 ligases: Siz1-Siz2 [7]; STUbLs: Six5-Six8 [7]	Nup1 [10]	BIR (type II survivors) [7]	[+]	Mlp1, Mlp2, Ulp1, Siz1-Siz2, and Six5-Six8	LexA-Ulp1C
R-loops [14,35]	ssDNA coating: RPA [14]	?	<i>Mono-SUMOylation</i> : RPA [14]; SUMO E3 ligase: Mms21 [14]; STUbLs: Six5-Six8 [14]	TREX2 [15,16]	Unequal sister chromatid recombination [10] Homologous recombination (HR) [14,35]	[-]	Mlp1, Mlp2	-
Telomeric C-circles ecDNA circles [15,16]	?	SAGA [15,16]	^(c)	TREX2 [15,16]	BIR (type II survivors) [16] detoxification? Prevention of aging?	[+]	TREX2	-

The factors involved in the relocation of the indicated structures to the NPCs are indicated and classified according to their biological function: DNA metabolism and the DDR; chromatin and chromatin-associated factors; SUMOylation pathway (type of modification, targets, and enzymes); NPC components. The repair pathways and the genetic situations assessed are indicated. Increased or decreased activities of the indicated pathways at the NPC are indicated by [+] or [-], respectively. Sc, *S. cerevisiae*; Sp, *S. pombe*. (a) *nup84Δ* does not affect NHEJ in Ref. [25] and affects only imprecise NHEJ in Ref. [32]. (b) Rad51 associates to TNR-stalled forks following their relocation to NPCs in *S. cerevisiae* [20], while its enzymatic activity is required for the repositioning of a replication fork barrier in *S. pombe* [13]. (c) TREX2 is not required for R-loop repositioning to NPCs [14]. (d) Six5 is not required for ecDNA circle association with NPCs [15].

partners, which might promote repair by relocating the damage to specific nuclear domains including NPCs [25–28]. Conversely, microtubules can substantially alter nuclear morphology (reviewed in Ref. [29]), forming nuclear membrane invaginations (including lamina, inner nuclear membrane proteins, and NPCs) that bring the nuclear envelope to DSBs upon damage induction [30]. It remains to be uncovered whether other types of DNA damages similarly interact with NPC components away from the nuclear periphery, notably in view of the existence of nucleoplasmic pools of Nups [31].

Nuclear pore complex association: a double-edged sword for damaged loci

The impact of DNA damage–NPC association on DNA repair and genome stability has been extensively investigated in various distinct DNA damage scenarios, utilizing dedicated assays and loss- or gain-of-function experiments (as outlined in Table 1). Based on these approaches, NPCs have been proposed to promote non-homologous end joining (NHEJ [4,32]), recombination with the sister chromatid [33,34], replication-dependent fork restart [13,20], or mutagenic break-induced replication (BIR) repair [25,32]. At eroded telomeres, NPCs similarly facilitate a BIR-type of repair aiding in maintaining telomere function by generating type II survivors [7]. Conversely, NPC association has been shown to reduce R-loop levels [35] and R-loop-induced recombination on transcribed genes [14]. Yet, despite these efforts, the precise role of NPCs in repair pathway choice or fork protection still remains enigmatic (Table 1). Indeed, it is likely that the outcome of NPC association varies depending on the damage type and during cell cycle progression. For instance, in the context of replication-associated stresses, the exact sequence of events leading to fork restart and the repair proteins under regulation appear to differ depending on the replication stalling event [18]. In the case of transcription-associated stresses, NPC association in G1, as observed upon R-loop formation, may preserve genome stability [14,35]. However, relocation in S phase could turn detrimental, as highlighted by the increased replication stress and DNA damage scored in situations of checkpoint or pre-mRNA processing deficiencies associated with extended NPC binding [36,37].

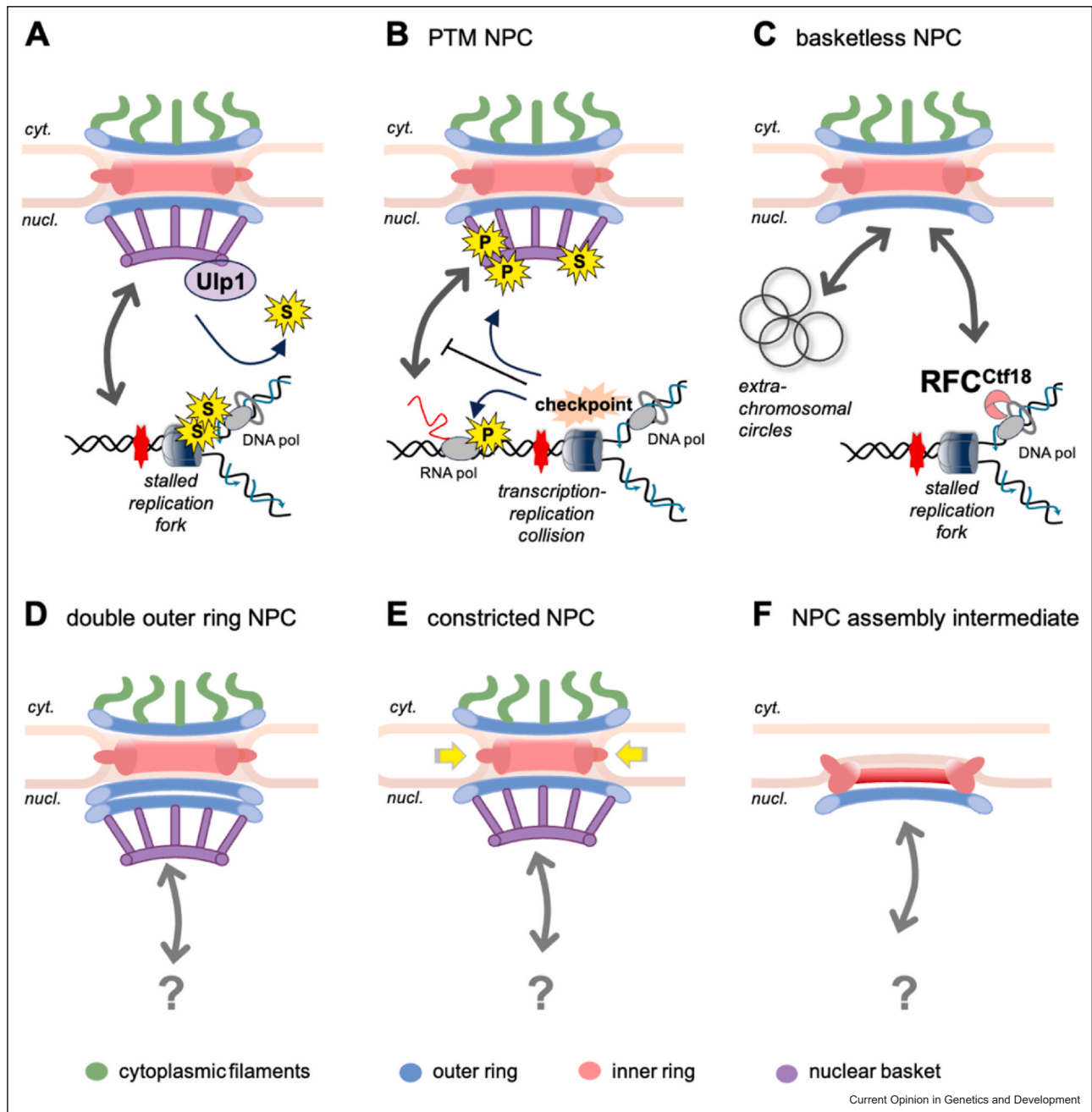
Beyond the limitations of repair assays performed on asynchronous populations, it is also important to acknowledge the biases introduced by loss-/gain-of-function experiments. Loss-of-function assays can lead to indirect effects, particularly in NPC mutants that could affect cell fitness, macromolecule import/export (e.g. [38]), or SUMOylation processes, away from the NPC [4]. Similarly, gain-of-function experiments, which rely on the targeting to damaged chromatin of a Nup fused to a DNA-binding domain, could lead to misleading outcomes if Nup function and/or expression are affected by tagging [10]. In

the future, novel experimental strategies with increased spatial and temporal resolution will thus be required to determine whether and how NPCs shield cells against DSB-induced genetic instability, or foster last-resort repair attempts at the expense of genome integrity.

Amid the diverse repair outcomes, common themes emerge regarding the molecular mechanisms through which NPCs could regulate DNA repair and fork restart. NPCs could serve as anchor points, facilitating encounters between damaged DNA and its homologous sequences used for repair. This concept is especially relevant for damaged telomeres, which naturally localize to the nuclear periphery, at the vicinity of nuclear pores [39]. Supporting this notion, the absence of the Nup84 complex reduces DSB-induced BIR between sub-telomeric repeats [25]. Similarly, telomeric C-circles, proposed as BIR templates for elongating eroded telomeres, concentrate at NPCs at the time of type II survivor formation, potentially enhancing their interaction with telomeres and promoting telomere elongation [16]. Intriguingly, NPCs, with their ability to selectively export RNAs, might enhance spatial proximity between DNA damage and RNA molecules, which have the potential to serve as templates for recombination [40,41]. Alternatively, NPCs might sequester damaged DNA away from unwanted recombination substrates, preventing deleterious recombination events, a phenomenon proposed for rDNA in yeast [12] and heterochromatin in *Drosophila* [42]. By facilitating mRNA export and eviction from transcription sites, the vicinity to NPCs may similarly disfavor encounters between RNA molecules and their DNA templates, alleviating R-loop formation [14,35].

Furthermore, NPCs associate with and locally concentrate specific factors, in particular the enzymes of the SUMO pathway, creating functional compartments that might regulate repair processes. Within these NPC-bound factors, the STUBL Slx5–Slx8 and the SUMO protease Ulp1/SEN1–2 have been implicated in the anchoring of DNA damages to NPCs and their resolution, respectively. A broad model posits that DNA repair proteins are regulated through modulation of SUMOylation and ubiquitinylation at NPCs, potentially leading to proteasome-mediated degradation, as previously proposed ([8], discussed in Refs. [18,43]). Importantly, factors needed for targeting DNA damage to NPCs may not necessarily be the same as those modulating repair in the NPC environment. For instance, Ulp1 is essential for restarting stalled replication forks but not for their targeting to NPC in *S. pombe* [13]. NPCs could also concentrate other factors directly involved in damage processing. A recent example is NUMEN, a membrane-bound endo-/exonuclease processing DSBs with 3'-overhangs, which localizes at the nuclear periphery and interacts with NPCs [44]. In this

Figure 2



NPC variants and their interactions with DNA structures. The different structural modules of the NPC are represented as indicated. PTMs are illustrated by stars (P, phosphorylation; S, SUMOylation). *DNA pol*, DNA polymerase; *RNA pol*, RNA polymerase.

context, removal of 3'-ssDNA overhangs by NUMEN is thought to favor NHEJ, particularly, though not exclusively, at perinuclear heterochromatic DSBs. Last, NPCs interact with RNA-binding proteins, which are increasingly implicated in DNA repair [41], possibly facilitating the recruitment of these proteins to sites of DNA damage, an aspect that will deserve further exploration.

Are specialized nuclear pore complexes involved in DNA-related transactions?

A growing body of evidence underscores the coexistence of structurally distinct NPC variants within a single nucleus (reviewed in Ref. [45]), sparking questions about their potential roles in the specific genomic processes described above. A first level of spatiotemporal variations among individual NPCs is provided by a spectrum of

PTMs targeting nucleoporins in response to various stimuli, including genotoxic stress. For instance, during replicative stress, nuclear basket subunits undergo phosphorylation by the Mec1^{ATR} replication checkpoint kinase and its downstream effector Rad53^{CHK1} [36,46]. These modifications have been proposed to directly trigger the release of transcribed genes from the NPC, thus minimizing the topological constraints that would lead to fork reversal [36]. Recent findings also reveal that the DNA replication checkpoint triggers the eviction of RNA polymerases from their templates [47], impacting their transcription-dependent association to NPCs during regular or challenged replication [46]. Other DNA damage-induced PTMs, such as Nup60 ubiquitylation [48] or SUMOylation [49], might further influence NPC–chromatin association, warranting further investigation.

Additional layers of structural variations among individual pores encompass differences in (i) subunit composition, with the notable absence of the nuclear basket in a subset of NPCs in fungi [50,51], (ii) stoichiometry, as revealed by the detection of NPC isoforms containing either a single or a double nucleoplasmic outer ring in *S. cerevisiae* [52], and (iii) conformation, as reflected by varying dimensions of the inner ring-delineated channel [53,54] (Figure 2). In this respect, ‘basketless’ NPCs were recently proposed to interact with different DNA metabolism intermediates in budding yeast. On the one hand, the Ctf18-containing clamp loader replication factor C (RFC^{Ctf18}) associates with a subset of NPCs devoid of the basket subunits Mlp1 and Mlp2, especially during S phase and replicative stress [55]. While this interaction could contribute to the re-localization of RFC^{Ctf18}-associated stalled forks to the NPC, it may also reflect the existence of specialized NPCs, which could promote the PCNA loading and checkpoint activities of RFC^{Ctf18} at challenged replisomes, as supported by the decline in PCNA chromatin levels scored in *nup170Δ* mutants. Another example of pore specialization is provided by the detection of basketless NPCs in interaction with ecDNA circles [56]. These NPC species would contribute to the proper retention of such toxic DNA molecules in the mother cell during mitosis, although their specific composition is also likely to impact nucleocytoplasmic transport, as suggested by their decreased association with several mRNA export factors.

Which mechanisms could generally specify the association of distinct DNA intermediates with particular NPC variants (Figure 2)? On the one hand, chromatin or DNA-binding interfaces could be accessible in certain NPCs while masked in others, as already suggested [57]. Supporting this hypothesis, the chromatin-binding ac-

tivity of Nup155 was found to be suppressed in the presence of Nup62 in flies [58]. Alternatively, the association with DNA structures may disrupt NPC organization, displacing individual Nups or Nup modules, as proposed in the case of DNA circles [56]. Finally, DNA loci could associate with assembling NPCs, locking them into an immature state, a worth-considering scenario since basketless pores represent a natural intermediate in interphasic NPC assembly in yeast [59].

A more intricate coupling between DNA metabolism and NPC assembly emerges from reported interactions between DNA replication factors and Elys, a chromatin-binding Nup pioneering postmitotic NPC assembly in metazoans (reviewed in Ref. [60]). Elys reportedly associates with distinct components of the origin licensing and replication initiation machinery, such as MCM2–7 helicases in *Xenopus* extracts [61] and the origin recognition complex in flies [62]. Elys contributes to the loading of both complexes onto chromatin [61–63], and prevents replication stress-associated genetic instability, possibly by enabling additional dormant origin licensing events [62]. Reciprocally, MCM2–7 is required for optimal Elys recruitment onto chromatin, NPC assembly, and nuclear growth [61]. Interactions between Nups and factors involved in DNA metabolism are thus likely to reciprocally influence both NPC assembly and genome integrity.

Concluding remarks

The last years of research have revealed an unsuspected versatility of NPCs in DNA-related processes, notably regarding the type of DNA lesions or intermediates locally engaged, the mechanisms ensuring their recruitment, and the repair pathways affected. In the future, refining our experimental strategies will be instrumental to further disentangle the specific functions of NPC components in DNA metabolism from their more canonical roles in nuclear structure and homeostasis, and to pinpoint their regulation according to the physiological or pathological status of the cell, as exemplified by the recently-reported circadian control of DSB association to the nuclear envelope [64]. The potential for NPC structural variants, as observed in the same nucleus or between species [45], to recruit and handle distinct types of DNA lesions, represents an additional, exciting hypothesis that will deserve careful investigation, at the crossroads of several research areas and communities.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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