# Nuclear Actin Dynamics in Gene Expression, DNA Repair, and Cancer

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## Abstract

Actin is a highly conserved protein in mammals. The actin dynamics is regulated by actin-binding proteins and actin-related proteins. Nuclear actin and these regulatory proteins participate in multiple nuclear processes, including chromosome architecture organization, chromatin remodeling, transcription machinery regulation, and DNA repair. It is well known that the dysfunctions of these processes contribute to the development of cancer. Moreover, emerging evidence has shown that the deregulated actin dynamics is also related to cancer. This chapter discusses how the deregulation of nuclear actin dynamics contributes to tumorigenesis via such various nuclear events.

**Keywords**: nuclear actin, chromosome architecture, chromatin remodeling, BAF complex, INO80 complex, transcription machinery, RNA polymerase, DNA repair, gene expression, and cancer

## 1. Introduction

Actin is a highly conserved protein family in mammals. It participates in multiple cellular processes, including muscle contraction, cell motility, cell division, organelle movement, material transportation, signal transduction, cell junction establishment, and cell shape maintenance [1-3]. The actin family is classified into three types of isoforms in humans: α-actins (ACTA1, ACTA2, and ACTC1), β-actins (ACTB and ACTBL2), and γ-actins (ATCG1 and ACTG2) (Table 1) [2]. They share 93% amino acid identity, with slight length variations at N-terminus [2, 4].

### 1.1. Actin dynamics in the cytoplasm

In the cytoplasm, actin exists as either a globular monomer (G-actin) or a filamentous polymer (F-actin) [1]. The G-actin structure is divided into two lobes by a deep cleft in the middle (Figure 1A). The upper cleft between subdomains 2 and 4 is the binding site for ATP, ADP, and cations. The lower cleft between subdomains 1 and 3 is the target site for actin-binding proteins (ABPs) [1, 4]. F-actin is a linear chain of G-actins [1]. It is the basic building structure of microfilaments with two ends, the (+) end (barbed end) and the (−) end (pointed end).

In a physiological condition, G-actin and F-actin are under a dynamical equilibrium between polymerization and depolymerization (Figure 1B) [5]. At the initial polymerization phase,

ATP-bound G-actins combine into an oligomer as a nucleus with actin-nucleating proteins, like formin and actin-related protein 2/3 (ARP2/3) complex (Table 2), under the existence of $Mg^{2+}$, $K^+$, or $Na^+$. Then, the nucleus of actin polymerization rapidly increases in length at both ends. This elongation phase is powered by the hydrolysis of ATP-G-actin, which transforms to ADP-G-actin and releases inorganic phosphate ($P_i$). Finally, a steady conformational state between F-actin and G-actin is reached, with no further elongation of F-actin. Briefly, when ATP is bound to G-actin with the existence of cations, G-actin polymerizes into F-actin. This process is reversible when the free ATP-G-actin amount or the cation strength is low.

The polymerization process that the (+) end grows whereas the (−) end loses subunits is called treadmilling, which drives the intracellular movement of F-actin (Figure 1C). Treadmilling is accelerated by ABPs (Table 2), such as cofilin and profilin (Figure 1D) [6]. Cofilin binds to ADP-G-actin at the (-) end to enhance its dissociation from the chain. Profilin binds to free ADP-G-actin and catalyzes the exchange of ADP for ATP, delivering ATP-G-actin back to the (+) end.

The actin dynamics are further regulated by capping proteins (CPs) (Table 2) binding to the (+) end, and tropomodulin, which binds to the (-) end, inhibiting the uncontrolled polymerization and depolymerization [7]. As a new actin polymerization regulator (Table 2), CRACD (capping protein-inhibiting regulator of actin dynamics) has been recently identified as a tumor suppressor in colorectal cancer, indicating the implication of deregulated actin dynamics in cancer [8-10].

### 1.2. Actin visualization

To visualize actin-related events, several actin-detecting probes have been generated by fusing the fluorophore or fluorescent protein to actin (actin-GFP), actin antibody (actin-chromobody), actin-modulating drugs (phalloidin, SiR-actin, and SPY-actin), or ABPs (F-tractin, Lifeact, and UtrCH) (Table 3) [11, 12]. Unlike live-cell imaging, optimal fixation conditions are crucial to represent physiologically relevant actin dynamics. Fixation by methanol, ethanol, or acetone destroys the native quaternary structure of F-actin, which creates dotted artifacts in fixed cells [13, 14]. Paraformaldehyde has been validated as the best fixation solution to retain actin structure [15, 16]. Furthermore, to avoid ethanol during the dehydration and hydration of paraffin-embedded tissues, cryo-section is the preferred choice to stain F-action by phalloidin in tissue samples [17].

The presence of nuclear actin was first described in the calf thymus cells in 1963 [18]. However, due to the lack of nucleus-permeable actin probes, the existence of nuclear actin has been in debate for decades [19]. Initially, nuclear actin was considered to be an artifact from cytoplasmic actin contamination [20]. Thanks to the development of microscopy and actin-detecting constructs fused with nuclear localization signal (NLS), convincing evidence of nuclear actin have been introduced [21-24]. For example, the endogenous nuclear F-actin and G-actin are detectable by using the actin-chromobody-GFP-NLS in the normal colon epithelial cells and mucinous colorectal cancer cells (Figure 1E).

### 1.3. Nuclear actin dynamics

Actin protein is constantly and rapidly shuttled into and out of the nucleus via the nuclear pore complex (NPC) to maintain the actin balance between the cytoplasm and the nucleus [25]. By active transport, G-actin is imported into the nucleus by importin-9 (IPO9) in a complex with cofilin and exported out by exportin-6 (XPO6) coupled with profilin [26]. ABPs and actin-related proteins (ARPs) also exist in the nucleus (Table 2) [27-29]. Additionally, SUMOylation, a type of post-translational modification, of actin interferes with the actin-XPO6 interaction to retain actin in the nucleus [30].

In this chapter, we focus on the roles of nuclear actin in various biological processes, including chromosome architecture organization, chromatin remodeling, transcription machinery regulation, and DNA repair, in the aspect of cancer [27, 31-34].

## 2. Nuclear Actin and Chromosome Architecture

### 2.1. The hierarchy of chromosome architecture

The two-meter length of mammalian DNA is organized into a highly condensed chromosome at a supreme level of hierarchy [35]. In the classical model, chromatin is described as an alternation of euchromatin and heterochromatin. Euchromatin is loose and transcriptionally active with enrichments of specific histone modifications (H3K4me3, H3K36me3, and H3K79me3), mainly located in the nuclear interior [36]. Heterochromatin is dense and transcriptionally repressed, marked by repressive histone modifications (H3K9me2, H3K9me3, and H3K27me3), located at the nuclear periphery [36, 37].

Based on the genome-wide chromosome conformation capture sequencing (Hi-C-seq) [38], the chromosome architectural hierarchy is divided into the nucleosomes, chromatin fibers, chromatin loops, topologically associating domains (TADs), chromosome compartments, and chromosome territories in a decreasing resolution (Figure 2) [39-42].

**Nucleosomes (10-30 nm):** Nucleosome is the fundamental unit of chromatin, containing a histone octamer (two copies of each H2A, H2B, H3, H4) wrapped with 147 bp DNA [43]. Adjacent nucleosomes are connected by the linker DNA associated with the linker histone protein (H1 or H5) to form a beads-on-a-string array at a diameter of 11 nm [43].

**Chromatin fibers (30 nm):** The beads-on-a-string arrays coil into a 30 nm diameter helical structure known as the chromatin fiber under the shape of solenoid or zig-zag [44].

**Chromatin loops (30-100 nm):** It is suggested that, on the linear chromatin fiber, the distal enhancers physically bind to the promoters of target genes at spatial proximity to initiate the transcription by looping out to form the chromatin loops [45, 46]. This process is mediated by anchoring several proteins, including transcription factors (TFs), RNA polymerase II, CCCTC-binding factor (CTCF), cohesin, and mediator [47]. These loops form the active chromatin hub (ACH) spanned by CTCF-CTCF homodimer with point-to-point interactions between loci [46]. The well-appreciated example of ACH is that the long-range cis-regulatory elements of *hemoglobin subunit beta* (*HBB*) interact strongly and facilitate transcription by forming the chromatin loops in erythroid cells [48]. The loops that are not spanned by CTCFs are called ordinary domains [41]. The formation of chromatin loops is regulated by the loop extrusion process [49]. In this process, the cohesin complex binds to a chromatin fiber and reels it to form the loops [50]. With the increasing density of loops, more advanced structures like TADs are formed.

**TADs (100-500 nm):** TAD is a chromatin region formed by bunches of topologically adjacent and preferentially interacting chromatin loops and ordinary domains [51]. TADs are separated by boundaries that are formed by CTCFs and cohesins [42]. Inside of a specific TAD or between similar TADs, chromatin loops interact with each other more frequently than sequences in the adjacent non-TAD regions [39, 42]. TADs were first identified as sub-chromosomal domains in the 1980s, and validated by Hi-C-seq, appearing as individual triangles on the heatmap [40, 52]. They can be further subdivided into smaller ones called subTADs when increasing the resolution [53].

**Chromosome compartments (500-1000 nm):** The chromosome is mainly compartmented by TADs [39]. It can be defined as A (euchromatic) or B (heterochromatic) by the principal component analysis of Hi-C-seq [54]. A is in a transcriptionally active state, while B is in a repressed state. Chromosome compartments can switch between each other in a cell-type-specific manner [55].

**Chromosome territories (1000-2000 nm):** Chromosome territory is the discrete space each chromosome occupies in the nucleus [56].

Recently, a new technique named targeted chromatin capture (T2C) combining a simulation method [57, 58] proposed a new model of chromosome architectural hierarchy that the

chromatin quasi-fibers (in a length of 80-120 nm) fold into stable chromatin loops and cluster into aggregate/rosette-like sub-chromosomal domains [52, 57, 59].

### 2.2. Organizing chromosome architecture by nuclear actin

Accumulating evidence suggests that nuclear actin plays a vital role in organizing chromosome architecture. For example, knock-out (KO) of the *Actb* gene encoding mouse β-actin upregulates the intensity of heterochromatin in the nuclear interior [60]. In humans, a higher proportion of heterochromatin was observed at the mitotic exit when nuclear F-actin polymerization was inhibited [61]. Furthermore, the impaired nuclear F-actin increases the degree but reduces the dynamics of chromatin compaction in the postmitotic nucleus, whereas the enhanced nuclear F-actin does reversely [61, 62]. The underlying mechanisms of how nuclear actin modulates chromosome architecture are described below.

**Actin and nuclear lamina:** Nuclear lamina affects chromosome architecture [46, 63]. Heterochromatin binds to the nuclear lamina at the nuclear periphery to form the region called lamina-associated domains (LADs) [63], whereas euchromatin loops out into the nucleus interior. When cells differentiate, constitutive LADs remain attached to the lamina, whereas facultative LADs become detached, and the genes they contain become actively transcribed. After mitosis, LADs relocate to the nuclear periphery. It was reported that the perturbation of perinuclear actin can deform the nuclear lamina integrity and consequently alter the heterochromatin localization and enhance chromatin condensation [64, 65]. This deformation may be via the linker of nucleoskeleton and cytoskeleton (LINC) complex, which couples the cytoplasmic actin with the nuclear lamina, and does the mechanotransduction [66]. Though the interactions between nuclear actin and nuclear lamina have not been elucidated, the chromosome architecture might likely be organized by nuclear actin via nuclear lamina based on the close connection between cytoplasmic and nuclear actin.

**Nuclear actin and chromatin remodeling** (for nuclear actin-related chromatin remodeling, see next section)**:** The Hi-C-seq and assay for transposase-accessible chromatin sequencing (ATAC-seq) of mouse embryonic fibroblasts showed that the deficiency of the BAF chromatin remodeling complexes induced by *Actb* KO is related to the transitions of chromosome compartments [67]. CTCF binds to the BRK (brm and kis proteins from fly) domain of SMARCA4, the core subunit of BAF complexes [68-70]. The cohesin occupancy at enhancers is also severely perturbed upon SMARCA4 depletion [71, 72]. Therefore, it is plausible that nuclear actin-related chromatin remodeling complexes might stabilize the chromosome compartments by CTCF or cohesin.

### 2.3. Chromosome architecture and cancers

Accumulating evidence demonstrates that distinct chromosome architecture is associated with cancer [73-82]. The computational model shows that chromosome architecture shapes the landscape of somatic copy-number alterations in cancer [76]. The chromosome decompaction caused by the loss of linker histone H1 leads to the activations of cell stemness-related genes and enhances lymphoma growth [80]. The dynamic changes of chromosome compartments caused by estrogen stimulation create active open chromatins enriched with cancer invasion signaling activities and promote estrogen receptor (ER)-positive breast cancer [82]. Interestingly, large-scale sequencing identified a new chromosome compartment restraining the malignant progression of colorectal cancers [77].

## 3. Nuclear Actin and Chromatin Remodeling

In the transcriptionally repressed state, DNA is inaccessible as a packaged nucleosome array. Chromatin accessibility refers to the degree to which chromatin-binding factors, such as TFs, RNA

polymerase II, or architectural proteins (CTCF and cohesin), physically bind to the open chromatin to initiate the transcription [83]. Chromatin remodeling complexes modulate chromatin accessibility by sliding, inserting, or ejecting the nucleosomal core with the energy of ATP hydrolysis [84]. There are four chromatin remodeling families in mammals (Table 4): the BAF family (canonical BAF complex [cBAF], polybromo-associated BAF complex [pBAF], and non-canonical BAF complex [ncBAF]), the CHD family (CHD1-2 complexes as subfamily I, CHD3-5 complexes as subfamily II, and CHD6-9 complexes as subfamily III), the INO80 family (INO80, SRCAP, and TRRAP complexes), and the ISWI family (ACF, CHRAC, NoRC, NURF, RSF, and WICH complexes) [85-89]. Among those chromatin remodeling families, BAF and INO80 families contain both ACTB and ARPs (ACTL6A, ACTL6B, ACTR5, ACTR6, and ACTR8) as core components [90-92].

This section focuses on the roles of nuclear actin and ARPs in modulating the BAF and INO80 chromatin remodeling families in cancer.

### 3.1. Nuclear actin in the chromatin remodeling complexes

In yeast, the subdomains 1-2 and 3-4 of Act1 (yeast homolog of actin) are twisted 6° by the interaction with both Arp4 (yeast homolog of ACTL6A) and the helicase-SANT-associated (HSA) domain of Snf2 (yeast homolog of SMARCA4) [93]. This spatial twist hinders the cleft of Act1 from binding with latrunculin, an actin polymerization inhibiting toxin, and masks the (+) end of Act1 to prevent the actin polymerization [93, 94]. The Act1 is also observed unable to bind with profilin, which might be due to its embedding into the Baf complex [93]. In contrast, these findings were not observed in the mammalian BAF complex, which needs further investigation [95]. In the yeast Ino80 complex, the (+) end of Act1 is also masked, making it unable to interact with profilin, while the subdomain 2 of Act1 is still accessible to DNase I [96].

### 3.2. Nuclear actin and cBAF complex

The human cBAF complex consists of three modules (Figure 3A): ATPase, ARP, and base modules (Figure 2) [88, 91]. The residues at 521-1647 amino acids (AAs) of SMARCA4 form the ATPase module, which grabs the nucleosome. The HSA domain (residues at 446-520 AAs) of SMARCA4 binds to the heterodimer constructed by ACTB and ACTL6A to form the ARP module, which maintains the rigid structure of HSA to couple the motions of the ATPase and base modules during chromatin remodeling. The pre-HSA region (residues at 350-445 AAs) of SMARCA4 is anchored into the base module, in which the SMARCB1 packs against the bottom of the nucleosome.

When the nucleosome is recruited, the cBAF complex sandwiches it to provide a structural basis for chromatin remodeling [91]. Upon ATP hydrolysis, the ATPase module is positioned to engage with the nucleosome and translocate DNA. The DNA translocation creates DNA tensions to eject nucleosomes or peels the DNA off from the adjacent nucleosomes, which creates nucleosome-depleted regions for chromatin-binding factors to access and bind.

In mice, the genetic deletion of the subdomain of *Actl6b*, an ARP component of neuron-specific BAF complex, induces impairments of phosphorylation of synaptic cofilin, memory, and synaptic potentiation [97]. These neurological impairments are rescued by restoring the nuclear actin dynamics using a phosphomimetic mutant of cofilin, an ABP accelerating actin depolymerization [97]. This study demonstrates the functional interaction between nuclear actin dynamics and the BAF complex.

### 3.3. BAF family and cancers

The genes encoding the subunits of the BAF family are highly mutated in many human cancers [98]. In animal models, the loss-of-function of subunits contributes to *in vivo* tumorigenesis, implying the overall roles of the BAF complex as tumor suppressors. For instance, the genetic mutations (loss-of-function) in the *SMARCC1* gene are frequently observed in colon and ovarian

cancer [99]. The truncated mutations of the *SMARCE1* gene are enriched in clear cell meningioma [100]. The mutation at the splicing site of the *BCL7A* gene interferes with its binding to the BAF complex in the diffuse large B-cell lymphoma [101]. In lung adenocarcinoma, the loss of *SMARCA4* promotes the malignant transformation of the CCSP (club cell secretory protein)-positive cells with early metastasis [102]. As a cBAF-specific subunit, *ARID1A* loss initiates transdifferentiation from ER-dependent luminal cells to ER-independent basal-like cells in breast cancer. This cellular plasticity is mediated by the reconfigured BAF complex activating the luminal lineage-determining TFs, including ESR1, FOXA1, and GATA3 [103]. As a pBAF-specific subunit, *PBRM1* loss reduces the binding of SMARCA4 to the *IFNGR2* promoter, decreasing the expression of downstream target genes and enhancing the resistance to immune checkpoint blockade in renal cancer [104].

In contrast, some subunits of the BAF complexes appear to play oncogenic roles. For example, the *ACTL6A* gene is amplified, and its encoded protein interacts with TP53 to promote cell proliferation and cancer cell stemness in head and neck squamous cell carcinoma [105]. As a ncBAF-specific subunit, BRD9 induces the binding of the ncBAF complex to the enhancers of the cancer-related gene, *STAT5A*, promoting leukemia cell survival [106]. Recently, protein structure-based assessment of the SMARCA4 showed the different impacts of various mutations in the *SMARCA4* gene on the chromatin remodeling activity [107-111]. In addition to the genetic alterations in the BAF complexes, the direct impacts of nuclear actin dynamics on the chromatin remodeling complex need further investigation.

### 3.4. Nuclear actin and INO80 complex

The human INO80 complex is constructed on the frame of INO80 (Figure 3B) [90, 112]. The N-terminus domain (residues at 1-267 AAs) of INO80 recruits metazoan-specific subunits, including INO80D, INO80E, MCRS1, NFRKB, TFPT, and UCHL5 [113]. The HSA domain (residues at 273-404 AAs) of INO80 directly binds with ACTR8 followed by ACTB, ACTL6A, YY1, and YY1AP1 to form the subcomplex 1 [114, 115]. The residues at 487-1556 AAs of INO80 contact RUVBL1-RUVBL2 hexamer to form the subcomplex 2, which serves as an ATPase. The architecture of subcomplex 2 is relatively rigid because the wheel-like insert domain (residues at 835-1083 AAs) of INO80 is inserted into the barrel-like RUVBL1-RUVBL2 hexamer to restrain its conformation. The subcomplex 2 accommodates a tail-like structure constructed by ACTR5, INO80B, and INO80C to form the subcomplex 2 plus.

When the nucleosome is recruited, the ATPase of the INO80 complex grabs the nucleosome against the ACTR5-INO80C heterodimer to provide a structural basis for chromatin remodeling [90]. Upon ATP hydrolysis, the ATPase pumps DNA towards the nucleosome dyad, unwrapping DNA from the nucleosome surface. When the ACTR5-INO80C heterodimer slips, the DNA wrap is pushed forward and slides across the nucleosome surface, releasing open DNA. In yeast, the requirement of Arp5-Ies6 (yeast homologs of ACTR5-INO80C) heterodimer for chromatin remodeling activity was also observed[116].

The yeast Ino80 complex has two different nucleosome binding states switched by the subcomplex 1 (Act1-Arp4-Arp8 module) [117, 118]. In state I, Arp8 (yeast homolog of ACTR8) grabs the linker DNA of the nucleosome via its Insert 2A (residues at 301-390 AAs) domain [119-121]. In state II, Arp8 folds toward the Tip49A-Tip49B (yeast homologs of RUVBL1-RUVBL2) hexamer to wrap the exposed histone surface of the nucleosome and moves Act1 and Arp8 toward the nucleosome to build direct contacts. Furthermore, *act1-2* (an A58T substitution in *ACT1*) compromises the function of the yeast Ino80 complex, with a significant reduction of ATPase activity, nucleosome binding affinity, and chromatin remodeling activity [96].

Consequently, the gene transcription can also be affected by the disruption of nuclear actin dynamics via the INO80 complex. Additionally, *ACTR5* KO-induced dysfunction of the INO80 complex impairs the opening of the cis-regulatory region of *heme oxygenase 1* (*HMOX1*),

resulting in a deficiency of transcriptional activator binding [122]. These studies suggest the crucial roles of nuclear actin and ARPs in INO80 complex-mediated gene regulation.

### 3.5. INO80 family and cancers

It has been well documented that the INO80 family regulates transcription, DNA replication, DNA repair and catalyzes the exchange of H2AZ1-H2B heterodimers with free H2A-H2B in biological processes [123]. In non-small cell lung cancer and melanoma, the INO80 complex is highly correlated with H3K4me1 and H3K27ac histone modifications and enhances the assembly of enhancers to activate the cancer-related genes [124-126]. ATAC-seq elucidates that this enhancer-mediated oncogenic transcription is due to the increased nucleosome occupancy configured by the INO80 complex [126]. During DNA replication in prostate cancer cells, the chromatin remodeling driven by the INO80 complex resolves the R-loop, a DNA-RNA hybrid structure for transcription, and reduces the R-loop-induced DNA damage in cancer cells [127].

The high expression of SRCAP is found in colon cancer [128]. In prostate cancer, *SRCAP* knockdown decreases the expression of prostate-specific antigen *KLK3* by reducing the binding of H2AZ1 to its enhancers [129].

TRRAP shields mutant TP53 protein against the degradation machinery via its HEAT repeat region (residues at 1050-1158 AAs) in lymphoma [130]. It also maintains the cell stemness derived from glioblastoma multiforme by transactivating the self-renewal-related gene, *Cyclin A2* (*CCNA2*). In contrast, its silencing decreases the tumorigenicity of cancer stem cells both *in vitro* and *in vivo* due to the reduction of H3 acetylation and H3K4me3 [131]. Similarly, *TRAAP* knockdown suppresses the expression of stemness-associated markers, including *NANOG*, *POU5F1*, and *SOX2* in ovarian cancer [132]. Once *TRRAP* or *KAT5*, a subunit of the TRRAP complex, is depleted, hepatocellular carcinoma cells become senescent and get arrested at the G2/M phase [133]. Interestingly, the report based on clinical samples and the survival data of breast cancer patients shows that lower expression of TRRAP is observed in tumors compared to normal tissues, and higher TRRAP expression indicates smaller tumor size with better overall survival [134].

Due to the potential oncogenic roles of the INO80 family in cancer, specific disruption of INO80-associated ARPs (ACTR5, ACTR6, or ACTR8) might be a plausible option for cancer prevention or treatment.

## 4. Nuclear Actin and Transcription Machinery

### 4.1. Nuclear actin and MRTFs

In 1984, Egly *et al.* found that nuclear actin stimulates RNA polymerase II-mediated transcription *in vitro* [135]. Similarly, Scheer *et al.* demonstrated the involvement of nuclear actin in modulating transcription in salamander oocytes [136]. Later, the vital role of nuclear actin in the initiation and elongation of transcription in eukaryotes was unveiled [137]. After these milestone studies on the potential role of nuclear actin in transcription, more researchers began to study the function of nuclear actin [135, 136]. To date, accumulating evidence suggests that in combination with TFs, ABPs, or transcription complexes, nuclear actin modulates gene expression from transcription initiation to transcription elongation [138].

Among the actin-mediated transcriptions, the regulation of myocardin-related transcription factor A (MRTFA) is one of the most well-demonstrated examples (Figure 4A) [139]. MRTFA is a transcription co-activator of serum response factor (SRF), which regulates the expression of muscle-specific, immediate-early, and cytoskeletal genes in response to changes in G-actin levels [140-142]. The N-terminus of MRTFA contains a domain with three RPEL (G-actin-binding sites) motifs that operate as a G-actin sensor, regulating both subcellular localization and nuclear activity of MRTFA [143-145]. G-actin can interact with the RPEL domains directly [146]. Within

the RPEL domain, a bipartite NLS is embedded, preventing the nuclear import of the pentameric actin complex [147, 148]. In unstimulated conditions, when G-actin levels are relatively high, MRTFA is predominantly localized in the cytoplasm due to efficient actin-dependent and exportin 1 (XPO1)-mediated nuclear export of MRTFA. This is because G-actin binding occludes the bipartite NLS in the RPEL domain [143, 148, 149]. However, upon serum stimulation that activates transient nuclear actin polymerization, G-actin is transformed into F-actin, which results in the release and nuclear accumulation of MRTFA by increased nuclear import, and decreased XPO1-dependent nuclear export, followed by the subsequent activation of SRF target gene transcription [21, 62, 150].

Additionally, nuclear actin polymerization and MRTFA/SRF-mediated transcription are also regulated by other factors, including F-actin-monooxygenase MICAL2 [151], cyclic-AMP(cAMP) signaling [152], and Ras association domain-containing protein 1 isoform A (RASSF1A) [153]. MICAL2 regulates nuclear actin through redox modification that decreases G-actin levels inside the nucleus. This, in turn, increases MRTFA accumulation in the nucleus and MRTFA/SRF-dependent gene transcription [151]. Recently, McNeill *et al.* showed that elevated c-AMP increases nuclear G-actin levels in vascular smooth muscle cells, suppressing cell proliferation and migration by inhibiting MRTFA/SRF and YAP/TAZ-TEAD-dependent gene expression [152]. RASSF1A is a tumor suppressor frequently epigenetically suppressed in tumors and forms a complex with XPO6 and RAN GTPase, promoting the XPO6-mediated nuclear export of actin, thus regulating transcription via MRTFA/SRF [153]. Interestingly, this pathway is deregulated in cancer cells, which leads to the accumulation of nuclear G-actin and suppression of MRTFA/SRF-mediated transcription [153]. Besides, there is another MRTF named MRTFB which can also stimulate SRF-dependent transcription. In contrast to MRTFA, MRTFB has a different tissue distribution and relatively weak affinities with SRF [154]. Kuwahara *et al.* found that in NIH3T3 cells, MRTFB also undergoes nuclear translocation react to Rho signaling and nuclear actin polymerization, even though it is slightly less responsive than MRTFA upon serum stimulation [155]. In human aortic endothelial cells, Hayashi *et al.* showed that the nuclear localization of MRTFA and MRTFB is affected by actin dynamics involved in gene expression [156].

Together, MRTF/SRF transcriptional activity is regulated by signal-induced nuclear actin polymerization and depolymerization cycle and G-actin binding to the RPEL domain of MRTFA [21, 157, 158]. It is noteworthy that many cytoskeletal genes, including actin, are also regulated by MRTF/SRF, suggesting that the actin-MRTF-SRF signaling axis forms a feedback loop where actin dynamics regulates the transcriptional homeostasis of the cytoskeleton [158, 159].

### 4.2. Nuclear actin and RNA polymerases

In the eukaryotes, RNA polymerases (Pols) I, II, and III catalyze DNA-dependent RNA synthesis [160]. Pol I synthesizes ribosomal RNA (rRNA), and Pol II and Pol III synthesize mainly mRNA and tRNAs, respectively [160]. Several studies showed that nuclear actin directly binds to all three RNA Pols (Figure 4B) [161-164]. Later, the impacts of nuclear actin-associated RNA Pols on gene regulation were unveiled.

**RNA Pol I:** As a molecular motor, nuclear F-actin interacts with the RNA Pol I complex together with nuclear myosin I (NM1) and is involved in the transcription of ribosomal RNA genes (rDNA) [165, 166]. Philimonenko *et al.* found that nuclear actin and NM1 are associated with rDNA, and microinjection of antibodies against actin or NM1 into the nuclei of cells decreased the Pol I-mediated transcription *in vivo* and *in vitro* [167]. Ye *et al.*'s study showed that drugs inhibiting actin polymerization or myosin function blocked Pol I-driven transcription *in vivo* and *in vitro* [168]. Meanwhile, actin mutants (S14C, G15S, and V159N) stabilizing F-actin tightly bind to Pol I and activate transcription [168, 169]. Conversely, a polymerization-deficient actin mutant does not interact with Pol I and fails to activate transcription [168]. Moreover, the association of nuclear actin and NM1 with Pol I is interrupted when ATP exists but is stabilized by ADP, and by anchoring

NM1 to DNA and nuclear F-actin to RNA polymerase, the nuclear actomyosin complex serves as a motor that works with nuclear RNA polymerases to activate transcription [170, 171]. These studies suggest the crucial role of nuclear actin polymerization in Pol I-mediated transcription [168].

**RNA Pol II:** In 1984, Scheer *et al.* showed that injection of actin antibodies into the nuclei of salamander oocytes inhibited the transcription [172]. Hofmann *et al.* found that actin is associated with actively transcribed genes and plays a pivotal role in the activation of transcription [161]. Later, *in vivo* and *in vitro* studies have recapitulated the requirement for actin in RNA Pol-mediated transcription activation, initiation, and elongation [159]. In 2019, to determine the nuclear actin interactome, Viita *et al.* employed two mass spectrometry (MS)-based techniques, affinity purification (AP)-MS and biotin identification (BioID)-MS [173]. The MS data identified nuclear actin as a component of the RNA Pol II pre-initiation complex [173]. Sokolova *et al.* performed chromatin immunoprecipitation sequencing (ChIP-seq) and genome-wide analysis in fly ovaries. For the first time, they showed that nuclear actin in physical conjunction with Pol II co-occupies the promoters associated with gene bodies of actively transcribed genes [174]. Furthermore, by using immunoprecipitation, immunofluorescence, and glutathione S-transferase (GST) pull-down assay, Qi *et al.* and Hu *et al.* showed that nuclear actin directly interacts with Pol II subunits POLR2E and POLR2G, as well as Pol III subunits POLR3C, POLR2F, and POLR2H [175, 176]. During the initiation and elongation of transcription, cyclin-dependent kinase 9 (CDK9), a subunit of positive transcription elongation factor b (P-TEFb) and RNA helicase A (RHA) are associated with G-actin in the nucleus, which physically links nuclear actin with Pol II [176, 177].

**RNA Pol III:** Utilizing protein purification of Pol III from human IMR90 cells expressing a double-tagged Pol III subunit, Hu *et al.* observed that actin is co-purified with Pol III [175]. They showed that actin is stably associated with one or more of the POLR3C, POLR2F, and POLR2H subunits of Pol III via direct interaction, required for Pol III-mediated transcription in vitro [175]. Moreover, ChIP experiments showed that actin occupies the promoter of the U6 gene actively transcribed by Pol III [178, 179]. Additionally, the treatment of cells with methane methylsulfonate, an inhibitor of Pol III, released the transcription initiation complex from the U6 promoter and uncoupled the actin protein from the Pol III complex [178, 180]. Moreover, it was shown that the monomeric form of actin is essential for Pol III-driven transcription [181].

In addition to nuclear actin, the actin polymerization and depolymerization regulators were shown to be engaged in RNA Pols. For instance, the ARP2/3 complex and its activators N-WASP (neural Wiskott-Aldrich syndrome protein), WASF1 (WASP family member 1), WASH (WASP family homolog), and motor protein myosin are associated with nuclear RNA Pols and transcription processes [182-185]. Recently, using next-generation transcriptome sequencing and super-resolution microscopy, Wei *et al.* showed that the formation of RNA Pol II complex is facilitated by the N-WASP/ARP2/3-dependent polymerization of nuclear actin filaments [186]. Together, these lines of evidence suggest that nuclear actin and its regulatory proteins are physically and functionally associated with RNA polymerases-controlled transcriptional activation, initiation, and elongation.

### 4.3. Nuclear actin and pre-mRNA splicing

Actin was also detected in pre-messenger ribonucleoprotein (pre-mRNP) [187], implying the potential roles of nuclear actin in pre-mRNA processing (Figure 4C) [188, 189]. In 2019, the mass spectrometry-based nuclear actin interactome approaches not only revealed the association of actin with pre-initiation complex (PIC), transcription elongation but also pre-mRNA splicing and processing [173]. Viita *et al.* found that alterations in nuclear actin levels disturb alternative splicing of reporter gene constructs, suggesting that nuclear actin affects pre-mRNA splicing directly or indirectly, likely by affecting the transcription elongation rate [173]. Another study combining bioinformatics with protein binding analysis showed that nuclear actin interacts with the unique region of the pre-mRNA of the Epstein-Barr virus (EBV) latent membrane protein 2

(LMP2) [190]. Treatment of EBV-positive cells with drugs inhibiting actin polymerization showed a significant decrease of spliced isoform levels of the pre-mRNA, indicating the role of nuclear actin in modulating viral RNA splicing [190].

### 4.4. Other mechanisms

**Ribonucleoproteins:** Besides the roles of nuclear actin in regulating transcriptional activation and mRNA splicing, nuclear actin is engaged in RNA processing and transportation [191]. Nuclear actin is also associated with small nuclear ribonucleoproteins (snRNPs) modulating mRNA processing and viral RNA nuclear export [191-193]. Moreover, nuclear actin binds to heterogeneous nuclear ribonucleoprotein (hnRNP) protein hrp65-2 in the Chironomus tentans cells and hnRNP U protein in the mammalian cells [189, 194, 195]. Sjölinder *et al.* showed that growing pre-mRNA recruits actin, hnRNP proteins, and chromatin remodeling complexes to actively transcribed genes for ongoing transcription [196].

**Wnt signaling:** Wnt signaling is a highly conserved pathway orchestrating various cellular processes and is hyperactivated in many human cancers [197-199]. Recent studies suggested that nuclear actin modulates Wnt signaling-mediated transcription via direct interaction with Wnt signaling-related components, including β-catenin, CRACD, and APC (adenomatous polyposis coli) (Figure 4D) [10, 200-202]. In 2016, Yamazaki *et al.* found that nuclear F-actin colocalizes with β-catenin, increases the nuclear accumulation of β-catenin, and enhances the transcriptional β-catenin downstream targeting genes of the Wnt/β-catenin signaling pathway [202]. Jung *et al.* identified CRACD as a regulator stabilizing the cadherin-catenin-actin complex via capping protein inhibition in the nucleus. The frequent inactivation of CRACD in colorectal cancer inhibits actin polymerization, resulting in G-actin release and accumulation in the nucleus with Wnt signaling hyperactivation mucinous colorectal cancer *in vivo* [10].

As a protein destruction complex, APC binds to and induces the degradation of β-catenin [203, 204]. The *APC* gene is highly mutated in colorectal cancer, resulting in the hyperactivation of Wnt/β-catenin signaling [205]. In addition to the cytoplasmic APC, APC contains the NLS and is also located in the nucleus [206, 207]. In conjunction with an actin-nucleating protein, formin mDia1, the C-terminus 'basic' domain of APC protein nucleates the formation of actin filaments and stimulates actin filament assembly [201]. Baarlink *et al.* found that the mDia1 triggers the nuclear actin polymerization in response to serum stimulation [208]. Therefore, nuclear APC likely regulates nuclear actin dynamics via actin nucleation.

Emerging evidence demonstrated that nuclear actin and ABPs are physically and functionally associated with various proteins related to gene expression [159]. Given the distinct feature of nuclear actin in cancer cells, the impacts of deregulated nuclear actin dynamics on aberrant gene expression in tumorigenesis need further interrogation.

## 5. Nuclear Actin and DNA Repair

In the mid-1930s, Timoféeff-Ressovsky *et al.* found that ionizing and ultraviolet (UV) radiation induces DNA damage [209]. At the end of the 1940s, Kelner and Dulbecco *et al.* discovered the DNA repair mechanism in cells and bacteriophages using UV radiation [210, 211]. Genotoxic stress induces DNA damage, which includes disruption or addition to the nucleotide of the DNA or the breakage of one chain of the DNA or DNA double-strand break (DSB) [212, 213]. Unresolved DNA damage results in a variety of human disorders and cancers [214, 215].

### 5.1. DSB repair

DNA damage response includes repair and tolerance [213]. However, severe DNA damage such as DSBs should be repaired to avoid cell death [216]. DSBs may lead to chromosomal rearrangements, including deletion, translocation, and amplification, which can trigger the

activation of oncogenes or the inactivation of tumor suppressors for tumorigenesis [215]. There are two major DSB repair mechanisms: non-homologous end joining (NHEJ) and homologous recombination (HR) (Figure 4E, F) [213]. NHEJ takes place in both dividing and non-dividing cells, whereas HR occurs only mainly in dividing cells during the late S-G2 phase because HR utilizes a homologous sister chromatid as a template [217, 218].

NHEJ is a fast and predominant DSB repair mechanism in mammalian cells [219]. NHEJ often results in the loss of genetic information at the site of the DSB [219]. At the beginning of NHEJ, the Ku (Ku70/Ku80) heterodimer recognizes and binds to the two DSB DNA ends directly, followed by recruitment of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) [220, 221]. Then, the two DNA-PKcs positioned at each DSB terminus align the two DNA ends together, activating processing factors such as Artemis, which generates overhangs at the DNA ends [222]. Finally, DNA polymerases fill in the gaps, followed by end-joining via X-ray repair cross complementing 4 (XRCC4)-DNA Ligase IV complex in collaboration with non-homologous end-joining factor 1 (NHEJ1) [223-225].

HR uses the sister chromatid as a template to repair DSB, which leads to a high-fidelity repair of DSBs [226]. HR mainly occurs in the late S-G2 phase and includes ssDNA overhang generation, strand invasion, homologous pairing, Holliday junction formation, DNA synthesis, branch migration, and Holliday junction resolution [227]. The key step of HR is initiated by recognition of the DSB by the MRN (MRE11-RAD50-NBS1) complex [228]. As a break sensor, the MRN complex is associated with DNA endonuclease RB-binding protein 8 (RBBP8) and recruits the serine-protein kinase ataxia telangiectasia mutated (ATM) to DSB sites, which result in the generation of 5′-3′ end resection and the 3′ ssDNA overhang [229-232]. Then, the ssDNA overhang is stabilized by replication protein A (RPA) binding, DNA repair protein 51 (RAD51) is loaded onto the ssDNA overhang [233]. Next, RAD52 is recruited to RPA, and the RAD52-RPA complex is replaced by the RAD51-BRCA2 complex [233, 234]. Then, RAD51-coated ssDNA promotes invasion of the template strand, which generates a Holliday junction [235]. Later, the DNA strand is synthesized by a polymerase using the sister strand as a template, followed by branch migration and subsequent resolution of the heteroduplex [236, 237]. Finally, the two broken DNA ends are rejoined by a DNA ligase [238].

### 5.2. Nuclear actin-mediated repair of DSBs

In the past decades, there has been increasing evidence showing the vital role of nuclear actin in the DSB repair process [159]. In 2012, Andrin *et al.* performed the pull-down assay with purified F-actin protein and found that F-actin binds to DSB repair proteins including Ku80, MRE11, and RAD51 *in vitro*, suggesting that actin polymerization may be engaged in DSB repair [239]. Later, utilizing actin probes, Belin *et al.* found that DNA damage induces the generation of long nuclear actin filaments, short nucleolus-associated filaments, and dense nuclear actin clusters in living cells [240]. In 2018, two independent studies demonstrated that nucleator ARP2/3 complex-mediated nuclear actin filament assembly is required for DSB repair in different cell lines [241, 242].

Nuclear F-actin participates in both NHEJ and HR repair pathways [239]. In the NHEJ pathway, depolymerization of endogenous nuclear actin alters the retention of Ku80 at DNA damage sites in human cells [239]. In the HR pathway, nuclear F-actin drives DSB dynamics in a somewhat different way between heterochromatin and euchromatin [243]. In fly and mouse cells, DSB detection and resection occur within the heterochromatin domain [244-246]. Firstly, the early DSB signaling, processing factor Mre11 and heterochromatin protein 1a (Hp1a) promote the recruitment of Arp2/3 and myosins to DSBs [241]. Secondly, Arp2/3 activation promotes actin polymerization and filament growth towards the nuclear periphery [247]. Thirdly, Smc5/6 blocks Rad51 recruitment and instead recruits Unc45 to activate nuclear myosins [247, 248]. Finally, the myosin-Smc5/6-chromatin repair complex travels along nuclear actin filaments and anchors DSBs to nuclear pores, where HR repair continues with Rad51 recruitment and strand invasion

[241, 242, 248]. In fly and mouse cells, nuclear F-actin is detected by the live-cell imaging with nuclear F-actin marker chromobody and F-actin staining with phalloidin [241]. The live-cell imaging shows that re-localization of heterochromatic DSBs occurs by directly moving along a nuclear actin filament network assembled at the repair sites by Arp2/3 and extension toward the nuclear periphery [241, 247]. In euchromatin, Mre11 and resection promote the movement of DSB repair sites via Arp2/3-induced short nuclear actin polymers, which also travel with euchromatic repair sites [241, 249]. In response to DSB in human cells, enriched ARP2/3 and nuclear actin polymerization at the DSB repair sites facilitate focus clustering, DSB resection, DSB movement, and HR completion without myosins [241, 242].

Genomic instability, one of the hallmarks of cancer, is mainly due to the impaired DNA repair pathway [250]. Therefore, cancer-actin dynamics affect genomic instability via nuclear actin-mediated DNA repair.

## 6. Concluding Remarks

Actin is the most abundant protein in the cells [1]. The canonical features of actin include cytoplasmic localization, GTPase activity, and highly dynamic transition between polymerization and depolymerization [1-3]. These properties led to the intense investigation of actin's roles in orchestrating the cytoskeleton, resulting in the seminal findings of actin cytoskeleton-mediated cell morphology, cell migration, and cell adhesion.

Evolved from these classical outlooks, accumulating evidence has unveiled that actin is also engaged in diverse nuclear processes. Beyond its roles as a structural protein composing the cytoskeleton, the nuclear actin is being highlighted in the context of chromosome architecture, chromatin remodeling complexes, transcription machinery, and DNA repair [27, 31-34, 67]. These actin-associated nuclear events were generally appreciated as the perspective of a similar mechanism of the cytosolic actin dynamics between polymerization and depolymerization. For instance, nuclear actin polymerization mechanically regulates chromosome architecture [67]. Additionally, the polymerized nuclear actin serves as a railroad facilitating the movement of DNA repair proteins [32]. Notwithstanding, it is noteworthy that monomeric and oligomeric nuclear actin also exists as a distinct structure, unlike the one in the cytoplasm. For example, monomeric nuclear actin in the chromatin remodeling complex displays a different structure from the cytoplasmic G-actin [93]. Besides such a conformational difference, the nuclear import and export of actin, ARPs, and their post-translational modifications may provide additional regulatory layers of nuclear actin dynamics [30]. Therefore, along with its role as a building block in the cytoplasm, both monomeric and oligomeric actin in the nucleus should be comprehensively appreciated as a critical component of various nuclear processes. Despite the current limitations in dissecting nuclear actin *in vivo*, the ongoing technical improvement in visualization and quantification is expected to unravel nuclear actin-associated biological events up-close.

The hallmarks of cancer include the loss of genomic/chromosomal integrity and aberrant gene expression, which are physically and functionally associated with nuclear actin. Thus, it is reasonable to assume that fine control of nuclear actin dynamics is a gatekeeper of tumorigenesis (Figure 5). Indeed, recent genome-wide studies showed that actin and actin regulatory proteins are genetically and epigenetically dysregulated in cancer [10, 105]. Therefore, further understanding of the pathophysiological impact of nuclear actin deregulation on chromosome architecture, chromatin remodeling complexes, transcription machinery, and DNA repair will lead to biomarker identification, therapy development, or biomarker-guided molecular targeting of cancer.

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**Tables**

| Gene symbol | Gene name | Expressing cells |
|---|---|---|
| ACTA1 | Actin alpha 1, skeletal muscle | Skeletal muscle cells |
| ACTA2 | Actin alpha 2, smooth muscle | Vascular smooth muscle cells |
| ACTB | Actin beta | Ubiquitous in non-muscle cells |
| ACTBL2 | Actin beta like 2 | Ubiquitous in non-muscle cells |
| ACTC1 | Actin alpha cardiac muscle 1 | Cardiac muscle cells |
| ACTG1 | Actin gamma 1 | Ubiquitous in non-muscle cells |
| ACTG2 | Actin gamma 2, smooth muscle | Enteric smooth muscle cells |

Table 1. Actin genes.

| Actin-nucleating proteins | Actin-binding proteins [6, 28] | Actin-related proteins [28, 251] | Capping proteins [7] | Capping protein regulators [8] |
|---|---|---|---|---|
| ARP2/3 complex [252] | Cofilin [253] | ACTL6A | ADD1 | CARMIL1 |
| Formin [254] | Gelsolin [255] | ACTL6B | ADD2 | CARMIL2 |
| Spire [256] | Profilin [257] | ACTL7A | CAPG | CARMIL3 |
| | Thymosin beta-4 [258] | ACTL7B | CAPZA1 | CD2AP |
| | | ACTL8 | CAPZA2 | CRACD [10] |
| | | ACTL9 | CAPZA3 | IQANK1 |
| | | ACTL10 | CAPZB | MTPN |
| | | ACTRT1 | | PLEKHO1 |
| | | ACTRT2 | | RCSD1 |
| | | ACTRT3 | | SH3KBP1 |
| | | ACTR1A | | WASHC2A |
| | | ACTR1B | | WASHC2C |
| | | ACTR2 | | |
| | | ACTR3 | | |
| | | ACTR3B | | |
| | | ACTR3C | | |
| | | ACTR5 | | |
| | | ACTR6 | | |
| | | ACTR8 | | |
| | | ACTR10 | | |

Table 2. Actin dynamics-related protein families.

| Probe | Description | Mechanisms | Pitfalls |
|---|---|---|---|
| Actin-chromobody [259] | A DNA plasmid encoding an anti-actin $V_HH$ nanobody fused to a fluorescent protein. | Fluorescent-labeled nanobody labels endogenous actin by antigen-antibody reaction. | High background when transient transfected into cells. Signal quenching after cell fixation. |
| Actin-GFP [260] | A DNA plasmid encoding human actin fused to GFP. | Ectopic expression of fluorescent-labeled actin into cells. | Interfere with the physiological actin dynamics. |
| F-tractin [261] | A DNA plasmid encoding N-terminus 10-52 AA peptides of rat inositol-trisphosphate 3-kinase (Itpk) [262]. | Itpk has a F-actin specifically binding domain at the N-terminus 1-66 AA region [263]. | Inhibit ABPs binding to F-actin. |
| Lifeact [264] | A DNA plasmid encoding N-terminus 1-17 AA peptides of yeast ABP140 [265]. | Lifeact binds to G-actin with an affinity 10-fold higher than F-actin. | Alter F-actin organization [266]. |
| Phalloidin [267] | Bicyclic heptapeptide from death cap mushroom. | Phalloidin specifically binds at the interface between subunits of F-actin, locking the F-actin structure and preventing depolymerization. | Prevent F-actin depolymerization. Cytotoxicity. |
| SiR-actin [268] | Silicon-rhodamine (SiR) conjugated to desbromo-desmethyl-jasplakinolide. | SiR is a fluorophore [269]. Jasplakinolide binds at the interface of G-actin oligomers at the nucleation phase [270, 271]. | Enhance F-actin polymerization. Cytotoxicity. |
| SPY-actin | Improved version of the SiR-actin by utilizing SPY dyes instead of SiR. | | |
| UtrCH [272] | A DNA plasmid encoding N-terminus 1-261 AA peptides of human utrophin. | The N-terminus of utrophin has calponin-homology (CH) domains, which specifically binds to F-actin [273]. | Alter F-actin organization. |

Table 3. Actin-detecting probes.

| BAF family | | | CHD family | | | INO80 family | | | ISWI family | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **cBAF** | **pBAF** | **ncBAF** | **Subfamily I (CHD1-2)** | **Subfamily II (CHD3-5)** | **Subfamily III (CHD6-9)** | **INO80** | **SRCAP** | **TRRAP** | **ACF** | **CHRAC** | **NoRC** | **NURF** | **RSF** | **WICH** |
| SMARCB1 | SMARCB1 | SMARCC1 | CHD1 | CDK2AP1 | ASH2L | ACTB | ACTB | ACTB | BAZ1A | BAZ1A | BAZ2A | BAP18 | RSF1 | BAZ1B |
| SMARCC1 | SMARCC1 | SMARCC2 | CHD2 | CHD3 | CHD6 | ACTL6A | ACTL6A | ACTL6A | SMARCA5 | CHRAC1 | SMARCA5 | BPTF | SMARCA5 | SMARCA5 |
| SMARCC2 | SMARCC2 | SMARCD1 | | CHD4 | CHD7 | ACTR5 | ACTR6 | ANP32E | | POLE3 | | HMGXB4 | | |
| SMARCD1 | SMARCD1 | SMARCD2 | | CHD5 | CHD8 | ACTR8 | DMAP1 | BRD8 | | SMARCA5 | | RBBP4 | | |
| SMARCD2 | SMARCD2 | SMARCD3 | | CSNK2A1 | CHD9 | INO80 | H2AZ1 | DMAP1 | | | | RBBP7 | | |
| SMARCD3 | SMARCD3 | BICRA | | GATAD2A | PARP1 | INO80B | H2B | EP400 | | | | SMARCA1 | | |
| SMARCE1 | SMARCE1 | BICRAL | | GATAD2B | RBBP5 | INO80C | RUVBL1 | EPC1 | | | | | | |
| ACTB | ACTB | ACTB | | HDAC1 | WDR5 | INO80D | RUVBL2 | EPC2 | | | | | | |
| ACTL6A | ACTL6A | ACTL6A | | HDAC2 | | INO80E | SRCAP | ING3 | | | | | | |
| ACTL6B | ACTL6B | ACTL6B | | MBD2 | | MCRS1 | VPS72 | KAT5 | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| BCL7A | BCL7A | BCL7A | MBD3 | NFRKB | YEATS4 | MEAF6 |
| BCL7B | BCL7B | BCL7B | MTA1 | RUVBL1 | ZNHIT1 | MORF4L1 |
| BCL7C | BCL7C | BCL7C | MTA2 | RUVBL2 | | MORF4L2 |
| SMARCA2 | SMARCA2 | SMARCA2 | MTA3 | TFPT | | MRGBP |
| SMARCA4 | SMARCA4 | SMARCA4 | RBBP4 | UCHL5 | | RUVBL1 |
| SS18 | BRD7 | SS18 | RBBP7 | YY1 | | RUVBL2 |
| SS18L1 | PBRM1 | SS18L1 | ZBTB7A | YY1AP1 | | TRRAP |
| ARID1A | ARID2 | BRD9 | | | | VPS72 |
| ARID1B | PHF10 | | | | | YEATS4 |
| DPF1 | | | | | | |
| DPF2 | | | | | | |
| DPF3 | | | | | | |

Table 4. Subunits of mammalian BAF, CHD, INO80 and ISWI chromatin remodeling complexes [85, 87-92, 112, 114, 115, 274-281].

## Figure Legends

**Figure 1. Cytoplasmic actin dynamics and nuclear actin visualization.**
(A) Structure of ACTA1 (PDB: 4PKG). (B) The process of actin polymerization with three phases: the nucleation phase, the elongation phase, and the steady phase. (C) The treadmilling of F-actin. The rates of G-actin assembly and disassembly depend on the concentrations of free ATP-G-actin on both ends. When the concentration of free ATP-G-actin is between 0.12 μM and 0.6 μM, the (+) end is elongated, and the (-) end is shortened, demonstrating the treadmilling of F-actin. (D) The regulation of actin turnover by actin-binding proteins (ABPs). In the cofilin cycle, cofilin binds to the (-) end of F-actin containing ADP-actin, inducing them to fragment and thus enhancing depolymerization. In the profilin cycle, profilin binds ADP-G-actin and catalyzes the exchange of ADP for ATP. The ATP-G-actin-profilin complex delivers actin to the (+) end with dissociation and recycling of profilin. (E) Live-cell imaging of nuclear actin by stably expressing actin-chromobody-GFP-NLS. The colon epithelial cell line (CCD841CoN) shows high levels of nuclear F-actin. Mucinous colorectal cancer cell line (LS174T) exhibits the reduced nuclear F-actin.

**Figure 2. The hierarchy of chromosome architecture.**
DNA chain (<10 nm) wraps around the histone octamer to form the nucleosome (10-30 nm). The beads-on-a-string arrays of nucleosomes coil into chromatin fibers (30 nm). The liner chromatin fibers loop out to form the chromatin loops (30-100 nm). Topologically adjacent and preferentially interacting chromatin loops construct into topologically associating domains (TADs) (100-500 nm). Topologically interacting TADs form the chromosome compartments (500-1000 nm). Chromosome territories (1000-2000 nm) are the discrete space for each chromosome in the nucleus.

**Figure 3. Human canonical BAF and INO80 chromatin remodeling complexes** [282]**.**
(A) Cryogenic electron microscopy (Cryo-EM) structure of human cBAF complex binding with the nucleosome (PDB: 6LTJ) [91]. (B) Cryo-EM structure of human INO80 complex binding with the nucleosome (PDB: 6HTS) [90].

**Figure 4. Nuclear actin functions in the nucleus.**
(A) G-actin inhibits the MRTFA/SRF-mediated transcription. Nuclear actin polymerization releases MRTFA from G-actin to activate SRF-mediated transcription upon serum stimulation. (B) Actin is involved in transcription. Actin and ABPs are associated with RNA polymerases I/II/III, and interacts with P-TEFb, snRNPs, and hnRNPs, regulating transcription initiation and elongation. (C) The association of nuclear actin with pre-mRNA splicing and processing. The molecular mechanism of actin-controlled pre-mRNA splicing is unclear. (D) Nuclear actin modulates Wnt signaling-mediated transcription via direct interaction with Wnt signaling-related components, including β-catenin, CRACD, and APC (not shown). (E, F) When double strand of DNA breaks in the nucleus, nuclear F-actin participates in the non-homologous end joining (NHEJ) and homologous recombination (HR) repair pathways.

**Figure 5. Nuclear actin, a gatekeeper of genomic integrity and gene expression.**
In normal cells, the well-balanced nuclear actin dynamics plays crucial roles in modulating chromosome architecture, chromatin remodeling complexes, transcriptional machinery, and DNA repair, which maintains genomic integrity and orchestrates gene expression for tissue homeostasis. Conversely, dysregulated actin dynamics impairs the fine control of chromosomal architecture, chromatin remodeling, transcriptional machinery, and DNA repair. Consequently, genomic instability, inactivation of tumor suppressor genes, and hyperactivation of oncogenes contribute to tumorigenesis.

# Figure 1

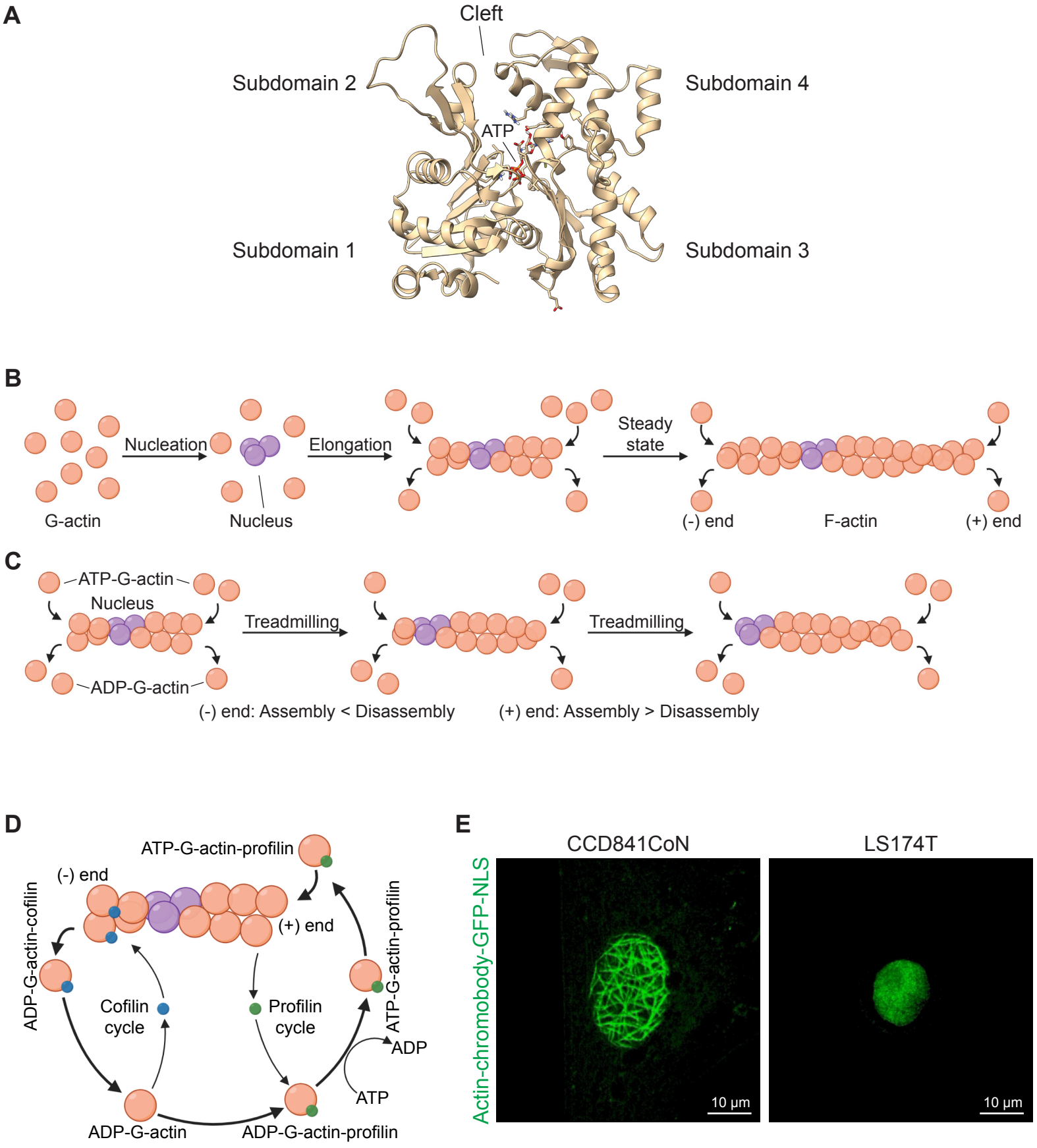

A
Cleft
Subdomain 2
Subdomain 4
ATP
Subdomain 1
Subdomain 3
B
Nucleation
Elongation
Steady state
G-actin
Nucleus
(-) end
F-actin
(+) end
C
ATP-G-actin
Nucleus
ADP-G-actin
Treadmilling
Treadmilling
(-) end: Assembly < Disassembly
(+) end: Assembly > Disassembly
D
ATP-G-actin-profilin
(-) end
(+) end
ADP-G-actin-cofilin
ATP-G-actin-profilin
Cofilin cycle
Profilin cycle
ADP
ATP
ADP-G-actin
ADP-G-actin-profilin
E
CCD841CoN
LS174T
Actin-chromobody-GFP-NLS
10 μm
10 μm

**Figure 2**

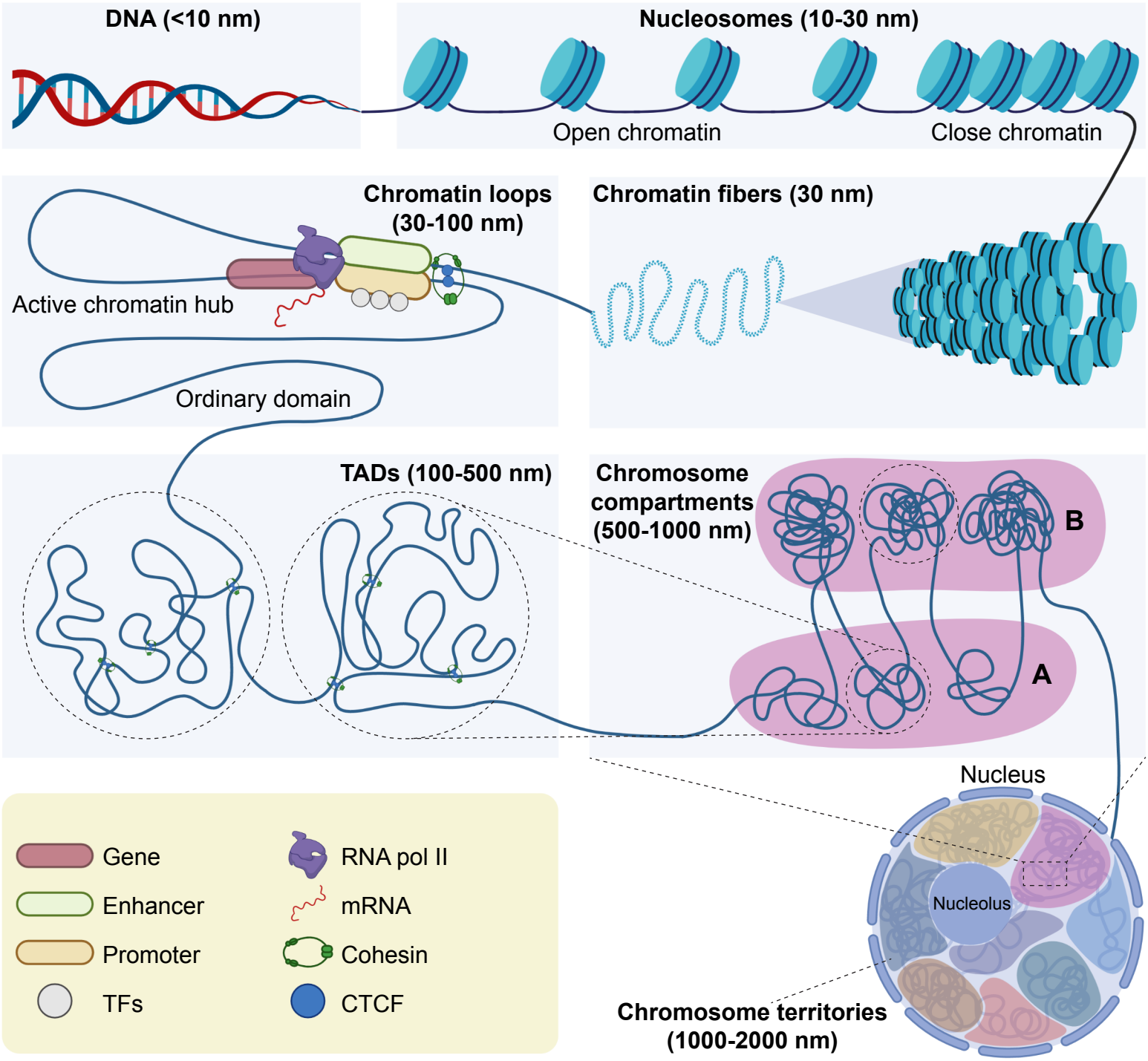

DNA (<10 nm)
Nucleosomes (10-30 nm)
Open chromatin
Close chromatin
Chromatin loops
(30-100 nm)
Active chromatin hub
Ordinary domain
Chromatin fibers (30 nm)
TADs (100-500 nm)
Chromosome
compartments
(500-1000 nm)
B
A
Nucleus
Nucleolus
Chromosome territories
(1000-2000 nm)
Gene
Enhancer
Promoter
TFs
RNA pol II
mRNA
Cohesin
CTCF

**Figure 3**

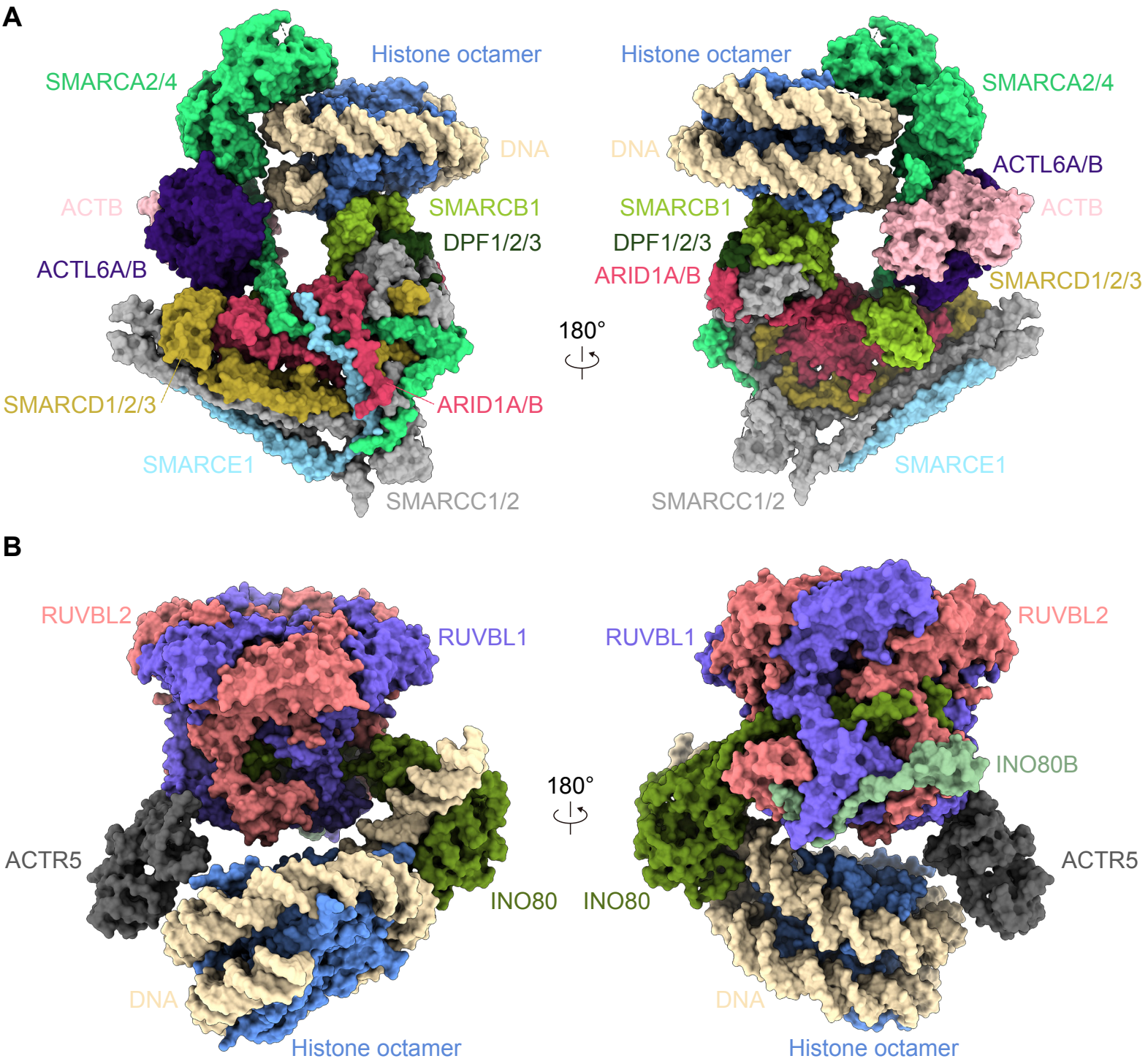

A
Histone octamer
SMARCA2/4
DNA
ACTB
SMARCB1
DPF1/2/3
ACTL6A/B
SMARCD1/2/3
ARID1A/B
SMARCE1
SMARCC1/2
180°
Histone octamer
SMARCA2/4
DNA
ACTL6A/B
SMARCB1
ACTB
DPF1/2/3
ARID1A/B
SMARCD1/2/3
SMARCE1
SMARCC1/2
B
RUVBL2
RUVBL1
ACTR5
INO80
DNA
Histone octamer
180°
RUVBL1
RUVBL2
INO80B
ACTR5
INO80
DNA
Histone octamer

**Figure 4**

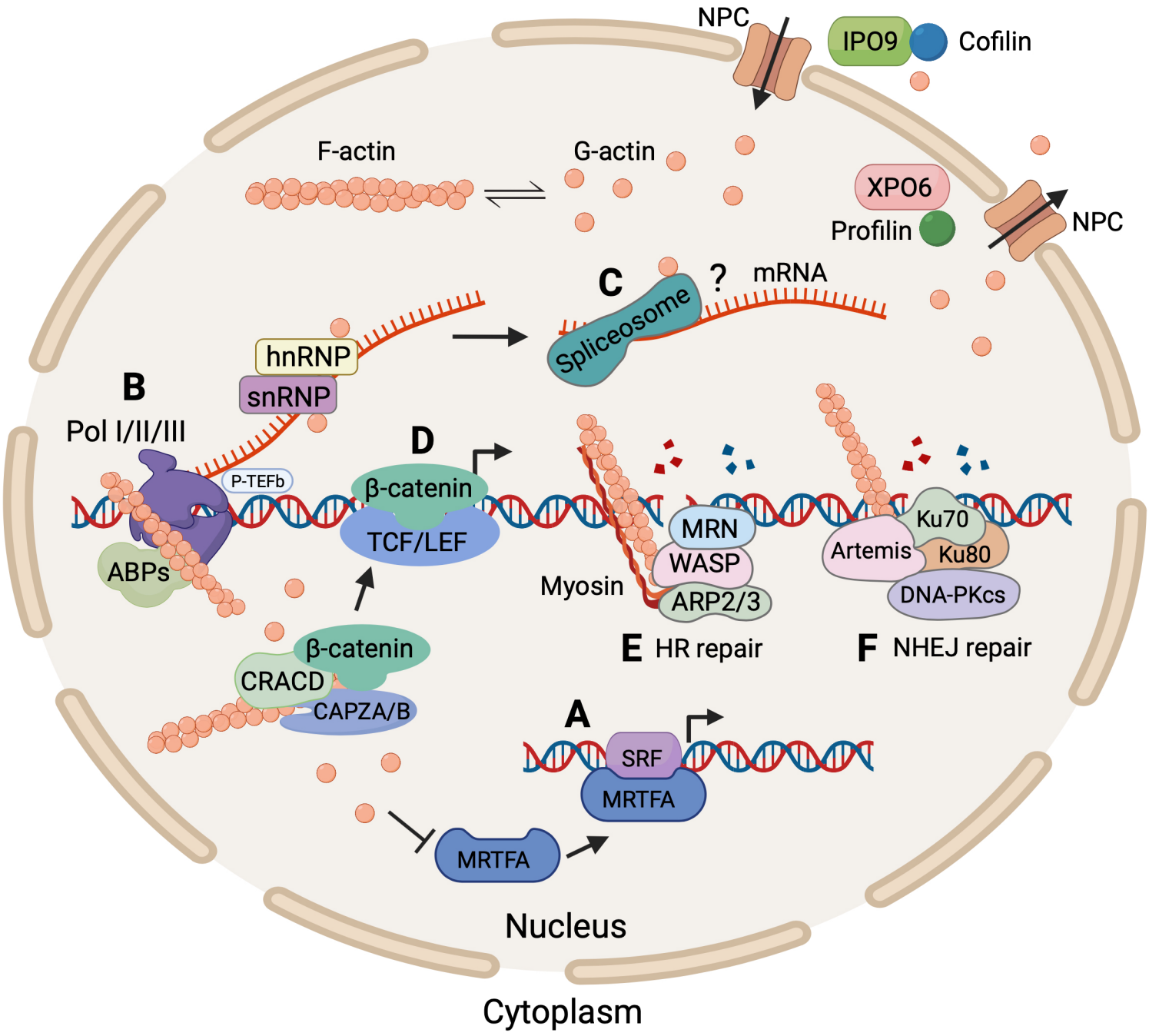
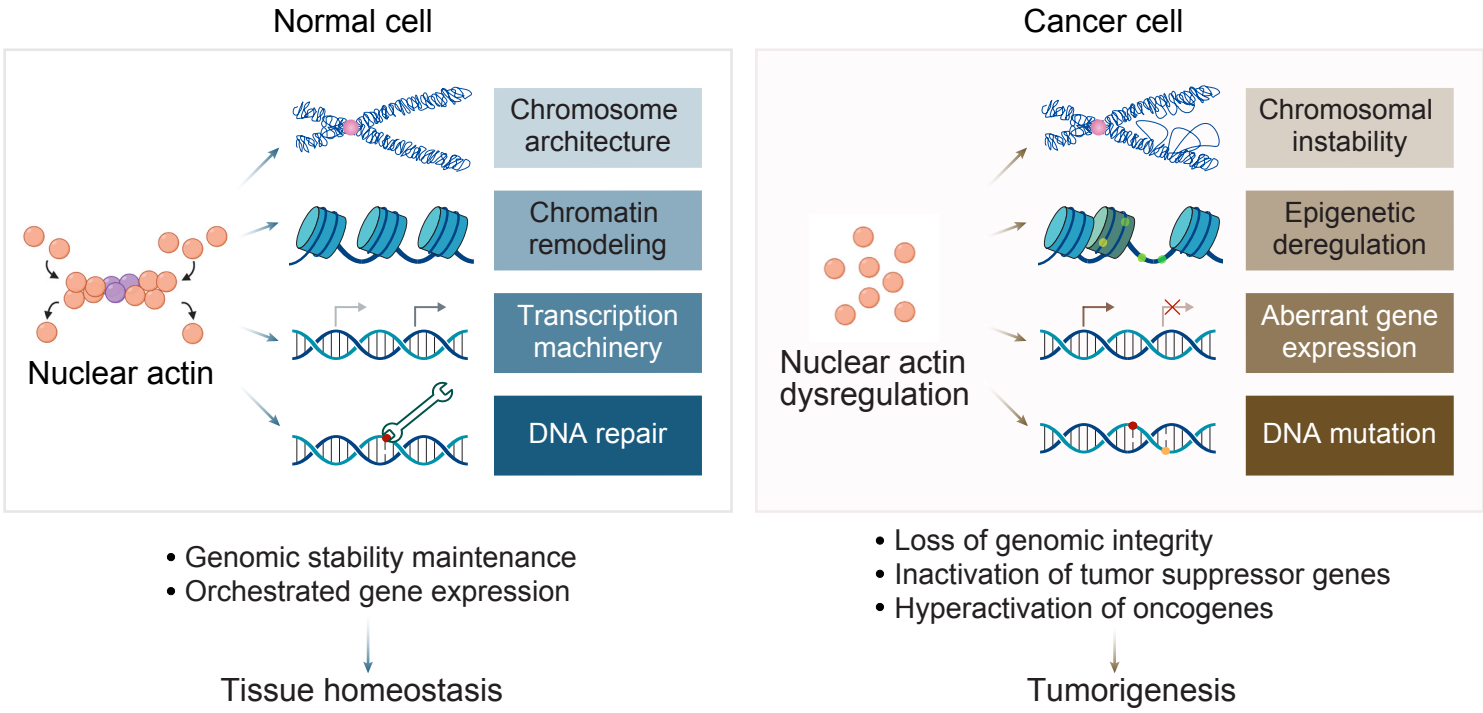

NPC
IPO9
Cofilin
F-actin
G-actin
XPO6
Profilin
NPC
C
?
mRNA
Spliceosome
hnRNP
snRNP
B
Pol I/II/III
P-TEFb
ABPs
D
β-catenin
TCF/LEF
β-catenin
CRACD
CAPZA/B
MRN
WASP
ARP2/3
Myosin
E HR repair
Ku70
Ku80
Artemis
DNA-PKcs
F NHEJ repair
A
SRF
MRTFA
MRTFA
Nucleus
Cytoplasm

**Figure 5**




- Genomic stability maintenance
- Orchestrated gene expression

Tissue homeostasis

- Loss of genomic integrity
- Inactivation of tumor suppressor genes
- Hyperactivation of oncogenes

Tumorigenesis