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Beyond Nucleosome Assembly - Chromatin Assembly Factor 1 as a Nexus of Genome Stability, Cell Identity and Cancer

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ABSTRACT

Chromatin assembly factor 1 (CAF-1) is an evolutionarily conserved histone chaperone complex that deposits newly synthesized histones H3-H4 onto nascent DNA. By coupling DNA synthesis to nucleosome assembly, CAF-1 restores chromatin after replication and repair, supports epigenetic inheritance, and helps maintain cellular identity. Its biological role, however, extends beyond chromatin packaging. Structural and functional studies now place CAF-1 at the intersection of replication-fork progression, replication-stress tolerance, DNA damage repair, translesion synthesis, R-loop control, lineage-specific transcription, and innate immune regulation. These functions are especially relevant in cancer, where rapid proliferation is accompanied by persistent replication stress, genome instability, and selection for epigenetic states that favor survival and plasticity.

Aberrant expression of the CAF-1 subunits CHAF1A and CHAF1B has been reported across solid and hematologic malignancies and is frequently associated with aggressive clinicopathologic features, treatment resistance, or poor outcome. Mechanistically, cancer cells may exploit CAF-1 to preserve fork fitness, facilitate DNA repair and lesion bypass, stabilize oncogenic chromatin states, restrict differentiation, and silence endogenous retroelements that would otherwise activate antiviral signaling. Recent studies linking CHAF1A to RAD51 loading, RAD18-dependent damage tolerance, and suppression of ERV-driven type I interferon responses illustrate how a canonical histone chaperone can influence both therapeutic resistance and tumor immunity. This review summarizes the molecular architecture and canonical functions of CAF-1, integrates emerging evidence across genome maintenance, cell identity, and cancer biology, and evaluates the opportunities and constraints involved in developing CAF-1 as a biomarker and therapeutic vulnerability.

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1. Introduction

Eukaryotic DNA is packaged into chromatin, whose repeating unit is the nucleosome. Approximately 147 base pairs of DNA wrap around an octamer containing two copies each of histones H2A, H2B, H3, and H4 [1, 2]. This organization enables compaction and regulation of the genome, but it also creates a fundamental problem during DNA replication. Parental nucleosomes must be disrupted ahead of the replication fork, while histones and nucleosomes must be rapidly reassembled behind it. Faithful chromosome duplication therefore requires coordinated replication of both the DNA sequence and the chromatin landscape.

Histone chaperones solve part of this problem by controlling histone folding, transport, storage, deposition, eviction, and recycling. They do not simply shield positively charged histones from nonspecific interactions; they also connect histone metabolism with DNA replication, transcription, repair, and chromatin remodeling [3-12]. Among these proteins, chromatin assembly factor 1 (CAF-1) is the principal replication-coupled H3-H4 deposition complex in mammalian cells. CAF-1 is recruited to newly synthesized DNA and works with proliferating cell nuclear antigen (PCNA), anti-silencing function 1 (ASF1), and other replication-associated factors to rebuild chromatin as DNA synthesis proceeds [5, 13].

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The traditional description of CAF-1 as a post-replicative packaging factor is useful but incomplete. CAF-1-dependent nucleosome assembly affects replication-fork dynamics, the handling of DNA lesions, the restoration of epigenetic information, and the accessibility of lineage-determining transcription factors. Depletion of CAF-1 can facilitate cell-fate conversion by increasing chromatin accessibility and weakening somatic heterochromatin, demonstrating that continuous nucleosome assembly contributes directly to maintenance of differentiated identity [14]. More recent evidence connects CAF-1 with PrimPol recruitment and post-replicative single-stranded DNA gaps, RAD51-dependent homologous recombination, KU70-associated non-homologous end joining, RAD18-dependent translesion synthesis, and suppression of R-loop-associated damage [15-18].

These functions converge in cancer. Malignant cells must duplicate their genomes rapidly despite oncogene-induced replication stress, transcription-replication conflicts, metabolic constraints, and genotoxic treatment. Efficient chromatin restoration can provide a fitness advantage by sustaining replication, limiting toxic DNA structures, and preserving transcriptional programs selected during tumor evolution. At the same time, CAF-1-mediated repression of repetitive elements can reduce tumor-intrinsic antiviral signaling and contribute to an immune-cold microenvironment. CAF-1 should therefore be considered a molecular node that links chromatin inheritance to several core cancer phenotypes rather than merely a marker of cell proliferation.

2. Molecular organization and chromatin inheritance

2.1 CAF-1 subunits, molecular partners, and structural basis of histone deposition

Human CAF-1 is a heterotrimer composed of CHAF1A (p150), CHAF1B (p60), and RBBP4 (p48). The three subunits act cooperatively, but each contributes a distinct set of molecular interactions. CHAF1A is the largest subunit and provides an organizational scaffold for binding DNA, histones, PCNA, and regulatory proteins. CHAF1B participates in histone handling and stabilizes assembly of the complex. RBBP4 is a WD40-repeat histone-binding protein that also occurs in other chromatin-regulatory complexes; its biological functions are therefore not restricted to CAF-1 [13, 19, 20].

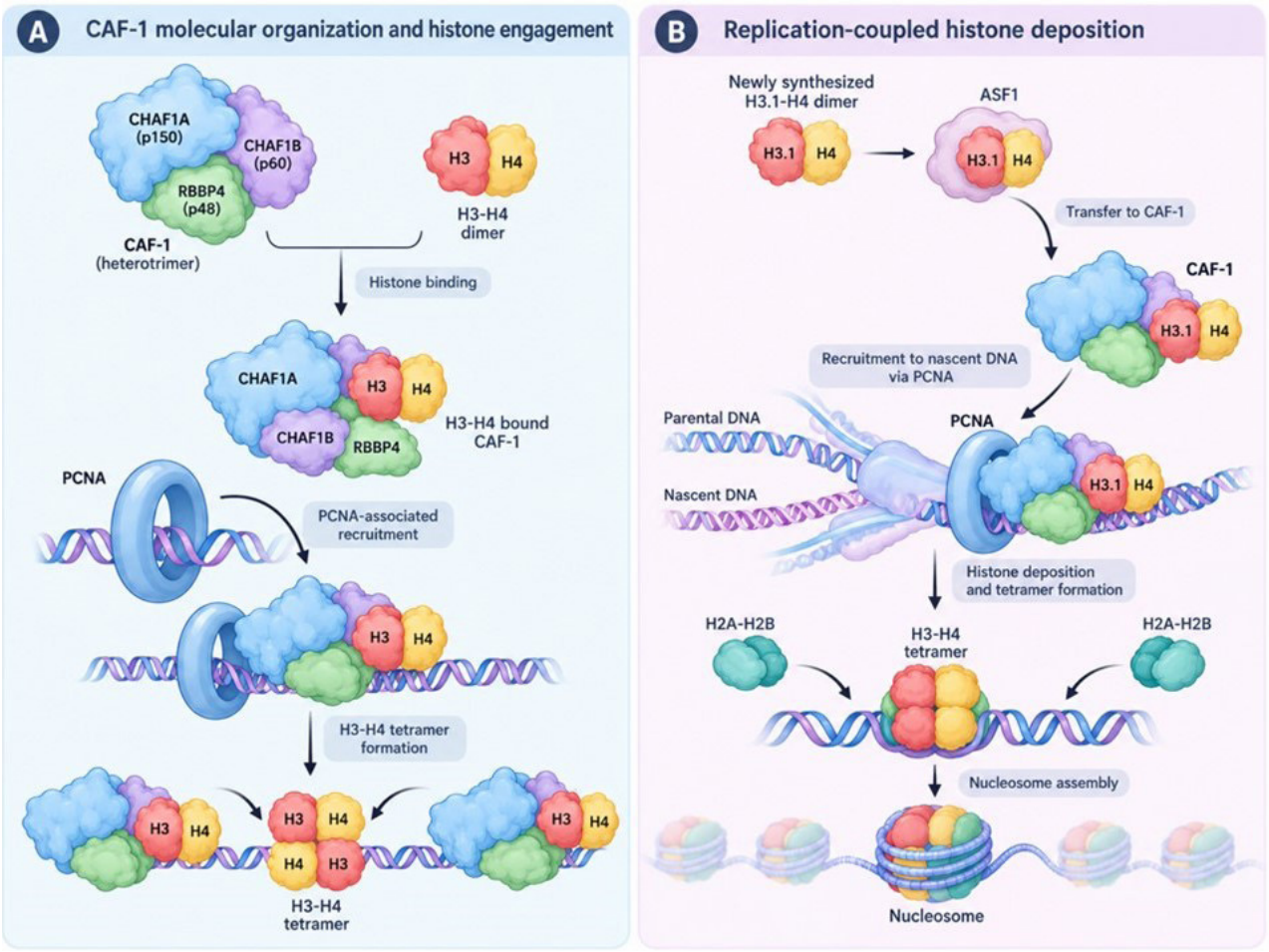
Recruitment of CAF-1 to nascent DNA is closely associated with PCNA, the processivity clamp that encircles DNA during replication and repair. The PCNA-CAF-1 interaction concentrates histone deposition activity at sites of DNA synthesis and helps couple the rate of chromatin assembly to local replication. ASF1 operates upstream by binding H3-H4 dimers and facilitating their transfer into the CAF-1 pathway. This relay reduces uncontrolled histone-DNA interactions while allowing histone deposition to occur with high spatial and temporal precision [5, 13].

The interdependence of the three subunits is important when interpreting cancer studies. Increased CHAF1A or CHAF1B expression may indicate higher abundance of the intact complex, but individual subunits can also engage partners outside canonical nucleosome assembly. RBBP4 is shared with several repressive and remodeling complexes, and CHAF1A and CHAF1B have each been linked to transcriptional or repair functions that may not require every CAF-1 component. Work on noncanonical PCNA binding, yeast CAF-1 architecture, and the p150 winged-helix domain further demonstrates that multiple interfaces cooperate to position the complex on DNA [21-24]. Consequently, a phenotype produced by perturbing one subunit should not automatically be attributed to global loss of CAF-1 activity.

Biochemical and structural work has refined the model of how CAF-1 handles histones. A single CAF-1 complex binds an H3-H4 heterodimer through coordinated contacts involving CHAF1A and CHAF1B. Two CAF-1-H3-H4 assemblies can then organize the dimers into a configuration favorable for H3-H4 tetramer formation and nucleosome assembly [13, 19, 22, 25, 26]. This model explains how CAF-1 can receive soluble histone dimers, protect their interaction surfaces, and release them at nascent DNA without requiring a preassembled soluble tetramer.

Recent structural studies provide a framework for visualizing these interactions. Human CAF-1 forms a heterotrimeric assembly in which CHAF1A and CHAF1B provide major histone- and DNA-associated interfaces, while RBBP4 contributes additional histone-binding capacity. Structural and biochemical studies support a model in which one CAF-1 complex engages an H3-H4 heterodimer and two histone-bound CAF-1 assemblies can cooperate to promote H3-H4 tetramer formation. Figure 1A summarizes the principal subunit organization and experimentally supported histone-contacting interfaces without implying that all partners have been captured simultaneously in a single high-resolution structure [13, 19, 22-26].

Figure 1. Molecular organization of CAF-1 and replication-coupled histone deposition.
(**A**) Schematic representation of the CAF-1 heterotrimer composed of CHAF1A/p150, CHAF1B/p60, and RBBP4/p48, and its interaction with histones H3-H4. CAF-1 binds H3-H4 dimers and is recruited to DNA through its association with proliferating cell nuclear antigen (PCNA). Histone-bound CAF-1 complexes cooperate to facilitate H3-H4 tetramer formation on newly synthesized DNA. The schematic integrates structural and biochemical evidence from multiple studies and is not intended to represent a single fully resolved CAF-1–histone–PCNA complex.
(**B**) Model of replication-coupled nucleosome assembly. Newly synthesized H3.1-H4 dimers are initially bound by anti-silencing function 1 (ASF1) and subsequently transferred to CAF-1. Interaction with PCNA recruits CAF-1 to nascent DNA at the replication fork, where H3.1-H4 is deposited and assembled into an H3-H4 tetramer. Subsequent incorporation of H2A-H2B dimers completes nucleosome assembly and restores chromatin structure behind the replication fork. Arrows indicate the sequential transfer, recruitment, and deposition steps.



CAF-1 is therefore best viewed as a dynamic assembly platform. DNA binding, histone recognition, PCNA recruitment, and partner exchange are coordinated rather than independent events. The structural framework also suggests opportunities for selective intervention. Disrupting a protein-protein interface involved in cancer-specific repair or immune-evasion functions may be more tolerable than eliminating the entire complex, which is required by normal proliferating tissues.

2.1 Replication-coupled chromatin inheritance

Figure 1B illustrates the replication-coupled histone deposition pathway. Newly synthesized H3-H4 dimers are escorted by ASF1 and transferred to CAF-1, while PCNA recruits CAF-1 to sites of ongoing DNA synthesis. CAF-1 then deposits H3-H4 onto nascent DNA, where cooperative assembly promotes H3-H4 tetramer formation and subsequent nucleosome completion [5, 13, 19, 27-29].

During S phase, canonical H3.1-H4 and H3.2-H4 dimers move through an ordered chaperone network before deposition onto newly synthesized DNA. ASF1 binds dimers and facilitates their transfer to CAF-1, which is recruited by PCNA to nascent DNA. Classic genetic and cell-biological studies established that CAF-1 is essential for coupling chromatin assembly to DNA replication, while newer work indicates that

Table 1. CAF-1 subunits and their principal biological roles

Subunit	Key molecular features	Representative partners	Principal functions	Interpretive caution
CHAF1A / p150	Largest scaffold; PCNA- and DNA-associated regions; histone-binding surfaces	PCNA, RAD51, KU70, RAD18	Targets CAF-1 to DNA synthesis; supports chromatin restoration, repair, lesion bypass, and repeat silencing	Several reported activities may be independent of intact CAF-1
CHAF1B / p60	Histone-associated middle subunit; stabilizes complex and histone transfer	ASF1, BCL6, TBL1XR1	Contributes to H3-H4 deposition, lineage regulation, stemness, and differentiation blockade	Expression often tracks proliferation; causal and marker effects must be separated.
RBBP4 / p48	WD40-repeat histone-binding protein shared with other chromatin complexes	Histone H4 and multiple chromatin regulators	Supports histone recognition and CAF-1 assembly	Phenotypes cannot be assigned uniquely to CAF-1 because RBBP4 has other complex memberships.

newly synthesized histones can be deposited through distinct mechanisms on leading and lagging strands [27-29]. Parental histones are redistributed in parallel, allowing pre-existing histone modifications to contribute to reconstruction of local epigenetic states. The combined deposition of recycled parental histones and newly synthesized histones rebuilds nucleosome density while preserving sufficient information for chromatin-modifying enzymes to restore domain-specific marks.

The segregation between replication-coupled and replication-independent histone pathways is central to this process. Canonical H3.1 and H3.2 are deposited primarily during DNA synthesis through CAF-1, whereas the H3.3 variant is incorporated through distinct chaperone systems, often independently of replication [30, 31]. This division influences not only the amount of chromatin formed but also the histone variant composition and regulatory potential of newly assembled nucleosomes.

Nascent chromatin is not a passive endpoint of DNA synthesis. Acute disruption of *de novo* assembly produces rapid, multilevel responses that affect fork velocity, histone transcription, and subsequent cell-cycle progression [32]. ASF1-dependent regulation of replicative histone RNA metabolism provides an additional link between histone supply and the assembly machinery [33].

This finding supports bidirectional communication: replication creates a demand for nucleosome assembly, while the assembly state behind the fork feeds back to the replication machinery and cellular checkpoints. CAF-1 occupies a strategic position in this feedback system because it couples histone supply to the location and timing of DNA synthesis.

Cancer cells intensify this demand. High proliferative rates require continuous histone production and deposition, while oncogenic signaling raises the frequency of stalled forks and incomplete replication. A tumor may therefore become disproportionately dependent on CAF-1 even when normal cells also require it. Such dependency is likely to be quantitative and context-specific rather than universal, shaped by replication-stress burden, repair capacity, cell lineage, and the availability of compensatory chromatin-assembly pathways.

3. CAF-1 in genome and epigenome maintenance

3.1 Replication stress and post-replicative gap formation

Replication stress arises when fork progression is slowed or interrupted by DNA lesions, secondary structures, nucleotide depletion, transcription-replication collisions, or oncogene-driven origin firing. Persistent stalling exposes single-stranded DNA, increases the probability of fork collapse, and can generate chromosome breaks. CAF-1-dependent maturation of nascent chromatin helps organize the DNA behind the fork and influences how replication intermediates are processed; genetic studies also link CAF-1 to sister-chromatid cohesion under replication stress [34].

CAF-1 has been reported to promote efficient recruitment of PrimPol to nascent DNA and thereby

influence formation of post-replicative single-stranded DNA gaps [15]. PrimPol can re-prime synthesis downstream of a blocking lesion, allowing replication to continue while leaving a gap that must later be repaired. The consequences are context-dependent: gap formation can preserve fork movement, but unresolved gaps can become toxic, particularly in tumors with homologous recombination defects. CAF-1 therefore participates in replication-stress biology at a stage where chromatin assembly, repriming, and repair pathway availability intersect.

3.2 DNA double-strand break repair

Chromatin must be remodeled during repair and restored afterward. CAF-1 has long been implicated in the reassembly phase, but newer studies suggest that CHAF1A can also influence recruitment of repair proteins. In lung cancer models, CHAF1A was reported to accumulate at damage sites in an ATM-associated manner and to support both major double-strand break repair pathways [16]. During S phase, CHAF1A cooperated with PCNA and RAD51 to promote RAD51 loading and homologous recombination; outside S phase, it facilitated KU70 recruitment and non-homologous end joining. Loss of CHAF1A impaired repair and increased radiosensitivity in experimental models.

These findings broaden the conceptual role of CAF-1. Chromatin restoration and repair-protein recruitment may form a reciprocal system in which the state of local chromatin influences repair efficiency, while repair progression creates new substrates for nucleosome assembly. Whether the reported RAD51 and KU70 functions require intact CAF-1, or instead reflect subunit-specific interactions of CHAF1A, remains an important mechanistic question.

3.3 Translesion synthesis and lesion bypass

Cells can survive some DNA lesions by bypassing rather than immediately removing them. Translesion synthesis uses specialized polymerases that replicate across damaged templates, often at the cost of increased mutagenesis. CHAF1A has been shown to interact with the E3 ubiquitin ligase RAD18 at stalled forks, promoting RAD18-dependent monoubiquitination of PCNA at lysine 164 and recruitment of Y-family polymerases [17]. This places CHAF1A upstream of a major lesion-bypass switch.

For tumors exposed to chemotherapy or endogenous genotoxic stress, enhanced lesion bypass can preserve viability even when accurate repair is incomplete. The CHAF1A-RAD18 interaction therefore offers a plausible mechanism linking high CHAF1A expression to treatment resistance. It may also represent a more selective therapeutic target than the global histone-deposition machinery if the interaction can be disrupted without abolishing all CAF-1 function.

3.4 R-loop homeostasis and transcription-replication conflicts

R-loops contain an RNA-DNA hybrid and displaced single-stranded DNA. Although they have physiological roles in transcription and genome regulation, persistent R-loops can obstruct replication, expose vulnerable DNA, and generate breaks. A genome-wide CRISPR study identified a cooperative relationship between EXO1 and CAF-1 in suppressing R-loop-associated damage [18]. EXO1 and CAF-1 were recruited through distinct routes and acted in complementary pathways; combined disruption caused marked R-loop accumulation and DNA damage. Earlier work had already connected CAF-1 with resistance to double-strand-break-inducing agents, Rad51-dependent template switching, UV-triggered chromatin assembly, nucleotide excision repair, mismatch repair, and oxidized-base repair [35-42].

This interaction extends CAF-1 biology from nascent chromatin to the management of transcription-replication conflicts. It also suggests potential synthetic vulnerabilities. Tumors with impaired R-loop processing, nuclease defects, or high transcriptional stress may depend more strongly on CAF-1 than tumors with redundant protective pathways. Such hypotheses require direct testing in genetically defined models.

3.5 Epigenetic memory and restriction of cell-fate plasticity

Replication transiently increases DNA accessibility and dilutes histone modifications. Newly replicated DNA must rapidly regain nucleosome density and domain-specific chromatin features if stable transcriptional programs are to persist across cell divisions. CAF-1 contributes to this reconstruction and thereby acts as a barrier against inappropriate activation of alternative lineage programs.

A landmark reprogramming study showed that reducing CAF-1 markedly increased the efficiency of transcription-factor-mediated cell-fate conversion

[14]. CAF-1 suppression increased chromatin accessibility, weakened somatic heterochromatin, and facilitated pioneer-factor engagement at otherwise resistant loci. Related studies connect CAF-1 with HP1-associated heterochromatin, establishment of facultative heterochromatin during pluripotency exit, lineage fidelity, provirus silencing, and H3K9me3-dependent chromatin reprogramming [43-47]. These results establish a direct connection between replication-coupled assembly and the preservation of somatic identity. They also reveal an apparent paradox for cancer biology: strong CAF-1 activity can preserve a malignant chromatin state, whereas reduced activity may increase plasticity and enable adaptation.

CHAF1B illustrates the lineage-specific dimension of this biology. In acute myeloid leukemia models, elevated CHAF1B interfered with differentiation-promoting transcriptional programs, including occupancy of CEBPA at selected regulatory regions. Reducing CHAF1B promoted differentiation and suppressed leukemogenesis while retaining substantial normal hematopoietic function [48, 49]. In normal germinal-center B cells, CHAF1B has also been reported to cooperate with BCL6 and TBL1XR1 in transcriptional repression programs required for germinal-center organization and differentiation [50].

CAF-1 also cooperates with DNA methyltransferases in lineage-restricted gene silencing and contributes to centromeric histone control, chromosome stability, and early embryonic development [51-54]. Together, these observations indicate that CAF-1 subunits can shape lineage state in ways that extend beyond their generic association with S phase.

The therapeutic implication is not simply that CAF-1 inhibition will force every tumor to differentiate. The outcome will depend on the chromatin landscape and transcription-factor environment of the targeted cell. In some cancers, partial suppression may unlock a latent differentiation program; in others, it could expand phenotypic heterogeneity and increase resistance. Models that measure cell-state trajectories over time will therefore be essential for distinguishing beneficial differentiation from harmful plasticity.

4. CAF-1 dysregulation in cancer

4.1 Proliferation, prognosis, and lineage plasticity

CAF-1 expression is tightly linked to cell-cycle activity, consistent with its replication-coupled role. Elevated CHAF1A or CHAF1B has been observed in many malignancies and is often associated with higher grade, advanced stage, metastasis, or shorter survival [55, 56]. Early pathology studies evaluated CAF-1/p60 as a marker that distinguishes proliferating from quiescent cells and reported prognostic associations in tongue, melanoma, salivary-gland, and other solid tumors [57-64]. This broad pattern has generated interest in CAF-1 as a proliferation and prognostic marker. Interpretation requires caution, because an association with outcome may arise from high proliferative fraction, a direct tumor-promoting function, or both.

Mechanistic studies support causal roles in selected tumors. In lung squamous-cell carcinoma, CHAF1B is increased and has been reported to bind the SETD7 promoter and suppress SETD7 expression, thereby promoting proliferation and tumor progression [65]. In esophageal cancer, co-expression of CHAF1A and PCNA has been associated with aggressive behavior and adverse prognosis, consistent with enhanced DNA replication and S-phase progression [66]. Additional experimental studies implicate CHAF1A or CHAF1B in colon, gastric, ovarian, hepatocellular, lung, neuroblastoma, glioblastoma, and lymphoid malignancies through effects on proliferation, apoptosis, migration, differentiation, metabolism, and responses to epigenetic therapy [67-82]. Integrated analyses in lung adenocarcinoma likewise identify CHAF1B as a candidate prognostic and immunotherapy-related marker, although bioinformatic associations require prospective and functional validation [83].

CAF-1 biology is not restricted to malignant cells. For example, CHAF1A has been linked to preadipocyte proliferation and differentiation in gestational diabetes mellitus [84]. Although outside the cancer setting, this observation reinforces the need to distinguish general growth-associated functions from tumor-selective dependencies.

These examples reinforce the need to separate three claims that are often conflated: CAF-1 may be a marker of proliferation, an independent prognostic biomarker, and a functional dependency. The evidentiary standard rises across those claims. Demonstrating clinical utility requires standardized assays, predefined thresholds, validation in independent cohorts, and proof that CAF-1 adds information beyond established pathology and molecular predictors.

Tumor relapse and progression often involve subpopulations with stem-like or plastic phenotypes. In glioblastoma, CHAF1B has been reported to be enriched in high-grade tumors and glioma stem-cell populations. Its depletion reduced self-renewal and

tumorigenicity, while CHAF1B-dependent IL-33 secretion promoted immunosuppressive microglial polarization and PI3K-AKT signaling [85]. This model is notable because it links a chromatin factor to both cell-intrinsic stemness and communication with the tumor microenvironment.

Across tumor types, CAF-1 may support stemness through at least two nonexclusive mechanisms: preserving chromatin states that sustain self-renewal and controlling secreted signals that remodel surrounding immune or stromal cells. Determining which mechanism dominates will be important for choosing biomarkers and combination treatments.

4.2 Treatment resistance

Several CAF-1 functions converge on resistance to therapy. Efficient homologous recombination and non-homologous end joining can reduce the effect of radiation; RAD18-dependent translesion synthesis can allow survival after DNA-damaging chemotherapy; and stable chromatin restoration can preserve transcriptional programs during treatment-induced stress [16, 17, 55]. Tumor-specific studies have associated CAF-1 subunits with PARP-inhibitor or radiation response in head and neck cancer, fluoropyrimidine response in gastric cancer, cisplatin resistance in lung adenocarcinoma, radioresistance in nasopharyngeal carcinoma, sorafenib resistance in hepatocellular carcinoma, metformin-mediated radiosensitization in oral squamous-cell carcinoma, and adaptive drug-resistance programs [67, 76, 79, 80, 86-88]. High CAF-1 expression may therefore be both a marker of rapidly cycling disease and a functional contributor to resistance.

The reverse is also biologically plausible: because CAF-1 is essential for chromatin assembly, severe inhibition can produce loss of chromatin assembly and cell death [89] and may therefore be toxic to normal proliferating tissues, including bone marrow and gastrointestinal epithelium. Therapeutic development must identify a window in which tumor-specific stress or genetic defects create greater dependence than in normal tissues. Intermittent dosing, partial inhibition, or disruption of selected interactions may offer more feasible strategies than complete complex ablation.

4.3 CAF-1 links chromatin regulation to tumor immune escape

Endogenous retroviruses and other repetitive elements are normally constrained by heterochromatin. When repression is weakened, bidirectional transcription can generate double-stranded RNA that activates antiviral sensors and type I interferon signaling, a process often termed viral mimicry. Genome instability can also release double-stranded DNA into the cytosol and activate cGAS-STING. Because CAF-1 contributes to both heterochromatin maintenance and genome stability, it is positioned to regulate these two immunogenic nucleic-acid pathways.

In intrahepatic cholangiocarcinoma, NAT10-mediated N4-acetylcytidine modification was reported to stabilize CHAF1A mRNA. Increased CHAF1A then supported repression of the HERV9NC retroelement; disruption of the NAT10-ac4C-CHAF1A axis increased double-stranded RNA accumulation and antitumor immune signaling [90]. This pathway provides a mechanistic chain from RNA modification to chromatin assembly, repeat silencing, and immune escape.

A complementary mechanism has been described in esophageal squamous-cell carcinoma. Elevated CHAF1A maintained H3K9me3-associated repression of endogenous retroviruses, thereby limiting dsRNA-MAVS-IRF3 signaling, while preservation of genome stability reduced cytosolic DNA and cGAS-STING activation [91]. CHAF1A depletion activated both pathways and improved antitumor immune responses; pharmacologic targeting enhanced anti-PD-1 activity in preclinical models. These findings suggest that CAF-1 can create an immunologic tradeoff: chromatin stability protects cells from aberrant nucleic acids, but tumors may exploit the same protection to avoid innate immune surveillance.

CHAF1B has also been connected with interferon biology. Targeting CHAF1B enhanced interferon activity against myeloproliferative neoplasm cells [92], while glioblastoma studies link CHAF1B to IL-33-dependent microglial polarization [85]. In hepatocellular carcinoma, inhibition of the CAF-1 complex activates cytosolic DNA and dsRNA sensing, providing independent support for a tumor-intrinsic immune-silencing role [93]. Studies of HIV and Epstein-Barr virus further show that CAF-1 can impose repressive chromatin on viral DNA and support latency, while CHAF1B also participates in immune-cell development[94-98]. Integrated analyses in Burkitt lymphoma and lung adenocarcinoma further associate CAF-1 subunits with immune-cell infiltration or immunotherapy-related features [83, 99, 100]. These latter observations are hypothesis-generating; immune correlations from bulk tumors can

Table 2. Representative cancer-associated CAF-1 mechanisms and translational implications

Context	CAF-1 feature	Proposed mechanism	Observed phenotype	Potential implication
Lung cancer	CHAF1A	RAD51 loading in S phase; KU70 recruitment outside S phase	Enhanced double-strand break repair and radioresistance	Radiotherapy sensitization; define cell-cycle-specific pharmacodynamics [16]
Multiple cancer models	CHAF1A	RAD18 recruitment and PCNA monoubiquitination	Translesion synthesis and lesion tolerance	Combine interface disruption with DNA-damaging therapy [17]
Esophageal squamous-cell carcinoma	CHAF1A	ERV repression plus preservation of genome stability	Reduced MAVS-IRF3 and cGAS-STING signaling; immune-cold state	Immune sensitization and anti-PD-1 combinations [91]
Intrahepatic cholangiocarcinoma	NAT10-CHAF1A axis	ac4C-dependent CHAF1A mRNA stabilization and HERV9NC repression	Reduced dsRNA accumulation and antitumor signaling	Target upstream RNA modification or CAF-1-mediated repeat silencing [90]
Glioblastoma	CHAF1B	Stemness maintenance; IL-33 secretion; microglial polarization	Self-renewal, tumorigenicity, and immunosuppressive microenvironment	Pair tumor-cell and microenvironment-directed approaches [85]
Acute myeloid leukemia	CHAF1B	Restriction of differentiation-factor occupancy	Differentiation blockade and leukemogenesis	Differentiation therapy strategy in molecularly selected disease [48]
Lung squamous-cell carcinoma	CHAF1B	Suppression of SETD7 transcription	Proliferation and tumor progression	Validate dependency and pathway-specific biomarkers [65]

reflect cellular composition and should be supported by spatial, single-cell, and functional evidence.

The emerging model is that CAF-1 influences tumor immunity through several layers: repression of immunogenic repeats, protection against cytosolic DNA, regulation of interferon competence, and alteration of paracrine signals. These mechanisms may coexist, but their relative importance is likely to vary by tumor lineage and baseline immune state. Biomarkers that measure repeat expression, cytosolic nucleic acids, interferon response, and CAF-1 dependency together may be more informative than CHAF1A or CHAF1B abundance alone.

4.4 Therapeutic targeting of CAF-1

At present, pharmacologic CAF-1 targeting remains at an early preclinical stage. Historically, most mechanistic studies have relied on genetic depletion of CHAF1A or CHAF1B because CAF-1 lacks an obvious catalytic active site and performs essential functions in normal proliferating cells. A recent study in esophageal squamous-cell carcinoma identified Baimaside through small-molecule screening as a candidate CHAF1A inhibitor. In preclinical models, Baimaside enhanced tumor-intrinsic innate immune signaling and potentiated anti-PD-1 therapy [91]. The other study also showed that the FDA-approved drug Trifluridine (TFD) functions as a novel latency-reversing agent by disrupting CHAF1A O-GlcNAcylation, thereby triggering its MIB1-mediated ubiquitination and subsequent degradation to reactivate latent HIV-1 reservoirs [98]. These works provide proof of principle that CHAF1A may be pharmacologically tractable, but the compound remains preclinical, and additional studies are needed to establish its biochemical binding mode, selectivity, pharmacokinetic properties, target engagement, safety, and therapeutic window. No CAF-1-directed agent has yet established clinical efficacy. Future approaches may therefore include selective disruption of cancer-relevant protein-protein interfaces, targeted degradation or proximity-based modulation, and combination strategies that exploit replication stress, DNA-repair defects, or tumor-intrinsic immune activation.

5. Outstanding questions

First, canonical complex activity must be distinguished from subunit-specific functions. Many studies perturb CHAF1A or CHAF1B and describe the result as a CAF-1 phenotype, yet the relevant interaction may not require the intact heterotrimer. Complementation with separation-of-function mutants, quantitative proteomics, and structural analysis can determine whether histone deposition, PCNA binding, or a noncanonical partner is responsible.

Second, the determinants of CAF-1 dependency across tumors remain unclear. Candidate variables include replication-stress burden, homologous recombination status, oncogenic driver mutations, R-loop accumulation, transposable-element load, baseline interferon competence, and differentiation state. Large-scale dependency data should be integrated with experimentally measured chromatin and replication phenotypes rather than expression alone.

Third, the consequences of partial versus complete CAF-1 inhibition need careful study. Complete depletion may arrest proliferation and damage normal tissues, whereas partial or transient inhibition may expose a tumor-specific vulnerability. The dose-response relationship may also differ by desired outcome: modest perturbation could be sufficient to induce viral mimicry, while stronger inhibition might be required to impair repair or force differentiation.

Fourth, the relationship between CAF-1 and cell plasticity is likely to be context-dependent. In some leukemias, CHAF1B reduction can promote differentiation [48]; in other settings, weakened chromatin inheritance could increase phenotypic diversity. Lineage-tracing and single-cell multi-omics should be used to determine whether CAF-1 targeting moves tumors toward a stable, therapeutically favorable state or creates new escape routes.

Fifth, clinical biomarker studies should move beyond bulk abundance. A useful CAF-1 response signature may combine subunit expression with measures of replication stress, DNA repair activity, repeat transcription, interferon signaling, and immune-cell context. Serial sampling will be needed to determine whether these features change during treatment and whether they predict benefit from radiation, DNA-damaging agents, or immunotherapy combinations.

Finally, pharmacologic tractability remains a central challenge. CAF-1 lacks an obvious enzymatic active site, so conventional inhibitor development may be difficult. The recent identification of Baimaside as a candidate CHAF1A-directed small molecule provides an initial proof of principle, but its selectivity, direct binding mechanism, pharmacologic properties, and generalizability across tumor types remain to be established[91]. Structural studies should prioritize interaction surfaces that are essential in cancer but dispensable for basal chromatin assembly. Parallel development of degradation strategies, proximity-based modulators, and biomarkers of acute target engagement may clarify which approach can achieve a usable therapeutic window.

6 Conclusions

CAF-1 has evolved conceptually from a replication-coupled histone deposition factor to a central regulator of chromatin inheritance, genome integrity, and cellular identity. Its position at nascent and repaired DNA enables it to coordinate histone deposition with fork progression, DNA damage tolerance, and reconstruction of epigenetic information. These functions are fundamental in normal cells but become especially consequential in tumors exposed to chronic replication and genotoxic stress.

Cancer cells can exploit CAF-1 at several levels: sustaining rapid proliferation, facilitating repair and lesion bypass, preserving malignant chromatin states, restricting differentiation, and limiting nucleic-acid-triggered antitumor immunity. The emerging links between CHAF1A, RAD51, RAD18, endogenous retroelement repression, and type I interferon signaling show that CAF-1 is more than a passive marker of proliferation. It may represent a mechanistically coherent vulnerability connecting genome maintenance with immune escape.

Translation will require precision. Future studies should identify tumor contexts with selective CAF-1 dependency, distinguish canonical complex functions from subunit-specific activities, establish standardized biomarkers, and determine whether partial or interaction-selective inhibition can be combined safely with DNA-damaging therapy or immunotherapy. Moving from descriptive overexpression studies to genetically and pharmacologically defined dependencies will be essential for converting CAF-1 biology into clinically meaningful strategies.

Conflict of Interest: The authors declare that they have no competing interests.

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