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Review

CtBP: A mediator of a metabolic switch from homeostasis to carcinogenesis

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ABSTRACT

The dimeric form of C-terminus binding protein (CtBP), which is responsible for a balanced transcription rate of genes involved in the homeostatic processes, is a global corepressor. CtBP dimerization and formation of the CtBP corepressor complex require NADH. Under a normal NADH/NAD+ ratio, CtBP is in the dimeric form while, when NADH/NAD+ decreases, it converts into a monomeric form. The monomeric form of CtBP inhibits histone acetyltransferase p300, which plays an important role in the packaging of newly replicated and repaired DNA into chromatin by acetylating the histone H3 core domain lysine 56 (H3K56). Further, by inhibiting p300, the monomeric form of CtBP inhibits NFκB, which plays an important role in the innate immune response toward neoantigens. Furthermore, NFκB causes the transcription of IL-6, which is important in the resolution of the innate immune response. Moreover, by inhibiting p300, the monomeric CtBP inhibits p53, the guardian of the genome. Thus, by inhibiting p300, the monomeric form of CtBP may be involved in carcinogenesis when NADH/NAD+ ratio decreases. In contrast, hypoxia increases the NADH/NAD+ ratio, generating the dimeric form of CtBP and relieving the inhibition of p300 by the monomeric CtBP. The higher NADH/NAD+ ratio and p300 activity under hypoxia mask the instability of cancer cells, confer invasive properties, cause COX-2 expression, increase the transactivation activity of the hypoxia-inducible factor (HIF), and cause drug resistance through NFκB. Thus, p300, regulated by NADH/NAD+ ratio through CtBP, works as a double-edged sword in cancer initiation and progression, respectively.

1. Introduction

CtBP has two homologs, CtBP1 and CtBP2, which bind with the C-terminus of the adenovirus E1A protein (Katsanis and Fisher, 1998). Both homologs work as corepressors, with higher expression of CtBP2 in the heart, skeletal muscle, and pancreas (Katsanis and Fisher, 1998). In developing mouse embryos, CtBP1 and CtBP2 are expressed broadly with different tissue preferences and have overlapping functions (Furusawa et al., 1999).

CtBP is a global corepressor that maintains a balanced expression of target genes of many important signaling pathways e.g., wnt pathway, notch pathway, hedgehog pathway, and genes e.g., p21 and E-cadherin (Jaiswal and Singh, 2023; Jaiswal and Singh, 2022). Further, it maintains homeostasis of many important cellular processes e.g. inflammatory response of microglia and astrocytes, pH homeostasis of cells, cholesterol homeostasis, and homeostasis of skeletal muscle (Jaiswal and Singh, 2023).

At the promoter of target genes repressed by CtBP, an activator and a repressor complex form (Jaiswal and Singh, 2023). The two complexes share a cofactor (Jaiswal and Singh, 2023). Through these two complexes CtBP balances the expression of target genes (Jaiswal and Singh, 2023) (Fig. 1A). The binding between CtBP and corepressors requires NADH (Zhang et al., 2002; Fjeld et al., 2003). Further, NADH causes CtBP dimerization (Banerjee et al., 2019; Thio et al., 2004) and the repressor complex contains the dimeric form of CtBP (Thio et al., 2004). Thus, the maintenance of cellular balances and homeostasis is NADH-dependent. On the other hand, a decrease in the NADH/NAD+ ratio due to a metabolic switch generates the monomeric form of CtBP (Fig. 1B).

Altered BRCA1 transcription may contribute to sporadic forms of breast cancer (Di et al., 2010). In this context, a decrease in NADH/NAD+ ratio causes histone deacetylase HDAC1 dismissal and increases BRCA1 transcription (Di et al., 2010), forming the BRCA1-CtBP-CtIP corepressor complex that represses the cyclin-dependent kinase inhibitor p21, increasing cell proliferation. The formation of the BRCA1-CtBP-CtIP corepressor complex is NADH-dependent. Thus, the alteration in gene expression of BRCA1 by this metabolic switch may be an important link between caloric intake and the tumor suppressor expression in

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mammary cells (Di et al., 2010), causing sporadic forms of breast cancer.

Further, the BRCA1-CtBP-CtIP corepressor complex also represses estrogen receptor (ER) activated gene expression (Ludes-Meyers et al., 2009). Similarly, LCoR interacts with CtBP1 and CtBP1 enhances LCoR-mediated repression of estrogen receptor (ERα) activated gene expression (Palijan et al., 2009). Since NADH is required for the dimeric CtBP-mediated repression, a reduction in NADH/NAD+ ratio increases the estrogen receptor-activated gene expression.

Besides the metabolic switch caused by a reduction in NADH/NAD+ ratio, many signaling pathways, including Notch, NF-κB, and nuclear receptor ligands, are repressed by two distinct corepressor complexes, CtBP1/2 and NCoR/SMRT, working as a gene expression "checkpoint" (Perissi et al., 2008). Gene expression activation requires the release of both CtBP1/2- and NCoR/SMRT-dependent corepressor complexes, through two exchange factors, the transducer β-like proteins TBL1 and TBLR1, that cause ubiquitylation and degradation of CtBP1/2 and NCoR/SMRT, respectively (Perissi et al., 2008). For corepressor degradation, TBL1 and TBLR1 are specifically phosphorylated by Ser/Thr kinases, e.g. PKCδ in TBLR1-dependent dismissal of NCoR. Thus, in gene expression regulation, there is a strategy of dual-factor repression checkpoints, in which dedicated exchange factors serve as sensors for signal-specific dismissal of distinct corepressors (Fig. 1C) (Perissi et al., 2008). Therefore, in addition to the metabolic switch (Fig. 1B), there is a signaling switch (Fig. 1C) in the CtBP-mediated maintenance of balanced gene expression and homeostasis of cellular processes. In this paper, we implicate the metabolic switch in carcinogenesis.

CtBP2 is overexpressed in many solid tumors and is prominent in tumor-initiating cell (TIC) programs (Chawla et al., 2019). In a mouse model of pancreatic ductal adenocarcinoma (PDAC) driven by mutant K-Ras, CtBP2 deletion abolished peritoneal metastasis, increased survival, and caused depletion of c-Myc, a critical protein for TIC activity and tumor progression in PDAC (Chawla et al., 2019). Further, 4-chloro-hydroxyimino phenylpyruvate (4-Cl-HIPP), an inhibitor of CtBP2, mimicked CtBP2 deletion, decreasing tumor burden (Chawla et al., 2019). Furthermore, the combination of 4-Cl-HIPP and gemcitabine synergistically decreased tumor growth (Chawla et al., 2019). Interestingly, global profiling of the role of CtBP in breast cancer reveals that it has a prominent role in genome instability (Di et al., 2013).

2. CtBP implements a metabolic switch

2.1. Gene expression regulation by monomeric and dimeric forms of CtBP

The monomeric form of CtBP1, found in low NADH/NAD+ conditions, directly associates with histone acetyltransferase p300 by binding to the PXDLS motif in the bromodomain of p300, inhibiting p300, and repressing target genes (Kim et al., 2005) (Fig. 2A). On the other hand, the dimeric form of CtBP, found in the higher NADH/NAD+ ratio condition, binds to other corepressors in an NADH-dependent manner and represses target genes (Fig. 1A). The repression mediated by the dimeric CtBP balances the transcription rate of genes involved in homeostasis processes including cell growth and differentiation (Jaiswal and Singh,

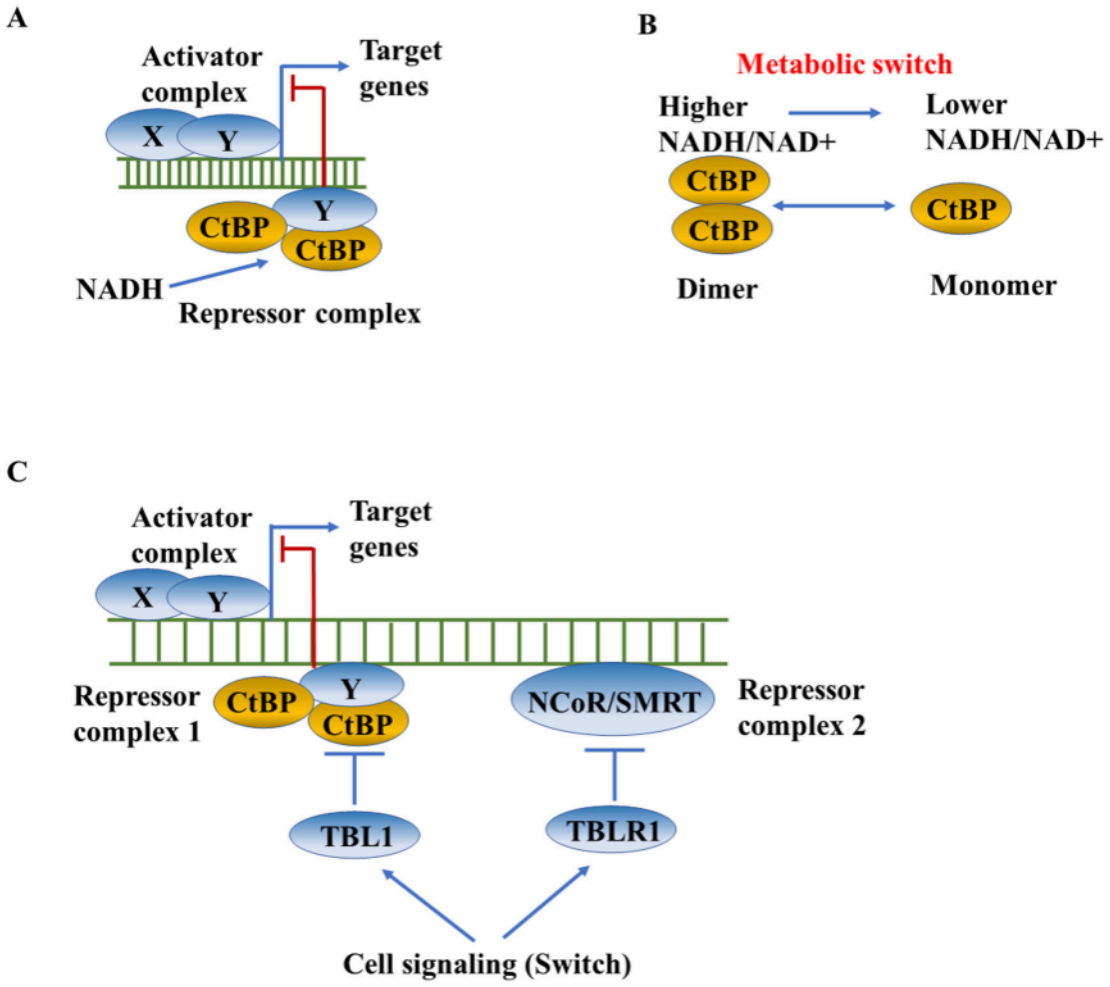

Fig. 1. A decrease in the NADH/NAD+ ratio generates the monomeric form of CtBP. (A) The dimeric CtBP-mediated repression motif. NADH is required for the dimeric CtBP-mediated repression. (B) A reduction in NADH/NAD+ ratio causes the formation of the monomeric form of CtBP (C) Cell signaling may switch on transcription by inhibiting the dimeric CtBP-mediated repression.

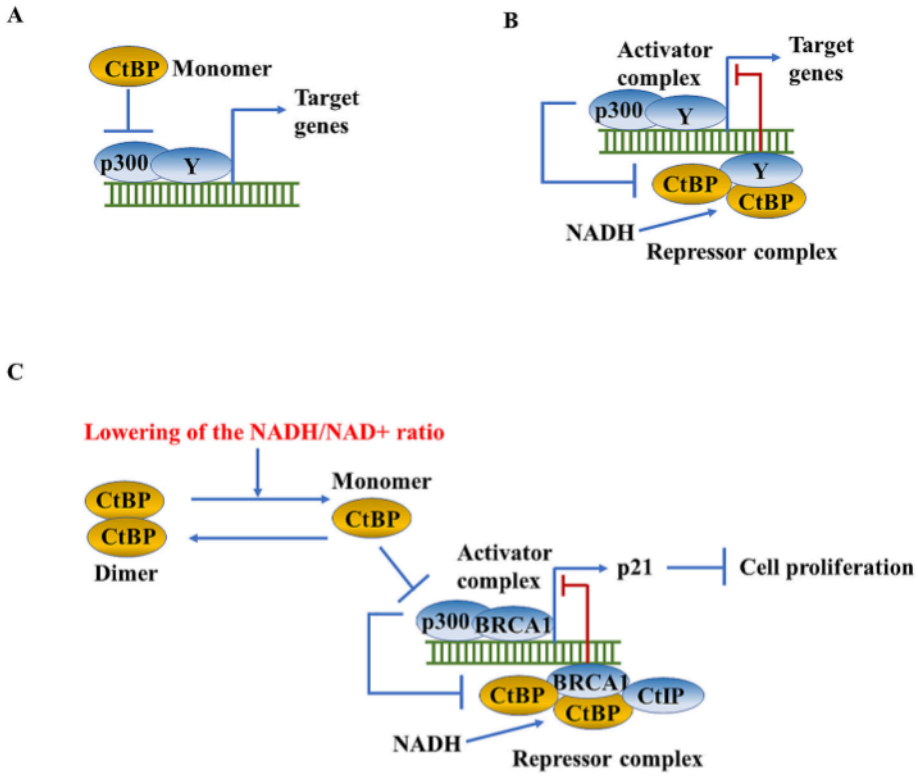

Fig. 2. The monomeric form of CtBP causes cell proliferation. (A) The monomeric CtBP inhibits p300, which is required for gene activation (B) p300, participating in the activator complex, inhibits the formation of the dimeric CtBP containing corepressor complex, causing gene activation (C) A lowering of NADH/NAD+ ratio causes the formation of the monomeric CtBP, which inhibits p300. Since p300 inhibits the formation of dimeric CtBP containing corepressor complex, the lowering of NADH/NAD+ ratio promotes the formation of the corepressor complex, which represses p21, causing cell proliferation.

2023). Thus, there are two general mechanisms of CtBP-mediated repressions: (1) The monomeric CtBP, found in the lower NADH/NAD+ ratio conditions, binds with and inhibits p300, causing repression of some target genes (2) The dimeric CtBP, found in the higher NADH/NAD+ ratio conditions, represses some other target genes by forming a corepressor complex with other corepressors in the NADH-dependent manner.

2.2. p300 relieves the repression caused by the dimeric CtBP, causing gene activation

CtBP was discovered based on its interaction with the C-terminus of adenovirus E1A protein, which binds with CtBP through the PXDLS motif in E1A (Chinnadurai, 2002). Acetylation of Lys-239, adjacent to the PXDLS motif, disrupts CtBP-E1A interaction (Zhang et al., 2000). Like its binding to E1A, the dimeric CtBP binds to the PXDLS motif of other corepressors (Zhang et al., 2000). In the other corepressors as well, the PXDLS motif is followed by a Lys residue (Zhang et al., 2000). Acetylation of this residue by p300 is a general mechanism that disrupts CtBP-corepressor interaction involved in the dimeric CtBP-mediated repression, leading to transcriptional activation (Zhang et al., 2000) (Fig. 2B).

In the above context, ZNF366 interacts with the estrogen receptor ERa through the zinc finger domains of the two proteins (Lopez-Garcia et al., 2006). Further, ZNF366 acts as a corepressor by interacting with other known corepressors of ERa, namely, RIP140 and dimeric CtBP, and represses estrogen-responsive target genes (Lopez-Garcia et al., 2006). Furthermore, dimeric CtBP interacts with the corepressor RIP140 through a sequence, PIDLSCK, in RIP140(Vo et al., 2001). Acetylation of the Lys residue in this motif by p300 reduced the binding of dimeric CtBP to RIP140(Vo et al., 2001). Thus, p300-mediated acetylation of RIP140 disrupts the RIP140-dimeric CtBP complex and activates the nuclear hormone receptor-regulated genes. Therefore, the disruption of corepressor-dimeric CtBP interactions due to the acetylation of the corepressor by p300 is a general mode of gene activation (Vo et al., 2001) (Fig. 2B).

2.3. The metabolic switch causes cell proliferation and decreases cell differentiation through p21

Since the monomeric form of CtBP inhibits p300, the metabolic switch of the reduction in the NADH/NAD+ ratio generating the monomeric form of CtBP upsets the balancing action of the dimeric CtBP. In this context, BRCA1 transactivates the cyclin-dependent kinase inhibitor p21(Somasundaram et al., 1997). On the other hand, the BRCA1-dimeric CtBP-CtIP corepressor complex causes p21 promoter deacetylation, inhibiting p21 transcription and promoting the G1-S transition of cells (Yu et al., 2019). Thus, the dimeric CtBP causes cell cycle progression by repressing p21. Lowering of NADH/NAD+ ratio converts some of the dimeric-CtBP to the monomeric form. Therefore, the dimeric and monomeric forms of CtBP coexist, inhibiting p300 (Kim et al., 2005) and the corepressor acetylation by p300 in the dimeric CtBP-mediated repression of p21 (Zhang et al., 2000; Vo et al., 2001). The decrease in corepressor acetylation increases the affinity between the dimeric CtBP and corepressors, increasing the repression of p21, thus causing cell cycle progression. Therefore, a lowering of the NADH/NAD+ ratio increases cell proliferation and inhibits cell differentiation by increasing the repression of the p21 gene (Jaiswal and Singh, 2023; Jaiswal and Singh, 2024) (Fig. 2C).

3. The monomeric form of CtBP causes global instability in the cell

3.1. Monomeric CtBP blocks cell surveillances of p53 and NFkB

The monomeric form of CtBP, which is found when the NADH/NAD+ ratio is low, inhibits NFκB transcriptional activity and activation of pro-inflammatory gene expression in macrophages and microglia (Shen et al., 2017), blocking the innate immune response. Consistently, inhibition of the CtBP dimerization replicated the effect of the reduced NADH/NAD+ ratio on NFκB activity (Shen et al., 2017), implicating the involvement of the monomeric form of CtBP in blocking NFκB transcriptional activity. Further, the monomeric form of CtBP blocks NFkB transcriptional activity by directly inhibiting p300, which is a part of the activator complex, and not by participating in the corepressor complex (Jaiswal and Singh, 2023; Kim et al., 2005).

Similarly, the monomeric form of CtBP blocks the p53 function through HDM2(Birts et al., 2020), which causes the degradation and nuclear expulsion of p53. Further, a low NADH/NAD+ causes SIRT1 upregulation, resulting in deacetylation and inactivation of p53, allowing cells to bypass apoptosis during DNA damage (Castro et al., 2016). Thus, in the cells that are in a high glycolytic state with a low NADH/NAD+ ratio e.g., during carcinogenesis, both NFkB-mediated innate immunity and p53-mediated genomic surveillance mechanisms are absent. Therefore, while the monomeric form of CtBP blocks cell surveillances caused by innate immunity, mediated by NFκB, and genome integrity maintained by p53, the dimeric CtBP balances the expression of genes involved in homeostatic processes in the cell (Jaiswal and Singh, 2023). Further, there is a switch from the second mechanism of repression, mediated by the dimeric form of CtBP, to the first mechanism, mediated by the monomeric form, which inhibits p300, when the redox state of a cell switches from a higher NADH/NAD+ ratio to a lower NADH/NAD+ ratio. Thus, when the metabolic state of cells switches from a higher NADH/NAD+ ratio to a lower NADH/NAD+ ratio, the state of cells switches from that of homeostasis to that of instability caused by the generation of the monomeric form of CtBP.

3.2. Monomeric CtBP disturbs the DNA damage response by inhibiting p300

For the maintenance of genomic integrity, the packaging of newly replicated and repaired DNA into chromatin is important (Vempati et al., 2010). Following replication and repair, the compaction of DNA into chromatin is accomplished by acetylation of histone H3 core domain lysine 56 (H3K56) (Vempati et al., 2010). This is accomplished by acetylation of H3K56 by p300. Consistent with its role in the DNA damage response, H3K56 is localized to the site of DNA damage and colocalizes with phospho-ATM, CHK2, and p53, the proteins involved in DNA repair (Vempati et al., 2010). H3K56 is acetylated by p300 and deacetylated by SIRT2 and SIRT3(Vempati et al., 2010). Thus, p300, through acetylation of H3K56, plays an important role in maintaining genomic integrity.

p300 is essential for p53 stabilization and p53-mediated growth arrest and apoptosis in response to DNA damage (Yuan et al., 1999b; Yuan et al., 1999a). Further, p300 acetylates p53, increasing its transcriptional activity in response to DNA damage (Liu et al., 1999). On the other hand, monomeric CtBP blocks p53 activity through HDM2(Birts et al., 2020). Since the monomeric CtBP inhibits p300 activity (Kim et al., 2005), and H3K56 and p53 functions (Yuan et al., 1999b; Yuan et al., 1999a; Birts et al., 2020), switching of the metabolic state from a higher NADH/NAD+ ratio to a lower NADH/NAD+ ratio, producing monomeric CtBP, causes genomic instability (Fig. 3A).

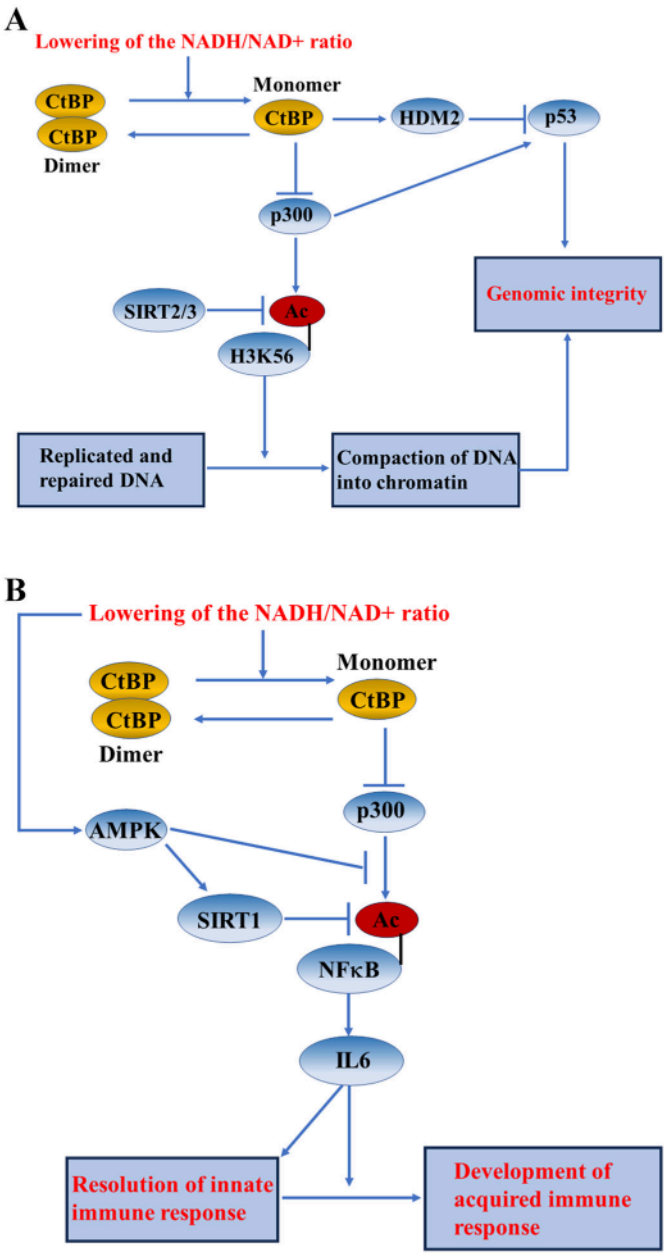

Fig. 3. The monomeric form of CtBP causes genomic instability. (A) A lowering of the NADH/NAD+ ratio causes the formation of the monomeric CtBP, which inhibits p53 and H3K56, compromising genomic integrity. (B)A lowering of the NADH/NAD+ ratio causes the formation of the monomeric CtBP, which inhibits NFκB and IL6 production, blocking the resolution of the innate immune response.

3.3. The monomeric CtBP disturbs cellular immunity by inhibiting NFkB-p300

An important event that defines the successful outcome of any inflammatory event is the transition from innate to acquired immunity (Jones, 2005). IL-6 is important in both the resolution of innate immunity and the development of acquired immune responses (Jones, 2005). In IL-6 deficiency, this process is defective (Jones, 2005). Thus, IL-6 has an important role in immune response (Tanaka et al., 2014). However, its dysregulated continual has a pathological effect on chronic inflammation and autoimmunity (Tanaka et al., 2014). Interestingly, IL-6 is an NFκB target gene (Zhang et al., 2016) and NFκB activity is increased by its acetylation by p300 and decreased by its deacetylation by SIRT1

(Zhang et al., 2016). In agreement, p300 mediates NFκB-induced inflammatory responses in astrocytes (Giri et al., 2004). Thus, monomeric CtBP, by inhibiting p300, reduces NFκB activity and IL-6 production when the NADH/NAD+ ratio decreases, negatively affecting the resolution of the innate immune response (Fig. 3B).

On the other hand, AMP kinase (AMPK) activation decreases NFκB interaction with p300 and increases SIRT1 expression, leading to a significant reduction in NFκB acetylation (Zhang et al., 2016). Further, AMPK is activated by NAD+ and inhibited by NADH (Rafaeloff-Phail et al., 2004). Thus, a reduction in NADH/NAD+ ratio activates AMPK, reducing NFκB acetylation by p300 and, inhibits the successful resolution of the innate immune response by reducing NFκB activity (Fig. 3B).

In interim summary, a metabolic switch from a higher NADH/NAD+ to a lower NADH/NAD+ ratio generates monomeric CtBP from the NADH-dependent dimeric form. Generation of the monomeric form and the reduction in the dimeric form of CtBP disturbs the dimeric CtBP-mediated homeostatic processes and causes global instability. Further, the monomeric CtBP blocks DNA damage response by blocking p300, H3K56, and p53, causing genomic instability. The genomic instability creates neoantigens. Furthermore, the monomeric CtBP also blocks the resolution of the immune response to the neoantigen by inhibiting NFκB activity and IL-6 production. Thus, switching the metabolic state to a lower NADH/NAD+ ratio may lead to carcinogenesis by blocking p300 activity through the monomeric CtBP. In agreement, p300 is considered a tumor suppressor, and truncation mutation in p300 has been implicated in carcinogenesis (Karamouzis et al., 2007). Consistently, the upregulation of p300 has been shown to work as a tumor suppressor in a human bladder tumor model (Kim et al., 2011). Further, exposure to carcinogen azoxymethane (AOM) downregulated p300 in the colon (Aizu et al., 2003).

The section above relates to cancer initiation due to a metabolic switch that lowers the NADH/NAD+ ratio, forming the monomeric form of CtBP, which inhibits p300. In the section below, we discuss the processes that lead to solid tumor formation from cancer initiation. One of the important events in this process is the oncogene activation, caused by the genomic instability created by the monomeric CtBP. The other important event is the expression of the hypoxia-inducible factor (HIF). Below, we show that p300, regulated by CtBP, works as a double-edged sword and plays a critical role in cancer progression as well, in addition to its role in cancer initiation.

4. p300 contributes to the progression of cancer

Blocking the production or action of androgens is the aim of standard therapy for non-organ-confined prostate cancer (Heemers et al., 2007). Although initially successful, androgen deprivation therapy eventually fails and androgen depletion-independent (ADI) disease emerges (Heemers et al., 2007). Interestingly, ADI prostate cancers still rely on a functional androgen receptor (AR) (Heemers et al., 2007). In this context, the expression of coregulatory proteins required for the formation of productive AR transcriptional complexes is the key to ADI AR activation (Heemers et al., 2007). Further, transcriptional coactivator

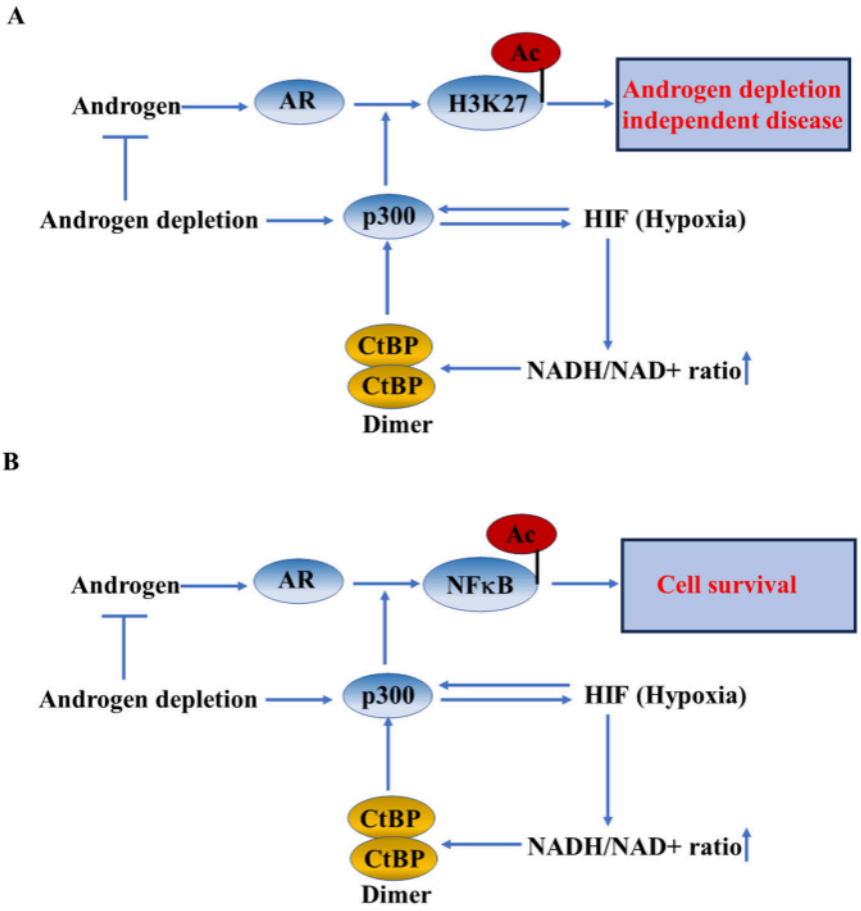

Fig. 4. The dimeric form of CtBP and p300 cause the progression of prostate cancer. (A) Hypoxia increases the NADH/NAD+ ratio. A higher NADH/NAD+ ratio in hypoxia produces the dimeric form of CtBP, which relieves the inhibition of p300 by the monomeric form of CtBP. p300 in turn activates HIF. The loop, thus formed, keeps the activity of p300 high. The higher p300 activity increases the activity of H3K27, causing androgen depletion-independent prostate cancer. (B) Hypoxia increases the NADH/NAD+ ratio. A higher NADH/NAD+ ratio in hypoxia produces the dimeric form of CtBP, which relieves the inhibition of p300 by the monomeric form of CtBP. p300 in turn activates HIF. The loop, thus formed, keeps the activity of p300 high. The higher p300 activity increases the activity of NFκB, causing survival of prostate cancer cells.

p300 is up-regulated in prostate cancer and is required for ADI activation of the AR (Heemers et al., 2007). Furthermore, p300 expression is associated with cell proliferation and predicts aggressive tumor features (Heemers et al., 2007) (Fig. 4A).

In prostate cancer, p300 causes the transcription of androgen receptor (AR)-responsive genes, even in the absence or presence of low levels of AR (Santer et al., 2011). Consistently, the depletion of p300 caused an increase in caspase-dependent apoptosis in androgen-dependent and castration-resistant prostate cancer cells (Santer et al., 2011). The increase in apoptosis was mediated by the inhibition of AR function and a decrease of the p65 subunit of NFκB (Santer et al., 2011). Further, cell invasion decreased upon p300 depletion and was accompanied by lower expression of matrix metalloproteinase MMP-2 and MMP-9 (Santer et al., 2011). Thus, p300 causes cell survival through NFκB and invasion through MMP-2/9 in prostate cancer (Fig. 4B).

Interestingly, p300 expression in prostate cancer cells is subject to androgen regulation (Heemers et al., 2007). In this context, the addition of synthetic and natural androgens decreased the expression of p300 and the reduction in p300 expression depends completely on the presence of a functional AR (Heemers et al., 2007). Conversely, androgen deprivation increased the p300 expression (Heemers et al., 2007). The increased p300 expression upon androgen deprivation is crucial for prostate cancer cell proliferation, causing G_1-S and G_2-M cell cycle transitions (Heemers et al., 2007). Thus, androgen deprivation increases the expression of p300, which causes antiandrogen therapy resistance in prostate cancer (Figs. 4A and B).

In addition, p300 is a coactivator of cyclooxygenase-2 (COX-2) promoter (Xiao et al., 2011; Deng et al., 2004). COX-2 is expressed in 40 % of invasive breast cancers (Singh et al., 2007). Its overexpression is involved in increased mobility, invasion, metastasis, and angiogenesis of many cancers (Singh et al., 2007; Singh et al., 2005; Liu et al., 2000). Further, in breast cancer, its overexpression is a prognostic marker for Stage III and correlates with other features e.g., negative estrogen receptor (ER), high Ki67, luminal B and triple-negative tumors, Bcl2 negativity, and p53 overexpression (Kim et al., 2012).

p300 associates with p65 NFκB in the nucleus, causing drug resistance in cancer. In breast cancer, nuclear translocation of p65NFκB and its association with p300 causes transcription of Bcl-2, conferring drug resistance to the cells (Sen et al., 2011). Further, the transactivation activity of hypoxia-inducible factors (HIFs) requires the recruitment of p300 by HIF-1α and HIF-2α that undergo oxygen-dependent degradation (Sang et al., 2003).

Therefore, p300, which is activated by the dimeric CtBP in solid tumors due to the increased NADH/NAD+ ratio in hypoxia, is important in cancer progression and p300 degradation causes apoptosis (Poizat et al., 2005) in cancer cells. On the other hand, in normal cells, the inhibition of p300 by monomeric CtBP causes global instability, which may cause carcinogenesis. Thus, p300 works as a double-edged sword.

5. p300 has the opposite effects on cell proliferation in normal vs. cancer cells

In normal cells, p300 reduces proliferation (Sandberg et al., 2005). In normal cells, p300 increases the acetylation and the amount of p53, leading to an increase in p21, inhibition of the cell cycle, reduction in cell proliferation, and increase in differentiation (Wong et al., 2010). Further, in normal cells, as a protective mechanism, an increase in cell cycling also increases apoptosis. Consistently, a decrease in p300 increases both proliferation and apoptosis in normal cells (Poizat et al., 2005; Sandberg et al., 2005). In contrast, in cancer cells, p300 increases proliferation (Inagaki et al., 2016; Debes et al., 2003). The higher p300 activity is achieved through hypoxia, which increases the NADH/NAD+ ratio (Lim et al., 2010), decreasing the monomeric CtBP and relieving the monomeric CtBP-induced inhibition of p300 activity.

6. Hypoxia promotes the stability of cancer cells by increasing the dimeric form of CtBP

The oxygen level of a cell's microenvironment is inversely correlated with the NADH concentration within the cell (Zhang et al., 2006). Thus, the hypoxic conditions increase the NADH/NAD+ ratio and dimerization of CtBP in the cell, re-establishing homeostasis and stability (Jaiswal and Singh, 2023). Therefore, cells in a solid tumor mask their underlying instability by increasing the NADH/NAD+ ratio through hypoxia, gaining resistance to drugs that target cancer cells' instability. Interestingly in this context, p300, which is activated in hypoxia by the dimeric CtBP (Figs. 4A, B), promotes transcriptional activity of HIF1 (Bárdos and Ashcroft, 2005). Thus, p300 and HIF form a self-sustaining positive feedback loop. Further, the increase in p300 activity under hypoxia increases the stability of cancer cells through the increase in activities of p53 and NFκB by p300.

7. Drugs that increase NADH/NAD+ ratio

Since a decrease in the NADH/NAD+ ratio causes genomic instability through the monomeric form of CtBP, contributing to heterogeneity in cancer, increasing the NADH/NAD+ ratio in combination therapy for the treatment of cancer may be promising. In this context, isoflavan analogs ME-143 and ME-344 inhibit mitochondrial oxidative phosphorylation complex I (NADH: ubiquinone oxidoreductase) and exhibit anti-cancer effects (Lim et al., 2015). Further, NADH oxidase activity at the external surface of plasma membrane vesicles from tumor cells has been observed (Morré et al., 1997). This activity is inhibited by the antitumor drug, Adriamycin (Morré et al., 1997). Furthermore, a 34-kDa circulating form of drug-responsive hydroquinone (NADH) oxidase was found in the sera of cancer patients that was absent from the sera of healthy volunteers (Cho et al., 2002). The antitumor drug-responsive NADH oxidase represents the first reported cell surface change universally associated with all forms of human cancer (Cho et al., 2002; Morré and Reust, 1997). Further, a monoclonal antibody (mAb) 12.1 that inhibited the NADH oxidase activity was developed (Cho et al., 2002). Similarly, oxaliplatin, which belongs to the platinum-based drug family (Chen et al., 2017), inhibited the tumor-associated NADH oxidase (tNOX) and increased the NADH/NAD+ ratio in the gastric cancer cell lines (Chen et al., 2017). On the other hand, a first-in-class small molecule, DX2-201, that inhibits NADH/Ubiquinone Oxidoreductase Core Subunit S7 (NDUFS7) has been discovered (Xu et al., 2023). DX2–201 suppresses the proliferation of several cell lines, and a metabolically stable analog, DX3-213B, showed significant efficacy in a syngeneic model of pancreatic cancer (Xu et al., 2023). DX2–201 showed synergy with multiple metabolic modulators, select OXPHOS inhibitors, and PARP inhibitors (Xu et al., 2023).

8. Conclusion

Dimeric CtBP maintains homeostasis of important cellular processes in an NADH-dependent manner. In contrast, the monomeric CtBP causes global instability by inhibiting p300 (Fig. 5). p300 maintains genomic integrity through acetylation of histone H3 core domain lysine 56 (H3K56), which causes the packaging of newly replicated and repaired DNA into chromatin. Further, the monomeric CtBP inhibits p53, which is important in the DNA damage response. Furthermore, the monomeric CtBP inhibits the innate immune response by inhibiting NFκB through p300, which promotes NFκB activity by acetylating it. The dysfunctional resolution of the innate immune response causes the propagation of neoantigens, which are important in carcinogenesis (Fig. 5). Thus, a switch in the metabolic state from a higher NADH/NAD+ ratio to a lower NADH/NAD+ ratio, generating the monomeric form of CtBP from the dimeric form, may cause carcinogenesis (Fig. 5). Notably, NADH oxidase is the first reported cell surface change universally associated with all forms of human cancer (Cho et al., 2002; Morré and Reust,

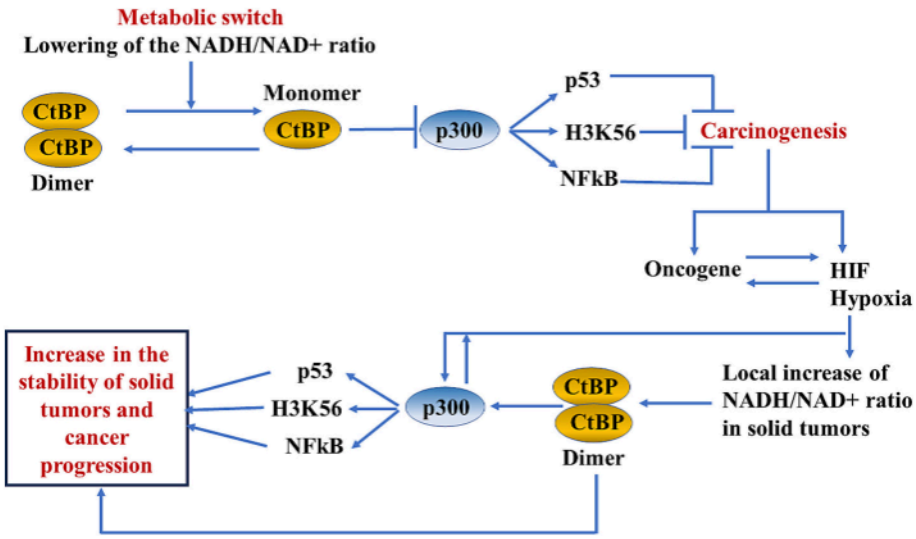

Fig. 5. The monomeric form of CtBP causes carcinogenesis while the dimeric form causes cancer progression. A lowering of the NADH/NAD+ ratio produces the monomeric form of CtBP, which inhibits p300. The inhibition of p300 inhibits p53, H3K56, and NFκB, causing carcinogenesis. Carcinogenesis may activate oncogenes through genomic instability. Oncogene activation and HIF are linked through a positive feedback loop. Hypoxia increases the NADH/NAD+ ratio in solid tumors, producing the dimeric form of CtBP, which increases the p300 activity. Moreover, HIF directly increases the activity of p300. The higher p300 activity in solid tumors increases the stability of tumors and causes the progression of cancer through p53, H3K56, and NFκB. Thus, p300 works as a double-edged sword: first, its inhibition by the monomeric form of CtBP causes carcinogenesis. Then, its higher activity in solid tumors due to the formation of the dimeric form of CtBP in hypoxia causes cancer progression.

1997).

The instability caused by the monomeric CtBP, leading to carcinogenesis, also creates vulnerability for cancer. Cancer masks this vulnerability through hypoxia, which locally increases the NADH/NAD+ ratio (Fig. 5), increasing the concentration of the dimeric form of CtBP and reducing the monomeric form. This also increases the activity of p300, which promotes important mitogenic and invasive properties of cancer cells in a hypoxic environment (Fig. 5).

p300, activated due to hypoxia, increases the stability of cancer cells through p53, H3K56, and NFκB (Fig. 5). Further, The transactivation activity of HIF requires the recruitment of p300 by HIF-1α and HIF-2α that undergo oxygen-dependent degradation (Sang et al., 2003). Thus, hypoxia increases the stability of cancer cells by locally increasing the NADH/NAD+ ratio, converting the monomeric form of CtBP to the dimeric form, increasing the activity of p300, and forming a self-sustaining positive feedback loop between HIF and p300 (Fig. 5).

The loop involving HIF (Hypoxia)-NADH/NAD+ ratio-dimeric CtBP-p300-HIF (Fig. 4A) may cycle in a self-sustaining manner, increasing each component of the loop. This autonomous cycling of the loop increases the activity of p300, increasing the stability of cancer cells. However, the increase in NADH/NAD+ ratio under hypoxia may also induce p53, causing apoptosis (Birts et al., 2020), which is reduced with the help of the survival protein NFκB by the same loop (Fig. 4B). Thus, the presence of the above loops may contribute to the intransigence of cancer. Moreover, the overexpression of CtBP in cancer may further increase the stability of cancer through the dimeric form of CtBP, formed under a higher NADH/NAD+ ratio due to hypoxia in solid tumors.

Activation of reversible epithelial-to-mesenchymal transition (EMT) is critical for cancer metastasis (Tsai et al., 2012). EMT involves a group of related cellular programs, each of which confers certain mesenchymal traits on epithelial cells (Ye et al., 2017). Further, three major groups of transcription factors: the ZEB, Snail, and Twist families, orchestrate the full molecular reprogramming occurring during an EMT (Sánchez-Tilló et al., 2012). In this context, CtBP represses epithelial genes, permitting EMT (Grooteclaes et al., 2003), and ZEB orchestrates its repression activities through the dimeric corepressor CtBP.(Postigo and Dean, 1999). Further, hypoxia-inducible factor 1 alpha (HIF-1α) promotes EMT and metastasis through direct regulation of ZEB (Zhang et al., 2015). Furthermore, HIF-1α binds to the hypoxia response element localized in the ZEB2 promoter and induces the expression of ZEB2-natural antisense transcript, which is known to increase the efficiency of ZEB2 translation (Nakuluri et al., 2019a; Nakuluri et al., 2019b). Moreover, ZEB upregulates VEGF expression and causes abnormal angiogenesis in cancer (Liu et al., 2016). Thus, hypoxia not only promotes the stability of cancer cells through the local increase in the NADH/NAD+ ratio, causing the formation of the dimeric form of CtBP in solid tumors, but also causes cancer-related abnormal angiogenesis, EMT, and metastasis through the dimeric CtBP-ZEB corepressor complex.

In cancer treatment, reducing the intransigence through reduction of heterogeneity while decreasing the stability of solid tumors are two important goals. While the heterogeneity of cancer can be reduced by the increase in the NADH/NAD+ ratio in the human body, the stability of solid tumors can be decreased by a local decrease of the NADH/NAD+ ratio in the hypoxic environment of solid tumors. Thus, reducing the interstitial pressure and normalization of the abnormal blood and lymphatic vasculature, fibroblasts, immune cells, and extracellular matrix associated with tumor microenvironment (Jain, 2013)while treating the patient with a drug that increases the NADH/NAD+ ratio in the human body may be a promising strategy for cancer treatment. Interestingly, the reduction of hypoxia may also decrease the expression of p300 (Tan et al., 2009), which increases the stability of solid tumors.

CRediT authorship contribution statement

Saumya Shukla: Resources, Methodology, Formal analysis. **Raghvendra Singh:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

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

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