Review

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A Review of Research on the Mechanism of Tumor Regulation by N-Acetyltransferase 10

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N-acetyltransferase 10 (NAT10) is an important acetyltransferase that regulates telomerase activity and participates in DNA damage reactions, ribosomal RNA (rRNA) transcriptional activation, cell division, microtubule acetylation, and other important cellular processes. Abnormalities in the expression or distribution of NAT10 result in diseases such as Hutchinson-Gilford progeria syndrome (HGPS) and various tumors, with serious consequences. Remodelin, an inhibitor of NAT10, delays HGPS progression; many studies have been conducted on its role in tumor therapy. A major breakthrough in the study of NAT10 was the discovery of mRNA N4-acetylcytidine (ac4C) modification, which can increase mRNA stability and translation efficiency significantly. In addition, NAT10 modifies the mRNA of ac4C, which is associated with tumor development. Here, we present a review of pertinent studies focusing on NAT10, particularly its role in cancer, to provide researchers with a concise and informative summary of the current state of knowledge about this topic. The conclusions drawn from this review could provide a new direction for tumor treatment.

Keywords: N-acetyltransferase 10; Hutchinson-Gilford progeria syndrome; tumor; remodelin; N4-acetylcytidine

Introduction

N-acetyltransferase 10 (NAT10), previously known as human N-acetyltransferase-like protein (hALP), belongs to the GCN5-related N-acetyltransferase family. According to the initial study, it triggers the activity of telomerase by upregulating human telomerase reverse transcriptase (hTERT) via its promoter [1]. NAT10 is located in the nucleolus and consists of 1025 amino acids with an acetyltransferase domain and a lysine-rich carboxyl terminus [2]. Aside from regulating telomerase activity, NAT10 also plays important roles in DNA damage reactions, ribosomal RNA (rRNA) transcriptional activation, cell division, and microtubule acetylation [3–6]. Studies have shown that NAT10 dysfunction plays a critical role in a variety of tumors, including melanoma, breast cancer, laryngeal cancer, colorectal cancer (CRC), hepatocellular carcinoma (HCC), and gastric cancer (GC) [7–15]. NAT10 is upregulated in most tumors, contributing to their malignant behavior [16]. In addition to its role in neoplastic diseases, NAT10 is also involved in the occurrence of non-neoplastic diseases, among which Hutchinson-Gilford progeria syndrome (HGPS) is the most well-known [17]. A follow-up of a patient with HGPS revealed signs of progressive premature aging, with the patient eventually dying of cardiovascular disease [17,18].

RNA N4-acetylcytidine (ac4C) refers to the acetylation of the cytosine N^4 position on RNA; it constitutes a highly conserved post-transcriptional modification (shown in Fig. 1A). This process is completed by the action of NAT10 [19,20]. It was previously believed that ac4C only exists in rRNA and tRNA, where it plays a crucial role (shown in Fig. 1B). For example, NAT10 participates in rRNA processing mainly by acetylating rRNA [3]. Ac4C facilitates the folding of tRNA tertiary structures during protein synthesis and aids in correct codon identification [21]. Nevertheless, recent research suggests that ac4C is also present in mRNA (shown in Fig. 1B) and that NAT10 can enhance its stability and translation efficiency with the help of mRNA ac4C [22]. NAT10 also promotes tumor metastasis via the ac4C-mediated modification of mRNA [15]. The discovery of mRNA ac4C is a major breakthrough in the study of NAT10, opening up new avenues to understanding transcriptomics and providing a new direction for medical research, particularly in oncology.

NAT10 is Involved in Cellular Processes

Ribosomes are composed of ribosomal rRNA and ribosomal proteins (RPs). Ribosomal ribonucleic acid (rRNA) production requires RNA polymerase I to produce the 47S precursor rRNA (pre-rRNA), which is further processed into 18S, 5.8S, and 28S rRNAs. In this process, the upstream binding factor (UBF) plays an important role in RNA polymerase I transcription as part of the pre-initiation

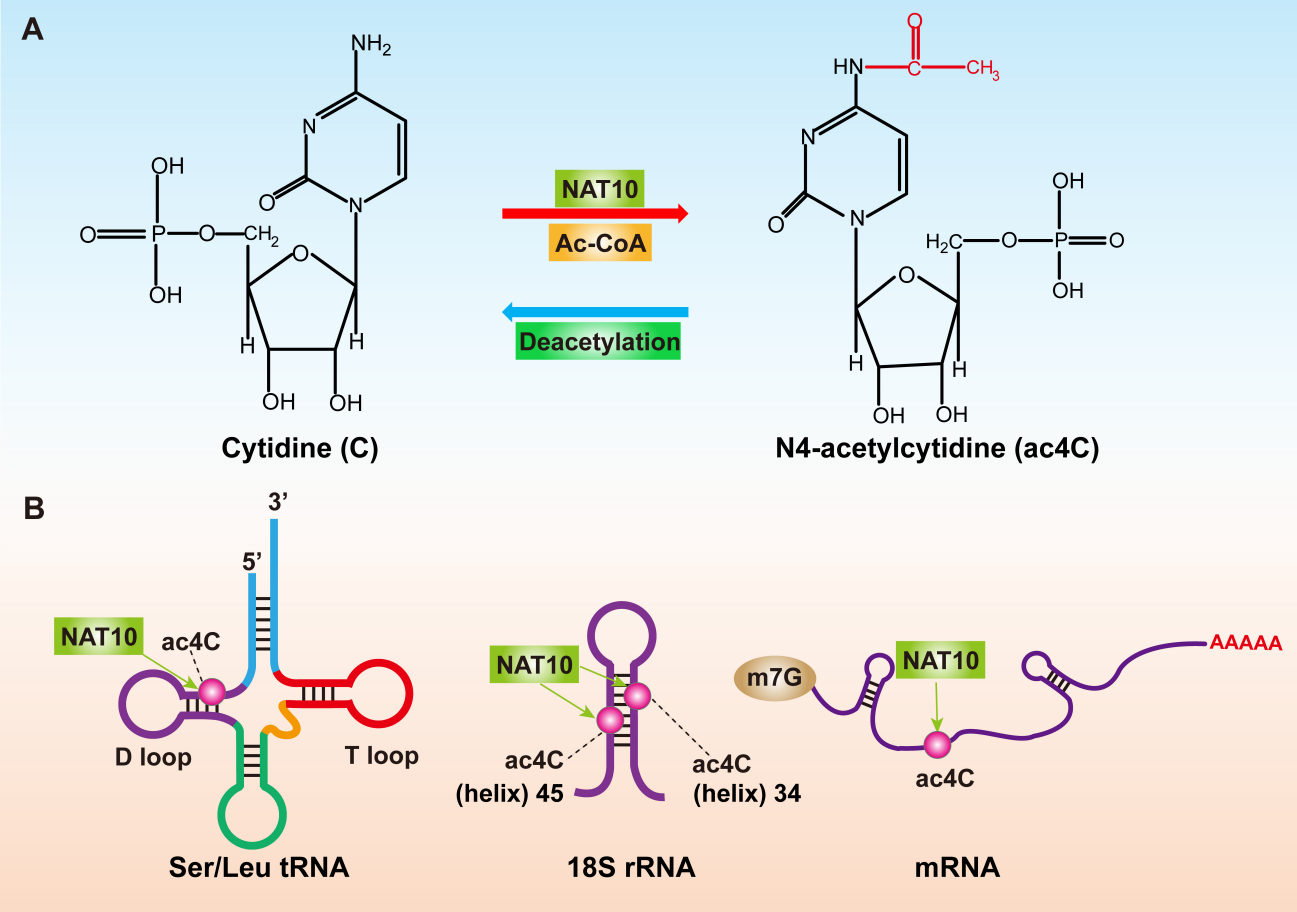

Fig. 1. RNA acetylation. (A) Chemical structure of N4-acetylcytidine (ac4C) and catalytic activity of N-acetyltransferase 10 (NAT10). (B) The position of RNA acetylation in human cells. The figure was drawn with Adobe Illustrator software (version 25.0, SAN Jose, CA, USA).

complex (PIC) [23–25]. The transcriptional activity of the UBF is regulated by its phosphorylation and acetylation [26]. UBF acetylation leads to the recruitment of PAF53, facilitating the assembly of the PIC and enhancing rRNA transcription [26,27]. However, NAT10 can bind to and acetylate the UBF and then activate RNA polymerase I to participate in the transcription of rRNA [28]. However, this function requires autoacetylation, i.e., lysine acetylation at NAT10 K426. Despite the accompanying mutation, NAT10 can still bind to UBF but cannot acetylate UBF or recruit RNA polymerase I to rDNA, leading to the inhibition of rRNA transcription [29]. NAT10 participates not only in the transcription of rRNA through autoacetylation but also in rRNA processing through rRNA acetylation [3,30].

Furthermore, NAT10 participates in the regulation of the cell cycle. The distribution of NAT10 changes dynamically at each mitotic stage. The intermitotic stage is mainly distributed in the nucleolus, whereas the mitotic stage is distributed in the midbody. NAT10 localized in the midbody can acetylate α-tubulin to increase its stability [16]. The study has shown that NAT10-knockout can cause nucleolar assembly defects and reduced α-tubule acetylation levels, leading to cytokinetic failure and cell arrest at G2/M [16]. Additionally, NAT10 can control cytokinesis by acetylating tubulin [16].

Under normal conditions or in the case of DNA damage, NAT10 can maintain genome stability by stabilizing p53; however, the two mechanisms of action are different. In the former, NAT10 stabilizes p53 by degrading murine double minute 2 (Mdm2) via ubiquitination, whereas when DNA is damaged, NAT10 is transferred from the nucleolus to the nucleoplasm to acetylate p53 and activate p53 transcription to increase its stability [8]. DNA damage induces increased expression of NAT10, and ectopic expression of NAT10 contributes to the survival of cells [4].

NAT10 and mRNA Ac4C

RNA ac4C modification is a highly conserved post-transcriptional modification. This process is completed by NAT10; the discovery of mRNA ac4C represents a new breakthrough in NAT10 research. There are 163 post-transcriptional RNA modifications, including m6A [31]. Despite the numerous modifications and complex functions

of RNA, little is known about them, principally because of limitations in technology. These rare bases, such as ac4C, were first found in the anticodon of the bacterial $tRNA^{Met}$ in 1978 [32]; it was previously believed that they are mainly present in rRNA and tRNA [3,33,34] but not in mRNA. However, recent study has shown that ac4C is also present in mammalian mRNAs [22]. Modification of ac4C only involves writers (NAT10); in contrast, m6A modification also involves erasers and readers. None of these have been identified as yet. This indicates that NAT10 has both acetyltransferase and RNA-binding activities [3]. It was found that NAT10-knockout resulted in significantly decreased ac4C levels [22]. NAT10 enhances mRNA stability and translation efficiency through mRNA ac4C, thereby promoting the expression of target genes [22]. Tumor research has always been a hotspot in medical research; there has been a considerable increase in the number of studies focusing on the crucial role of post-transcriptional modification in tumors. Following that of m6A modification, the role of ac4C modification in tumors has attracted attention.

NAT10 and Tumors

Melanoma

In their study of B16-F10 melanoma cells, Oh *et al.* [11] found that gene silencing or inhibition of NAT10 expression caused melanin synthesis disorder by inhibiting the expression of microphthalmia-associated transcription factor (MITF) and its target genes, dopachrome tautomerase (*DCT*) and tyrosinase, within cells. Inhibition of NAT10 expression can cause the downregulation of MITF, leading to significant downregulation of proteins such as cyclin D1 and cyclin-dependent kinase 2 (CDK2), which promote the transition from the G1 to S phase, whereas endogenous factors, such as p21, which inhibits the transition from the G1 to S phase, were significantly upregulated. This indicates that NAT10 may block the cell cycle at the S stage through MITF/cyclin D1/CDK2/p21-mediated cell cycle progression, thereby inhibiting the proliferation of melanoma cells, and suggests that NAT10 plays a key role in promoting tumor growth in malignant melanomas. However, this study had a number of limitations. First, the number of experimental cells was too small to establish the universality of the results. Second, the mechanism of MITF regulation by NAT10 was not clear. Finally, the inhibitory effect of remodelin on tumor cells (IC50) was not verified.

Laryngeal Cancer

NAT10 also plays an important role in laryngeal cancer [13]. In this context, NAT10 is negatively regulated by Myc target 1 (MYCT1), which in turn is negatively regulated by cAMP-responsive element-binding protein (CREB). Thus, NAT10 is indirectly positively regulated by CREB. Compared to that in normal tissues, the protein expression of CREB in laryngeal cancer tissues was significantly increased, with higher expression observed in the tumor tissues of patients with lymph node metastasis. Furthermore, the CREB protein is associated with tumor differentiation and clinical stage. In Hep2 cells, elevated levels of CREB can facilitate its binding to the MYCT1 promoter and downregulate MYCT1, thereby increasing the expression of NAT10. In summary, CREB facilitates the metastasis of laryngeal cancer cells through the MYCT1/NAT10 axis. Nevertheless, this study also had some limitations. The number of cells was too small to establish the universality of the conclusion, and animal experiments were lacking. In this study, NAT10 was found to be a downstream protein in the pathway, which only explains its function in laryngeal cancer; further study is required to fully investigate its specific regulatory mechanism.

Breast Cancer

A recent study suggested that NAT10 is significantly upregulated in breast cancer tissue [35]. Whether *in vivo* or *in vitro*, NAT10 reacts with MORC family CW-type zinc finger 2 (MORC2) and acetylates its lysine residue at the K767 site, whereas sirtuin 2 (SIRT2) antagonizes NAT10 and deacetylates MORC2. When breast cancer cells were treated with DNA-damaging drugs, MORC2 acetylation was upregulated; this process was mediated by NAT10 but was independent of SIRT2 activity. After the use of such drugs, NAT10 is transferred from the nucleolus to the nucleoplasm, which enhances the effect of MORC. MORC2, acetylated by NAT10, binds to histone H3 phosphorylation at threonine 11 (H3T11P), resulting in a reduction in the expression of H3T11P and further inhibition of CDK1 and cyclin B1 transcription, which leads to the arrest of breast cancer cells in the G2 phase and increased resistance to DNA-damaging drugs. These observations indicate that NAT10 could be a potential target for treating breast cancer. This study is a good illustration of the functional role and mechanism of NAT10 in breast cancer; further validation through *in vivo* experiments would enhance the credibility of these findings. Human THUMP domain protein 1 (THUMPD1) is a specific adaptor protein that regulates tRNA acetylation by interacting with NAT10 [34]. THUMPD1 reduces E-cadherin production and promotes the invasion and migration of breast cancer cells via the AKT-GSK3-Snail pathway. THUMPD1 may promote tumor invasion via two mechanisms—one involves synergy with NAT10, while the other operates as a downstream factor of NAT10 [36]. However, the role and regulatory mechanism of NAT10 in breast cancer remain speculative and require validation through specific experiments.

HCC

NAT10 expression is increased in HCC cells, with higher expression levels observed in mesenchymal cells than in epithelial HCC cells; knocking down NAT10 can inhibit the invasive abilities of HCC cells [7]. However, this

study does not present any clinically relevant information about NAT10, there is a lack of in vivo validation, and more importantly, the mechanism of action of NAT10 remains understudied. Li *et al*. [37] found that NAT10 expression was increased in HCC tumor tissues and was correlated with the prognoses of patients with HCC. NAT10 increases the stability of mutant p53 and promotes the proliferation of p53 mutant HCC cells by antagonizing the effects of Mdm2. However, similar to other studies, this study also lacked *in vivo* validation. NAT10 is a nucleolar acetyltransferase that enhances the occurrence of tumors when transferred to the nucleoplasm, cytoplasm, and cell membrane; additionally, its location in terms of distribution is related to the survival of patients. It has been shown that NAT10 expression in HCC tissues significantly increases at both the protein and mRNA levels, and the distribution of NAT10 also changes compared with that in normal para-carcinoma tissues [9]. In adjacent tissues, NAT10 was mainly distributed in the nucleolus, whereas it was mainly found in the nucleoplasm in tumor tissues. Moreover, NAT10 was distributed in the cell membrane in some patients, and the degree of tumor differentiation in these patients was poor. Another study also reported that NAT10 in the cell membrane and cytoplasm could promote the acetylation of α-tubulin and increase the stability of the tubules, thus promoting the migration of HCC cells [38]. Compared to those with nuclear NAT10, patients with cytoplasmic NAT10 had poor prognoses, whereas those with plasma membrane NAT10 had the worst prognoses. Compared to other studies, this study, in addition to showing that NAT10 is associated with tumorigenesis, also demonstrated the relationship between the location of NAT10 distribution in cells and patient outcomes. Additionally, the study also showed that NAT10 promotes the invasion and migration of HCC cells by affecting the cytoskeleton. However, validation through *in vivo* experiments was lacking. NAT10-mediated ac4C modifications have also been reported in liver cancer [39]. The authors found that NAT10 can enhance the metastasis and apoptosis resistance of liver cancer cells in endoplasmic reticulum stress (ERS) and ERS states. In this mechanism, NAT10 increases the stability and expression of heat shock protein 90 alpha family class A member 1 (HSP90AA1) by upregulating the ac4C level of *HSP90AA1* mRNA, thereby promoting the metastasis of ERS-HCC cells and their resistance to levatinib. This study was the first to demonstrate the role of NAT10 in HCC through ac4C modification, enriching the understanding of HCC progression. However, the study lacked *in vivo* validation of HCC cell metastasis. To summarize, studies have investigated the role of NAT10 in the proliferation and metastasis of HCC, exploring various perspectives to verify its importance; however, they all lack *in vivo* validation.

CRC

There have been many studies on the role of NAT10 in CRC. Although the expression of NAT10 is increased in many cancers [16], it is reduced in CRC [8,12]. Compared with that in normal non-tumor tissues, NAT10 expression was found to be significantly reduced in CRC tissues. NAT10 can inhibit the proliferation of CRC cells. After knocking down NAT10, the proportion of G2/M phase cells increased, and the cell cycle of colorectal cancer was accelerated [8]. Mechanically, NAT10 regulated p53 activation through acetylation of p53 and ubiquitination of Mdm2, mediating CRC cell cycle regulation and apoptosis. Unfortunately, there were many limitations of this study. First, the expression of NAT10 in CRC cells was not verified. Second, no experiments were conducted on the overexpression of NAT10 in CRC cells; additionally, animal studies were lacking. Third, although the expression of NAT10 in tumors was verified, the correlation between the expression of NAT10 and the clinicopathology of patients was not analyzed. In CRC, NAT10 was found to be negatively correlated with miR-6716-5p [12]. In patients with CRC, especially those with liver metastases, the expression of miR-6716-5p was increased. By binding to the 3′-UTR of *NAT10* mRNA, the increased miR-6716-5p expression led to a decline in the expression of NAT10, thus promoting the invasion and migration of CRC cells. This study demonstrated the regulation of NAT10 and E-cadherin by miR-6716-5p but did not verify the regulation of E-cadherin by NAT10. Additionally, there was no direct verification of the functionality of NAT10. The distribution as well as expression of NAT10 changed in CRC [10]. In adjacent normal tissues, NAT10 was mainly distributed in the nucleolus; in contrast, it was more diffuse in CRC tissues and only slightly distributed in the nucleolus but more so in the nucleoplasm, and more than half of the patients showed cytoplasmic and plasma membrane distribution. In CRC, NAT10 is regulated by glycogen synthase kinase-3β (GSK-3β). Inhibition of GSK-3β expression increases the stability and nuclear export of NAT10, and its redistribution changes the cytoskeleton and increases the motor ability of tumor cells, thereby promoting tumor metastasis. Consequently, NAT10 distribution in the cell membrane was mainly observed at the invasive leading edge of tumors, reflecting the depth of tumor invasion and metastasis and a worse prognosis. This study revealed the underlying mechanism whereby NAT10 promotes CRC metastasis in terms of subcellular distribution and cytoskeleton. Senescent cells secrete a variety of proinflammatory factors such as cytokines, proteases, and chemokines, which are collectively called the senescence-associated secretory phenotype (SASP). The SASP can affect the tumor microenvironment through either autocrine or paracrine signaling. NAT10 can regulate DNA replication by affecting the balance between histone acetylation and methylation and increasing the formation of micronuclei (MN), thereby activating the

SASP and promoting CRC progression [40]. This study not only shows that NAT10 can act within CRC cells but also demonstrates that NAT10 acts by influencing SASP secreted outside the cell. It was found that the levels of NAT10 and ac4C modification were significantly upregulated in CRC [41]. In addition, cell experiments have shown that NAT10 can inhibit the apoptosis of CRC cells, enhance the proliferation, invasion, and migration of CRC cells. *In vivo*, NAT10 promotes tumor growth and liver/lung metastasis. From a mechanistic perspective, NAT10 upregulates its mRNA ac4C modification by binding to the 3′-UTR region of kinesin family member 23 (*KIF23*) mRNA, thereby increasing the stability of *KIF23* mRNA. This causes KIF23 protein levels to rise, activating the Wnt/β-catenin pathway, and more β-catenin is transported to the nucleus, leading to CRC progression. This study explained the tumor-promoting effect of NAT10 in CRC from the perspective of ac4C, providing comprehensive insights that spanned both breadth and depth, and explained the mechanism underlying the role of NAT10 in CRC. The role of NAT10 has been extensively studied in various tumors, particularly CRC. Each research group has tried to interpret it from a different perspective and has reached different conclusions, some even contradictory. For example, some research groups showed that the expression of NAT10 in CRC tissues is increased, while others believed that it is reduced. Some studies suggest that NAT10 can affect the proliferation of CRC cells, while others indicate that NAT10 can only affect the invasion and migration of CRC cells but has no effect on cell proliferation. Some studies have shown that NAT10 can affect the proliferation and migration of CRC cells at the same time. Given these contradictory research conclusions, it is worth investigating whether these differences arise from variations in experimental cell types or other causes. Furthermore, many studies have only been validated *in vitro* and lack *in vivo* validation.

GC

GC is one of the most common malignant tumors of the digestive tract. The root causes of the difficulties related to treatment of GC are distant metastasis and deep tumor infiltration [42]. The study has found that NAT10 is widely upregulated in GC, which is clinically associated with a poor prognosis and lymph node metastasis. NAT10 promotes the invasion and migration of GC cells through its role in the epithelial-mesenchymal transition (EMT) [15]. NAT10-knockdown downregulated the mRNA and protein levels of vimentin (VIM) and matrix metalloproteinase-2 (MMP2) but did not affect the expression level of E-cadherin (CDH1). Overexpression of NAT10 upregulated the expression of VIM and MMP2 but did not affect the expression of CDH1. It is well known that VIM and MMP2 promote the regulation of EMT, while CDH1 inhibits the EMT. NAT10 promoted EMT in GC cells *in vitro*. In terms of mechanism, NAT10 can directly interact with collagen type V alpha 1 chain (*COL5A1*) mRNA to upregulate the ac4C modification level of *COL5A1* mRNA to maintain its stability. This study was the first to apply ac4C modification in tumor research, opening up a new avenue for investigating the mechanisms underlying tumor development.

Bladder Urothelial Carcinoma (BLCA)

In The Cancer Genome Atlas database, NAT10 in Bladder urothelial carcinoma (BLCA) tissues was significantly upregulated. Wang *et al*. [43] found that the expression of NAT10 in bladder cancer was increased, and patients with high expression of NAT10 were more likely to have lymph node metastasis than those with low NAT10 expression. In addition, they were more likely to progress to advanced stages (stages III + IV). This suggests that NAT10 may play a role in improving and estimating the prognosis of BLCA progression. NAT10 is associated with the proliferation, invasion, migration, and stem-like properties of BLCA cells. With respect to mechanism, NAT10 affects the stability and translation efficiency of B-cell lymphoma 9-like (*BCL9L*), SRY-box transcription factor 4 (*SOX4*), and serine/threonine kinase 1 (*AKT1*) mRNA by modifying ac4C in specific regions. In addition to affecting the progression of BLCA, it can also increase the resistance of BLCA cells to cisplatin by promoting DNA damage repair [44]. The mechanism involves cisplatin-mediated induction of the activation of NFκB signaling, which promotes the transcription of NAT10, which in turn recruits heterogeneous nuclear ribonucleoprotein Q (HNRNPQ) and thyroid hormone receptor-associated protein 3 (THRAP3) to desmoyokin (*AHNAK*) mRNA. A complex is formed, which is then modified with ac4C to enhance mRNA stability by preventing nuclease digestion.

Other Tumors

There are currently few studies on NAT10 expression in acute myeloid leukemia (AML). However, it has been reported that NAT10 expression is increased in patients with AML and that it is higher in patients with nucleophosmin 1 (NPM1) mutation than in those without, although there is no difference in the overall response (OR) between these groups [45]. NAT10 expression in patients in the OR group was significantly lower than that in the non-remission group. The progression-free survival and overall survival of patients with AML with higher NAT10 expression were also shorter, suggesting that NAT10 can serve as a prognostic marker for AML. Unfortunately, this study only analyzed clinical data and did not examine the functional role and specific mechanism of NAT10 in AML; hence, the role of NAT10 in AML needs to be further studied. In epithelial ovarian cancer, NAT10 affects the growth of tumor cells by participating in the formation of microtubules, thereby playing a role in the occurrence of tumors [46]. In colon and lung cancer cells, NAT10 mainly affects cell survival and apoptosis rather than migration and inva-

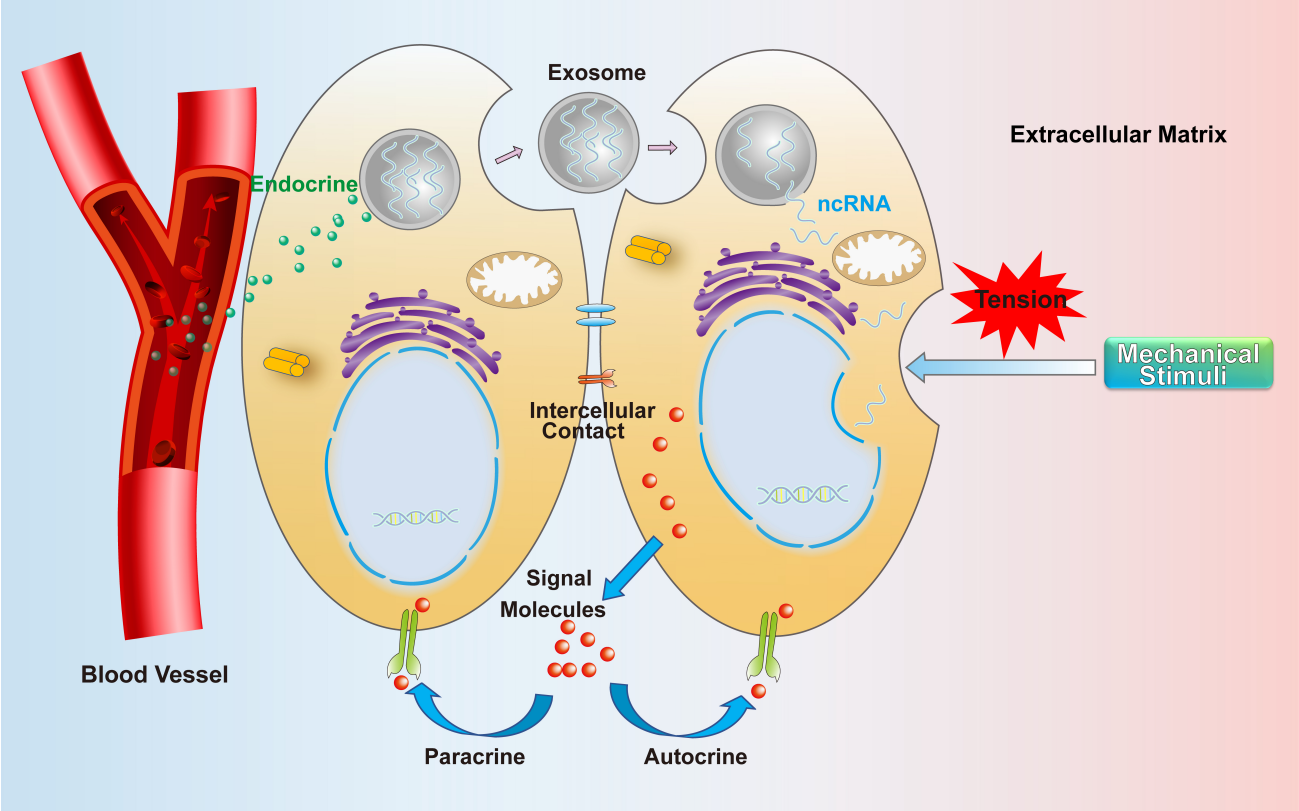

Fig. 2. The transmission of extracellular signals. The figure was drawn with Adobe Illustrator software (version 25.0, SAN Jose, CA, USA).

sion [47]. NAT10 recruits RelA/p65 to the myeloid cell leukemia 1 (MCL1) promoter region and promotes MCL1 transcription. After NAT10-knockdown, MCL1 is downregulated, the proliferation of colon and lung cancer cells as well as their sensitivity to 5-FU decreases, and apoptosis increases. NAT10-mediated ac4C modification is also associated with the tumor glucose metabolism and immunosuppression [48]. In cervical cancer (CCa), NAT10 expression is significantly elevated and is associated with a poor prognosis. HOXC8 activates NAT10 by binding to its promoter, thereby stimulating the ac4C modification of forkhead-box protein P1 (*FOXP1*) mRNA, improving its translation efficiency and inducing the expression of glucose transporter 4 (GLUT4) and ketohexokinase (KHK). In addition, the NAT10/ac4C/FOXP1 axis activity leads to increased glycolysis in CCa cells and a sustained increase in lactic acid secretion. The enrichment of lactic acid further enhances the immunosuppressive properties of tumor infiltrating regulatory T cells (Tregs). This study not only linked ac4C to the progression of CCa but also demonstrated the association of NAT10 with immunosuppression and glucose metabolism, fully illustrating the role of NAT10 in the progression of CCa.

NAT10 and HGPS

In addition to being transmitted through signal molecules and intercellular contact, extracellular signals can also be transmitted as mechanical stimuli from the extracellular space to the nucleus in the form of tension, which can then be transformed into biochemical signals that cause changes in cell structure and function (shown in Fig. 2) and even gene expression [49]. In addition to separating the nucleus from the cytoplasm, the nuclear membrane is crucial for maintaining the morphology and function of the nucleus. Changes in the nuclear membrane can lead to cell dysfunction, which manifests as various diseases (including tumors) at the macro level. Nuclear lamins are type V intermediate filament proteins that form a filament layer underneath the inner nuclear membrane, which is a key factor affecting the structure and function of the nuclear membrane [50,51]. Nuclear lamins can be classified into A- and B-type lamins based on their structural and biochemical characteristics, expression patterns, and behavior during mitosis [52]. In addition to unicellular organisms and plants, B-type lamins are found in all metazoan cells, whereas A-type lamins are only found in *Drosophila* and vertebrates, wherein they are mainly expressed in differentiated cells and are absent in embryonic stem cells [50,53–55]. Furthermore, A-type lamins mainly include lamins A and C, both of which are produced via the selective splicing of the

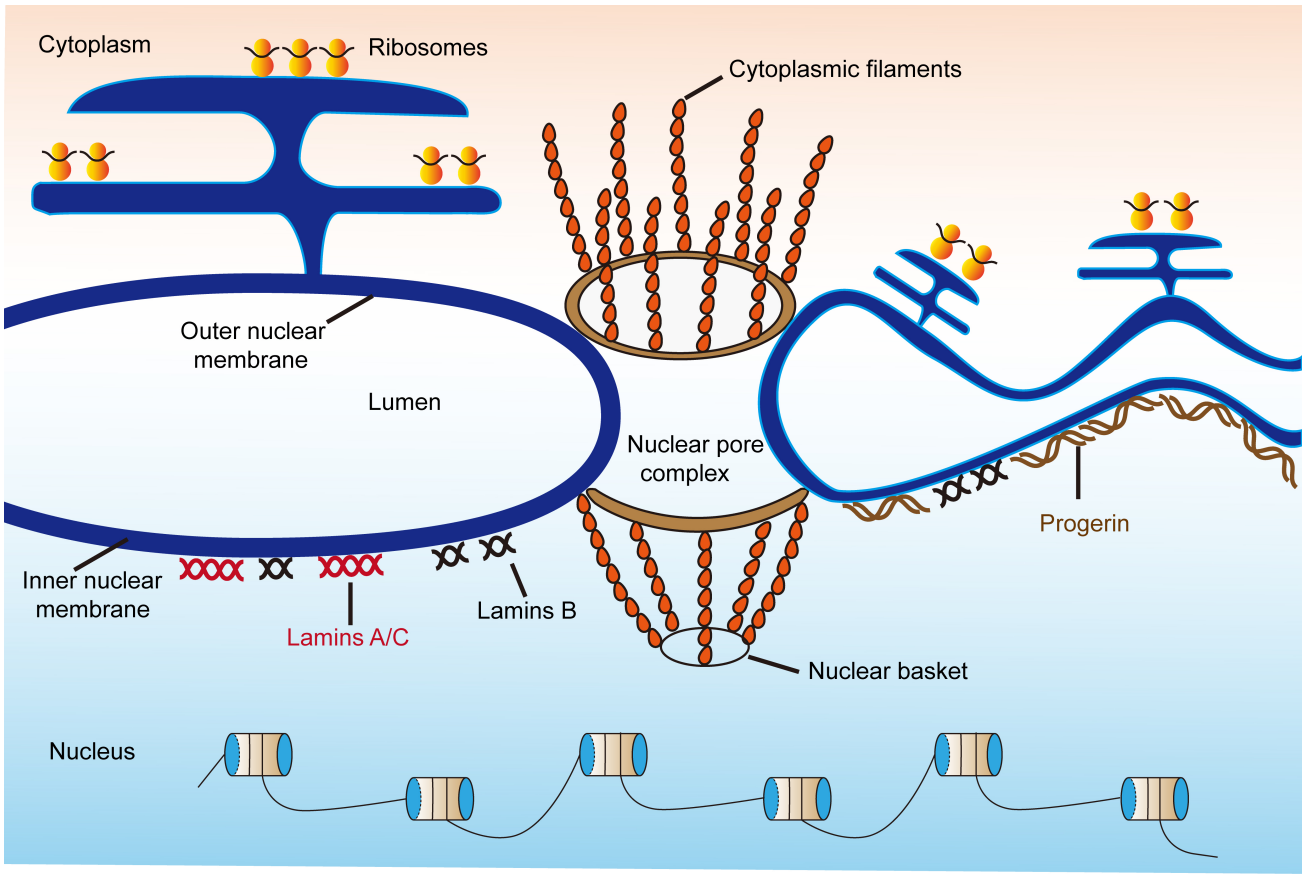

Fig. 3. Expression of progerin alters nuclear organization. The figure was drawn with Adobe Illustrator software (version 25.0, SAN Jose, CA, USA).

same gene, *LMNA*, whereas lamins B1 and B2, the two main subtypes of B-type lamins, are produced by *LMNB1* and *LMNB2* respectively [56–58]. Nuclear lamins not only play an important role in the transmission of intracellular and extracellular signals but also participate in various cellular processes such as cell differentiation, transcription, replication, and DNA damage repair [55,59–62]. When mutations occur in the genes that encode nuclear lamins, they can lead to severe medical conditions known as laminopathies, the most prominent of which is HGPS [62,63]. HGPS is a rare but fatal disease that is characterized by premature aging. It is caused by a mutation in the *LMNA* 11 exon, which causes the lamin A pre-mRNA to not splice properly, giving rise to an abnormal lamin A called progerin (shown in Fig. 3) [64,65]. In HGPS cells, progerin accumulates on the inner nuclear membrane, distorting the shape of the nucleus and chromatin, leading to increased genomic instability and rapid cell senescence [66,67]. Patients are characterized by extremely short stature, early hair loss, low weight, lipodystrophy, osteolysis, scleroderma, and facial features similar to those of the elderly. Cardiovascular injury was found to be the main cause of death in these patients [17,18]. Previous treatments with HGPS mainly targeted progerin and reduced its levels to improve the health status of patients; however, this mode of treatment was not very effective. The study has shown that NAT10 plays an important role in the occurrence of HGPS by influencing the shape of the nucleus and participating in microtubule recombination [68]. Inhibiting the activity of NAT10 in laminopathic cells can reduce the anchorage of microtubules to the centrosomes, thereby exerting external forces on the nuclear membrane, promoting the repair of the laminopathic cell nuclear shape, and enhancing the overall adaptability of the cells. Recent research has indicated that NAT10 is a potential new therapeutic target for HGPS. Chemical inhibition or gene knockout of NAT10 has been shown to delay weight loss and cardiovascular disease and to significantly enhance the health status of HGPS mouse models [69].

NAT10 Inhibitor: Remodelin

Remodelin is an inhibitor of NAT10 and can correct nuclear structure and chromatin reorganization to improve laminopathies [68]. It is also used to treat tumors and combat tumor resistance, reverse the EMT induced by doxorubicin, and weaken the resistance of breast cancer cells to doxorubicin [14]. Remodelin also plays a role in HCC [70]. Doxorubicin and hypoxia can induce EMT in HCC cells, thereby causing doxorubicin resistance, and NAT10 plays an important role in this process. After knockdown or treat-

Table 1. Clinical significance of NAT10 in tumors.

Cancer	Role	Change	Mechanism	Reference
Melanoma	Promotor	Up	NAT10 promotes cell proliferation through the MITF/cyclin D1/CDK2/p21 axis.	[11]
Laryngeal Cancer	Promotor	Up	CREB promotes laryngeal cancer cell migration via MYCT1/NAT10 axis.	[13]
Breast Cancer	Promotor	Up	NAT10 affects the proliferation of breast cancer cells by regulating the acetylation level of MORC2.	[35]
	Promotor	Up	NAT10 promotes invasion and migration of breast cancer cells by regulating the THUMPD1/AKT-GSK3-Snail/E-cadherin axis.	[36]
HCC	Promotor	Up	NAT10 promotes HCC cell metastasis by mediating EMT.	[7]
	Promotor	Up	NAT10 increases mutant p53 levels by counteracting Mdm2 action in HCC cells.	[37]
	Promotor	Up	NAT10 promotes the acetylation of α-tubulin and increases the stability of microtubules, thus promoting the migration and invasion of HCC cells.	[38]
	Promotor	Up	NAT10 promotes the metastasis of HCC cells by up-regulating the ac4C modification level of *HSP90AA1* mRNA.	[39]
GC	Promotor	Up	NAT10 promotes EMT in GC cells by up-regulating the ac4C modification level of *COL5A1* mRNA.	[15]
CRC	Suppressor	Down	NAT10 regulates p53 activation through acetylating p53 at K120 and ubiquitinating Mdm2.	[8]
	Suppressor	Down	miR-6716-5p promotes metastasis of CRC through downregulating NAT10 expression.	[12]
	Promotor	Up	GSK-3β influences the invasion and migration of CRC cells by regulating the stability and subcellular distribution of NAT10.	[10]
	Promotor	Up	NAT10 promotes CRC progression through increasing MN formation and SASP pathway activation.	[40]
	Promotor	Up	NAT10 regulates the Wnt/β-catenin signaling pathway to promote CRC progression via ac4C acetylation of *KIF23* mRNA.	[41]
BLCA	Promotor	Up	NAT10 affects the stability and translation efficiency of *BCL9L*, *SOX4* and *AKT1* mRNA by modifying ac4C.	[43]
	Promotor	Up	NAT10 promotes cisplatin resistance in BLCA cells by modifying *AHNAK* mRNA ac4C.	[44]
CCa	Promotor	Up	The NAT10/ac4C/FOXP1 axis promotes progression and facilitates immunosuppression in CCa.	[48]

MITF, microphthalmia-associated transcription factor; CREB, cAMP-responsive element-binding protein; MYCT1, Myc target 1; MORC2, MORC family CW-type zinc finger 2; THUMPD1, Human THUMP domain protein 1; HCC, hepatocellular carcinoma; EMT, epithelial-mesenchymal transition; Mdm2, murine double minute 2; *HSP90AA1*, heat shock protein 90 alpha family class A member 1; GC, gastric cancer; *COL5A1*, collagen type V alpha 1 chain; CRC, colorectal cancer; GSK-3β, glycogen synthase kinase-3β; SASP, senescence-associated secretory phenotype; ac4C, N4-acetylcytidine; KIF23, kinesin family member 23; BLCA, Bladder urothelial carcinoma; FOXP1, forkhead-box protein P1; CCa, cervical cancer; CDK2, cyclin-dependent kinase 2; MN, micronuclei; *BCL9L*, B-cell lymphoma 9-like; *SOX4*, SRY-box transcription factor 4; *AKT1*, serine/threonine kinase 1; *AHNAK*, desmoyokin.

ment with remodelin to inhibit NAT10 expression, EMT was reversed by increasing the sensitivity of HCC cells to doxorubicin. In a mouse xenograft model of HCC, remodelin delayed tumor growth and reduced the rate of tumor cell proliferation, thereby increasing the therapeutic effect of doxorubicin. In addition to directly inhibiting NAT10 expression to play an anti-tumor role, it also indirectly inhibits the expression of hypoxia-inducible factor-1alpha (HIF-1α) induced by hypoxia, inhibits angiogenesis, and plays an anti-inflammatory role [71].

Conclusion

NAT10 is an important nucleolar protein that not only regulates telomerase activity but also participates in DNA damage reactions, rRNA transcriptional activation, cell division, microtubule acetylation, and other cellular processes [3–6,38]. Abnormal expression or distribution of NAT10 causes diseases such as HGPS and various tumors [7–14,68], often with severe consequences. Although a large number of studies have been carried out on NAT10, these mainly focused on tRNA and rRNA; research on tu-

mors from the perspective of ac4C modification is limited. NAT10 plays a vital role in various tumor processes, including proliferation, metastasis, and drug resistance, which indicates that it may be used as a predictor and prognostic indicator and may represent a potential therapeutic target for diseases, particularly those related to tumors [22]. Although researchers have attempted to explain the mechanism of action of NAT10 on tumors from various perspectives, including NAT10 subcellular distribution, metabolism, immunity, and epigenetics (Table 1, Ref. [7,8,10–13,15,35–41,43,44,48]), many of the studies have certain limitations, the most common being the lack of *in vivo* validation of the findings and the small number of cells to establish the generalizability of the conclusions. In addition, different researchers have reached inconsistent conclusions regarding the same tumor, some of which were contradictory. The reasons for these differences should be explored in future studies. An increasing number of studies have also focused on revealing the role of NAT10 in tumors through the modification of mRNA ac4C. Remodelin is an effective NAT10 inhibitor that, while unable to cure HGPS, can delay the disease process and exhibit therapeutic effects. Its role in tumor treatment is under constant exploration and appears promising. However, many difficulties, such as the potential existence of writers other than NAT10 in ac4C and whether there are any erasers, remain to be addressed. Although some inhibitors targeting NAT10, other than remodelin, have been reported, this facet also requires further investigation. It appears likely that in the near future, we will be able to attain a deeper understanding of NAT10 and mRNA ac4C that will aid in elucidation of the role of mRNA ac4C in tumors, providing a new direction for tumor treatment.

Abbreviations

NAT10, N-acetyltransferase; HGPS, Hutchinson-Gilford progeria syndrome; ac4C, N4-acetylcytidine; hALP, human N-acetyltransferase-like protein; hTERT, human telomerase reverse transcriptase; GC, gastric cancer; RPs, ribosomal proteins; rRNA, ribosomal RNA; pre-rRNA, precursor rRNA; UBF, upstream binding factor; PIC, pre-initiation complex; MITF, microphthalmia-associated transcription factor; *DCT*, dopachrome tautomerase; MYCT1, Myc target 1; CREB, cAMP-responsive element-binding protein; MORC2, MORC family CW-type zinc finger 2; Mdm2, murine double minute 2; SIRT2, sirtuin 2; ERS, endoplasmic reticulum stress; *HSP90AA1*, heat shock protein 90 alpha family class A member 1; THUMPD1, Human THUMP domain protein 1; HCC, hepatocellular carcinoma; CRC, colorectal cancer; GSK-3β, glycogen synthase kinase-3β; SASP, senescence-associated secretory phenotype; KIF23, kinesin family member 23; EMT, epithelial-mesenchymal transition; VIM, vimentin; MMP2, matrix metalloproteinase-2; CDH1, E-cadherin; *COL5A1*, collagen type V alpha 1 chain; HNRNPQ, heterogeneous nuclear ribonucleoprotein Q; THRAP3, thyroid hormone receptor-associated protein 3; BLCA, Bladder urothelial carcinoma; AML, acute myeloid leukemia; MCL1, myeloid cell leukemia 1; NPM1, nucleophosmin 1; OR, overall response; FOXP1, forkhead-box protein P1; GLUT4, glucose transporter 4; KHK, ketohexokinase; CCa, cervical cancer; Tregs, regulatory T cells; HIF-1α, hypoxia-inducible factor-1alpha; CDK2, cyclin-dependent kinase 2; MN, micronuclei; *BCL9L*, B-cell lymphoma 9-like; *SOX4*, SRY-box transcription factor 4; *AKT1*, serine/threonine kinase 1; *AHNAK*, desmoyokin.

Availability of Data and Materials

Not applicable.

Author Contributions

Study Design and Supervision, WM, TC and YL; Formal analysis and Conceptualization, WM and YL; Manuscript Writing and Figure Design, TC; Manuscript Review, WM and YL; Funding Acquisition, WM; Final Approval of the Manuscript, all authors. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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