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Review

NF-κB nucleoli crosstalk in stress response and the regulation of apoptosis

Jingyu Chen[1], Lesley A Stark[2]*

[1] Edinburgh Cancer Research Centre, Institute of Genetics and Molecular Medicine (IGMM) University of Edinburgh; Scotland. Jc2037@cam.ed.ac
[2] Edinburgh Cancer Research Centre, Institute of Genetics and Molecular Medicine (IGMM) University of Edinburgh; Scotland. Lesley.Stark@IGMM.ed.ac
* Correspondence: Lesley.Stark@IGMM.ed.ac.uk Tel.: +44 131 651 8531

Abstract: Nucleoli are emerging as key sensors of cellular stress and regulators of the downstream consequences on proliferation, metabolism, senescence and apoptosis. NF-kB signalling is activated in response to a similar plethora of stresses, which leads to modulation of cell growth and death programs. Although these pathways are distinct, it is increasingly apparent that they converge at multiple levels. Exposure of cells to certain insults causes a specific type of nucleolar stress that is characterised by degradation of the PolI complex component, TIF-IA, and increased nucleolar size. Recent studies have shown that this atypical nucleolar stress lies upstream of cytosolic IkB degradation and NF-kB nuclear translocation. Under these stress conditions, the RelA component of NF-kB accumulates within functionally altered nucleoli to trigger a nucleophosmin dependent, apoptotic pathway. In this review, we will discuss these points of crosstalk and their relevance to the anti-tumour mechanism of aspirin and small molecule CDK4 inhibitors. We will also briefly discuss how NF-kB-nucleoli crosstalk may be more broadly relevant to the regulation of cellular homeostasis and how it may be exploited for therapeutic purpose.

Keywords: Nucleolus; RRN3; I-kappaB, stress, aspirin, CDK4, RelA, p65, cancer, neurodegenerative disorders

Introduction

NF-κB is the collective name for a family of inducible transcription factors that play a pivotal role in many cellular processes including immune response, inflammation, proliferation and apoptosis[1,2]. In addition to classical stimuli such as cytokines and pathogens, NF-κB is induced by a plethora of environmental and cytotoxic insults[3]. The mechanism by which these multiple insults induce the pathway, and what determines the downstream consequences on proliferation and apoptosis, has remained unclear. However, recent studies suggest that nucleoli play a role. An atypical nucleolar stress response pathway has been identified that lies upstream of NF-κB signalling[4]. It has also been shown that following induction, the RelA component of NF-κB can accumulate in nucleoli to trigger apoptotic pathways[5,6]. This nucleoli-NF-κB crosstalk is important for the anti-tumour effects of aspirin and small molecule CDK4 inhibitors, suggesting therapeutic relevance. In this review, we will discuss nucleolar stress and the various levels of convergence between this and the NF-κB pathway. We will also discuss the relevance to the anti-tumour mechanisms of aspirin, CDK4 inhibitors and other therapeutic agents. Finally, we will touch on other processes that may be regulated by this crosstalk.

1. P53 dependent and independent nucleolar stress

The nucleolus is a highly dynamic, membraneless, nuclear organelle[7]. It is primarily recognised as the hub of ribosome biogenesis. However, it also acts as a critical stress sensor and regulator of downstream responses to stress such as differentiation, cell cycle arrest, autophagy, DNA repair, senescence and apoptosis[8,9]. Perturbations in nucleolar function are associated with aging and many common and severe diseases including neurodegenerative disorders, progeria and cancer, highlighting its regulatory importance and its potential as a therapeutic target[9].

Ribosome biogenesis is the most energy consuming process in the cell and as such, is tightly linked to metabolic and proliferative activity. The rate limiting step is transcription of ribosomal DNA (rDNA) by the polymerase I (PolI) complex[10,11]. If cells are exposed to harmful conditions i.e nutrient starvation, cytotoxic agents, physical insults or viral infections, rDNA transcription is inhibited, the structure of the organelle is dramatically modified (see below) and a cascade of events is initiated that influences cell phenotype[7,12]. This process is broadly termed nucleolar stress and can take different forms, dependent on cell context and the nature of the insult[13,14]. Over 4500 proteins have been isolated from mammalian nucleoli and over half of these are involved in processes out with ribosome biogenesis[15-17]. It is thought to be the dynamic flux of these proteins between nucleoli and other cellular compartments in response to stress that is ultimately responsible for the downstream phenotypic effects[15,16].

The most characterised form of nucleolar stress is the MDM2-p53 axis, which is covered in depth in some excellent reviews[18-21]. Briefly, upon stress-mediated perturbation of ribosome biogenesis, ribosomal proteins (RP) L5 and 11 are released from nucleoli in a NEDD8/PICT1 dependent manner. These proteins then accumulate in the nucleoplasm and bind to the p53 E3 ligase, MDM2. This inhibits MDM2 activity preventing the ubiquitination and proteasomal degradation of p53. Consequently, p53 is stabilised and activates target genes involved in cell cycle arrest, senescence and apoptosis. While this pathway is clearly important, recent reports from yeast, flies and mammalian cells indicate that in some contexts, perturbation of ribosome biogenesis can modulate cell growth, death and autophagy in a p53 independent manner[13,14,22,23]. For example, Donati et al demonstrated that specific interference with the PolI factor, *POLR1A*, induces cell cycle arrest in mammalian cells in the absence of p53[24]. They proposed a model in which RPL11 binding to MDM2 blocks the MDM2-E2F interaction, thus causing E2F degradation and cell cycle arrest. Similarly, the Russo lab demonstrated that the apoptotic response to nucleolar stress can occur in the absence of functional p53[25]. In this study, RPL3 was overexpressed to mimic perturbations of ribosome biogenesis. This caused formation of an RpL3, Sp1, NPM complex at the p21 promoter and consequently, cell cycle arrest and apoptosis. In another example, it was shown that nucleolar stress destabilizes the proto-oncogene PIM1, causing increased levels of p27Kip1 and cell cycle arrest in p53-/- cells[26]. Proteomic studies indicate that hundreds of proteins that shuttle from the nucleolus in response to cytotoxic stimuli have p53 independent functions, supporting the notion of important p53 independent nucleolar stress pathways[15,16].

2. TIF-IA- NF-κB nucleolar stress

Like p53, NF-κB plays a critical role in maintaining cellular homeostasis under stress and emerging evidence indicates this transcription factor pathway also lies downstream of perturbed nucleolar function.

2.1 Stress activation of the NF-κB pathway

In mammalian cells there are five members in the NF-κB family namely, RelA (p65), RelB, c-Rel, p105/p50 (NF-κB1), and p100/p52 (NF-κB2)[27,28]. These proteins homo- and hetero-dimerize through their Rel homology domain to create a variety of transcription factor complexes (56). In resting cells, these complexes are retained in the cytoplasm by a family of IκB inhibitory proteins (IκB , IκB , IκB and Bcl-3). When the cell is exposed to a wide array of stimuli including inflammatory cytokines, bacterial pathogens, cytotoxic agents, nutrient deprivation, hypoxia and physical insult, IκB proteins are phosphorylated by inhibition of IκB (IKK) kinase (IKK1/IKK ,IKK2/ IKK /Nemo) complexes[27]. This phosphorylation targets IκB for ubiquitination and degradation by the 26S proteasome. NF-κB complexes are then free to translocate to the nucleus where they influence expression of numerous (>150) genes including those involved in inflammation, immune response, senescence, cell cycle and apoptosis[3].

Classic NF-κB stimuli such as tumour necrosis factor (TNF) and interleukin-1 (IL-1) induce rapid IKK activation/IκB degradation and the upstream pathway responsible for this rapid activation is very well documented[29,30]. In contrast, stress stimuli (including UV-C radiation, nutrient deprivation and chemopreventative/therapeutic agents) tend to activate the pathway with a much slower and delayed kinetic[3,31]. A number of mechanisms have been proposed for this delayed activation. For example Kato et al demonstrated that UV-C-mediated degradation of IκB is dependent upon a p38-CK2 axis[32] while Jiang et al demonstrated that phosphorylation of translation initiation factor 2α (EiF2) is required for activation of the NF-κB pathway by a variety of stresses[33,34]. More recently, it was shown that an atypical form of nucleolar stress, characterised by degradation of the PolI complex component, TIF-IA, lies upstream of NF-κB signalling in response to specific stress stimuli[4].

2.2 TIF-IA degradation -a novel form of nucleolar stress

TIF-IA, the mammalian homolog of yeast Rrn3p, plays a key role in the initiation of rDNA transcription as it binds both Pol I and the TBP-containing factor TIF-IB/SL1, thereby tethering PolI to rDNA and generating a functional transcription pre-initiation complex[10,11,35,36]. TIF-IA is also key in transducing environmental signals to the PolI transcriptional machinery[12,37]. If nutrient availability is altered or the cell is under stress, the phosphorylation status of TIF-IA is modulated by a complex network of kinases and phosphatases, which ultimately activate or inactivate the protein to fine tune the transcriptional output (Figure 1)[38]. Although TIF-IA is mainly known for its role in the nucleolus, the protein shuttles dynamically between this and other cellular compartments. Indeed, using a GFP-TIF-IA approach, Szymański et al found that 48% of the protein is present in the cytoplasm while only 7% is located in the nucleolus (although the concentration in the nucleolus is higher)[39]. The mechanisms that control the cellular localisation of TIF-IA are still unclear, but are known to be targeted by specific stresses[40]. It is also unclear if the protein plays a role in other

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compartments. What is clear is that the gene is an important regulator of cell proliferation and apoptosis. Genetic deletion in mice leads to embryonic lethality while deletion or depletion in mouse embryonic fibroblasts (MEFs), cancer and neuronal cells causes cell cycle arrest and apoptosis[41,42].

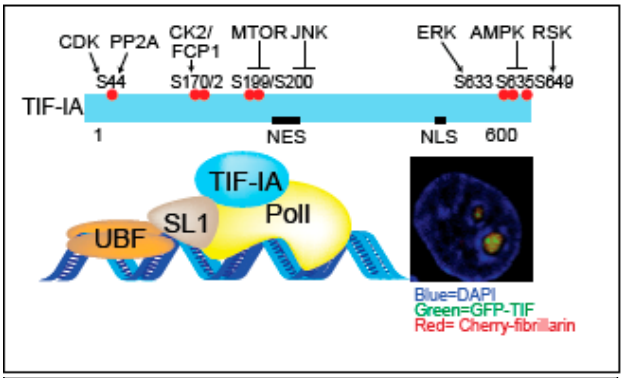

Figure 1: TIF-IA is targeted by multiple kinase and phosphatase pathways in response to cellular stress (Top). This controls the transcriptional activity of the pre-initiation complex, of which TIF-IA is a vital component (bottom). NES-nuclear export signal. NLS-nuclear localisation signal. Insert; Confocal image showing the localisation of GFP-TIF-IA in fibrillar centres of nucleoli and cherry-fibrillarin in the surrounding dense fibrillar component in fixed colorectal cancer cells. DAPI marks the DNA.

Given the considerable overlap in stresses that target TIF-IA/perturb ribosome biogenesis and those that activate NF-κB, our lab explored the connection. In doing so, we uncovered a novel pathway by which nucleolar function is altered by stress (Figure 2)[4]. We found that multiple stress stimuli, including aspirin, UV-C and the second messenger ceramide, not only alter the phosphorylation status of TIF-IA, but also induce degradation of the protein. This effect was not observed in response to TNF or the DNA damaging agent, camptothecin, indicating specificity. The mechanism by which TIF-IA is degraded in response to stress is complex and involves both proteasome and lysosomal pathways. It is dependent on de-phosphorylation of TIF-IA at Serine 44 and the PolI complex associated factors upstream binding factor (UBF) and p14ARF. It also lies downstream of CDK4 inhibition, which is a common response to stress stimuli of the NF-κB pathway.

As would be expected, stress-mediated degradation of TIF-IA was associated with inhibition of rDNA transcription. It was also associated with striking morphological changes to nucleolar structure and activation of the NF-κB pathway.

2.3 Nucleolar enlargement as a consequence of TIF-IA degradation

Nucleoli have a dynamic structure that varies considerably dependent on cell type, cell cycle phase and environmental conditions[7,43-45]. The organelle is divided into three sub-compartments namely; fibrillar centres (FC), dense fibrillar component (DFC) and granular component (GC). Transcription of rDNA takes place at the interface between FCs and DFCs while processing of pre-rRNA and assembly with ribosomal proteins takes place in the DFC and GC. Ribosomal DNA arrays are clustered in nucleolar organiser regions (NORs), which are present on the short arms of all five acrocentric chromosomes[46]. NORs show various levels of activity and while nucleoli form around transcriptionally active NORs, inactive arrays are extra-nucleolar, embedded in and contributing to the heterchromatin that surrounds the organelle[44]. Generation and maintenance of the tri-partite nucleolar substructure is dependent on transcription of rDNA in active NORs and liquid-liquid phase separation (LLPS) of nucleolar components[44,47]. If rDNA transcription is inhibited by

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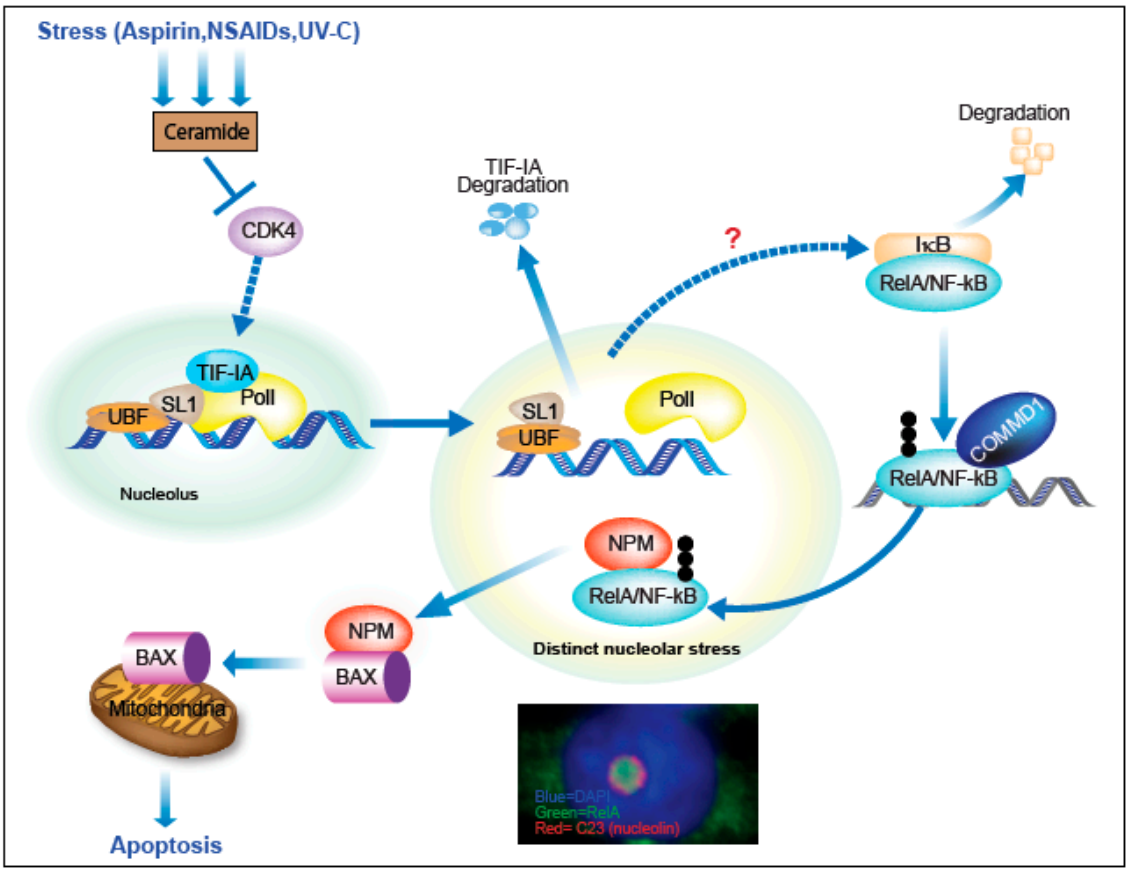

Figure 2-TIF-IA-NF-κB-nucleoli stress response pathway. When cells are exposed to a variety of specific stresses, ceramide is generated leading to inhibition of CDK4. This inhibition induces degradation of TIF-IA (in a manner dependent upon UBF and p14ARF), which in turn causes increased nucleolar size, gross changes in nucleolar morphology and degradation of IκB. IκB degradation allows RelA/NF-κB to translocate into the nucleus and recruit a COMMD1 dependent ubiquitin ligase complex. Ubiquitination of RelA by this specific complex targets the protein to nucleoli, where it binds nucleophosmin (NPM), causing this protein to relocate out of nucleoli to the cytoplasm, where it is free to bind BAX and transport BAX to the mitochondria to mediate apoptosis. ?- The link between altered nucleolar function and IκB degradation id unknown. Inset: Immunomicrograph showing enlarged segregated nucleoli and nucleolar accumulation of RelA in response to aspirin (5mM, 16h). DAPI depicts DNA.

cytostatic/cytotoxic stresses, this tripartite structure undergoes a rapid and dramatic rearrangement. The FC and DFC become segregated from the GC and form "caps" at the nucleolar periphery[43,45,48]. In most cases, this nucleolar segregation is associated with a significant reduction in the area of the organelle.

A role for TIF-IA in the maintenance of nucleolar structure was initially suggested by genetic deletion of the gene in MEFs, which caused loss of nucleolar morphology and a reduction in nucleolar size[41]. Stress-mediated inhibition of TIF-IA by targeted phosphorylation is also associated with decreased nucleolar size[12,40]. In contrast, we found that stress-mediated degradation of TIF-IA is paralleled by a striking increase in nucleolar size, alongside segregation of nucleolar components[4]

(Figure 2). This stress-mediated increase in nucleolar size was paralleled by inhibition of rRNA transcription and was blocked when TIF-IA degradation was blocked, indicating the two events are linked. Similar to these data, Fatyol et al found that the MG132 proteasome inhibitor induces a significant increase in nucleolar volume while inhibiting rRNA transcription and inducing morphological changes to nucleoli [49]. Interestingly, we have found that low dose MG132 causes TIF-IA degradation in a similar manner to stress (unpublished data). The NEDD8 inhibitor MLN4924 has also been shown to cause an increase in nucleolar size alongside nucleolar stress[50].

2.4 Activation of the NF-κB pathway as a consequence of TIF-IA degradation

The first evidence that NF-κB signalling may lie downstream of perturbation in nucleolar function came from experiments showing siRNA-mediated depletion of PolI complex components, (including TIF-IA) causes degradation of IκBα, S536 phosphorylation of RelA (a marker of activation), nuclear translocation of RelA, increased NF-κB transcriptional activity and increased transcription of NF-κB target genes[4]. Interestingly, this effect was not mimicked by the PolI inhibitors actinomycinD, CX5461 or BMH-21, suggesting that unlike p53 nucleolar stress response, activation of NF-κB signalling is not directly linked to inhibition of rDNA transcription. Kinetic studies revealed that stress-mediated degradation of TIF-IA preceded cytoplasmic activation of NF-κB suggesting a potential link. Indeed, it was found that blocking degradation of TIF-IA, using specific siRNAs and a dominant negative mutant, blocked the effects of specific stresses on the NF-κB pathway[4] (Figure 2). These data revealed a novel TIF-IA-NF-κB nucleolar stress axis.

The TIF-IA-NF-κB nucleolar stress response pathway was evident in multiple cell types and in tumours from colon cancer patients treated ex vivo with the chemopreventative agent aspirin (see below) indicating broad and *in vivo* relevance[4]. Multiple proteins that regulate the NF-κB pathway reside within nucleoli, which could account for this connection. Interestingly, CK2, which has previously been shown to be involved in UV-C-mediated activation of the NF-κB pathway[32], is bound to TIF-IA in the PolI complex [51] [32]. Similarly, phosphorylation of EiF2a in response to ER stress has been shown to both inhibit TIF-IA activity[52] and to activate NF-κB[33,34]. NIK (NF-κB inducing kinase), which acts upstream of the IkappaB kinase (IKK) complex, shuttles through nucleoli [53]. The ribosomal proteins L3 and S3 have also been shown to complex with IκB and modulate NF-κB activity [53-55].

2.5 TIF-IA-NF-κB nucleolar stress and the induction of apoptosis

Although stimulation of the NF-κB pathway is generally regarded as anti-apoptotic, in particular contexts, and especially in response to cellular stress, NF-κB acts to promote apoptosis[56,57]. Indeed, those stresses that stimulate the NF-κB pathway through TIF-IA degradation (eg aspirin, UV-C, ceramide) are known to require nuclear translocation of NF-κB for their pro-apoptotic activity[58-62]. In keeping with a pro-apoptotic role for the TIF-IA-NFκB pathway, it was found that blocking TIF-IA degradation not only blocked nuclear translocation of NF-κB/RelA in response to aspirin and CDK4 inhibition, but also blocked the apoptotic effects of the agents[4]. The mechanism by which stress-mediated nuclear translocation of NF-κB promotes apoptosis has been the subject of debate. However, recent studies indicate nucleolar sequestration of NF-κB proteins, particularly RelA, plays an important role[5].

3. Nucleolar sequestration of RelA and apoptosis

While some proteins are released from nucleoli under conditions of cell stress, others translocate to the organelle[63-65]. Indeed, nucleolar sequestration of transcription factors and regulatory proteins is now recognised as an important mechanism for controlling gene expression and maintaining cellular homeostasis. For example, NF-κB repressing factor has recently been shown to accumulate in nucleoli in response to heat stress, causing repression of rDNA transcription[66]. P53, LC3II and a variety of ubiquitinated proteins accumulate in nucleoli in response to proteasome inhibition[63,64,67,68], while exposure of cells to heat shock, hypoxia and acidosis causes accumulation of proteins with a specific nucleolar detention sequence (i.e., von Hippel-Lindau, DNA methyltransferase 1 (DNMT1) and the DNA polymerase subunit POLD1) in nucleolar foci [65,69]

When exploring the mechanisms by which nuclear translocation of NF-κB induces apoptosis, it was found that in response to specific pro-apoptotic stress stimuli (e.g., aspirin, serum deprivation and UV-C radiation), the RelA component of NF-κB translocates from the cytoplasm to the nucleoplasm and then to nucleoli, causing an accumulation of the protein in the organelle[5]. Nucleoplasmic to nucleolar translocation of RelA was found to be dependent upon an N-terminal nucleolar localization signal (NoLS). Using a dominant-negative mutant deleted for this motif, it was shown that nucleolar sequestration of RelA is causally involved in reduced basal NF-κB transcriptional activity and the induction of apoptosis (Figure 2)[5]. Since this initial study, nucleolar localisation of RelA has been observed in response to the NSAIDs sulindac, sulindac sulphone and indomethacin[61], the naturally occurring derivative of estradiol and antitumor agent, 2-methoxyestradiol (2ME2)[70]; a potent Trk inhibitor and anti-tumour agent, K252a[71]; expression of the homeobox transcription factor, Hox-A5[72], small molecule inhibitors of the CDK4 kinase[73,74] and the proteasome inhibitors MG132 and lactocystin[75]. In the majority of these studies, nucleolar sequestration of RelA is associated with a decrease in NF-κB-driven transcription. Furthermore, in all studies, it is associated with, or causally involved in, the induction of apoptosis. Nucleolar sequestration of p50 has also been reported. Dadsetan et al. demonstrated that the anti-TNF therapy, infliximab, induces "massive" nucleolar localisation of NF-κB/p50 in the hippocampus of rats with a portacaval shunt (PCS). They also demonstrated that this nucleolar localisation is associated with a decrease in transcription of NF-κB target genes and a reduction in neuroinflammation[76]. Subsequent studies have demonstrated that nucleolar translocation of RelA, is dependent upon ubiquitination, facilitated by the multifunctional protein, COMMD1[75,77].

It was originally assumed that nucleolar translocation of RelA mediates apoptosis because the protein is sequestered away from the promoters of anti-apoptotic genes. However, it is now known that once in the nucleolus, RelA triggers a cascade of events that actively promotes apoptosis (figure 2)[6]. That is, nucleolar RelA causes nucleophosmin (NPM)/B23 to relocate to the cytoplasm, bind BAX then transport BAX to the mitochondria to initiate apoptosis[6,78,79]. Indeed this, and a number of other studies have demonstrated a critical role for both BAX and NPM in the pro-apoptotic effects of stress stimuli of the NF-κB pathway[79]. Interestingly, stress stimuli such as aspirin and UV-C that utilise an NPM-BAX pathway to induce cell death also cause degradation of TIF-IA and atypical nucleolar stress, suggesting that these initial effects on nucleoli may prime cells for subsequent nucleolar accumulation of RelA and cytoplasmic translocation of NPM (Figure 2).

4. *Therapeutic relevance of nucleoli-NF-κB crosstalk.*

High levels of nucleolar activity are a hallmark of cancer and contribute to tumour growth by allowing de-regulated protein synthesis and uncontrolled activity of nucleolar cell growth/death pathways[9,80]. Changes in nucleolar morphology and function are also common in age related neurodegenerative disorders and increasing evidence suggests that this dysfunction contributes to disease progression, as well as the normal aging process[38,81-84]. Similarly, dysregulated NF-κB activity is common in cancer, neurodegenerative disorders and aging and contributes to the progression of these diseases/aging through promotion of a chronic inflammatory environment and modulation of genes that regulate cell growth/death[30,85,86]. Hence, both these pathways are attractive therapeutic targets.

One agent that has been found to trigger nucleoli-NF-κB crosstalk to target both these pathways simultaneously is aspirin[4,5]. Incontrovertible evidence from laboratory, clinical and epidemiological studies indicates that aspirin and related non-steroidal anti-inflammatory drugs (NSAIDs) have anti-neoplastic properties and considerable potential as cancer chemopreventative/therapeutic agents[87-90]. Epidemiological and experimental evidence also suggests aspirin use protects against neurological disorders such as Alzheimer's disease[90,91]. However, the agent cannot be recommended for preventative purpose due to its side effect profile.

In experiments aimed at understanding the mechanism of action of aspirin against colorectal cancer, it was found that the agent causes degradation of TIF-IA and inhibition of rRNA transcription[4]. Furthermore, it was shown that this degradation is causally linked to stimulation of the NF-κB pathway, nucleolar sequestration of RelA, repression of NF-κB activity and the induction of apoptosis (Figure 2)[4,5,92]. A link between TIF-IA degradation and NF-κB signaling was observed in multiple colon cancer cells lines, in cell lines derived from human pre-malignant intestinal lesions and in 4/7 human tumours treated *ex vivo* with low doses of the agent, suggesting pharmacological relevance[4]. In contrast to aspirin, the small molecule PolI inhibitor CX5461, which has shown considerable promise as an anti-cancer therapy and is currently in clinical trials for hematologic malignancies and triple negative breast cancer[80,93,94], had no effect on NF-κB signalling. Similarly, the small molecule PolI inhibitor, BMH-21, that is also showing promise as an anti-cancer agent[95], did not stimulate the NF-κB pathway. These data highlight the complexity of targeting nucleoli in cancer and the differential downstream consequences. They also reveal a novel and exciting mechanism of action of aspirin that warrants further investigation

Increased CDK4 activity is a common occurrence in cancer and contributes to cancer progression by allowing unrestricted proliferation of tumour cells[74,96,97]. In keeping with this critical role, small molecule CDK4 inhibitors (CDK4i) have shown considerable promise as anti-cancer agents and are currently in phase I/II clinical trials in a variety of malignancies. However, their precise mechanism of action is unclear. Previous studies from this lab had demonstrated that small molecule CDK4 inhibitors stimulate the NF-κB pathway and that this is essential for their pro-apoptotic activity against colorectal cancer cells[73]. More recently, Chen et al demonstrated that CDK4 inhibition causes degradation of TIF-IA, which is causally linked to stimulation of the NF-κB pathway and the induction of apoptosis (Figure 2)[4]. These data identify small molecule CDK4 inhibitors as another

class of agents that simultaneously inhibit rDNA transcription and NF-κB activity. Unlike aspirin affects, which are generally restricted to colon cancer cells[98], CDK4 inhibition caused degradation of TIF-IA-NF-κB stimulation in multiple cell types suggesting this crosstalk is may be broadly relevant for the maintenance of cellular homeostasis and the induction of apoptosis.

Summary

Both the nucleolus and the NF-κB pathway play a vital role in maintaining cellular homeostasis under conditions of stress. Both pathways are also implicated in aging and are dysfunctional in age related diseases such as cancer and neurodegenerative disorders. Emerging evidence indicates that there are multiple levels of crosstalk between these two pathways that are important for maintaining cellular homeostasis and regulating apoptosis. However, this evolving field is in its infancy and there are still a number of important questions to be answered. For example, in what contexts is this novel nucleolar stress response pathway active and does it contribute to the aetiology of age related disease. With regard to this point, it is interesting to note that both nucleoli and NF-κB are dysfunctional in senescence, a hallmark of aging. Further understanding of the mechanisms that regulate the stability of TIF-IA, and those that link altered TIF-IA levels to activation of the cytoplasmic NF-κB pathway, would allow development of small molecules that act to specifically and simultaneously target dysfunctional rDNA transcription and NF-κB activity. Similarly, identification of the apoptotic pathways triggered by RelA within this organelle would allow the development of RelA mimetics that mediate apoptosis by targeting dysfunctional nucleoli. Indeed, further understanding in this area could reveal a whole new class of targets to be exploited for therapeutic purposes. It could also reveal biomarkers of response for aspirin and CDK4 inhibitors, that have already been shown to utilise nucleolar-NF-κB crosstalk to act against cancer cells.

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Conflict of interest

There is no conflict of interest.

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