Transcription inhibition: A potential strategy for cancer therapeutics

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Abstract

Interference with transcription triggers a stress response leading to the induction of the tumour suppressor p53. If transcription is not restored within a certain time frame cells may undergo apoptosis in a p53-dependent and independent manner. The mechanisms by which blockage of transcription induces apoptosis may involve diminished levels of anti-apoptotic factors, inappropriate accumulation of proteins in the nucleus, accumulation of p53 at mitochondria or complications during replication. Many chemotherapeutic agents currently used in the clinic interfere with transcription and this interference may contribute to their anti-cancer activities. Future efforts should be directed towards exploring whether interference of transcription could be used as an anti-cancer therapeutic strategy.

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1. Introduction

The goal of most cancer therapeutic approaches is to kill off the cancer cells in tumours. Cancer cells can die by programmed cell death, such as apoptosis or autotrophy, or by necrosis or mitotic catastrophe [1]. One possible mechanism that makes tumour cells more sensitive to certain cancer therapeutic agents than normal tissues is that they have various defects in their DNA damage responses. For example, tumours often have mutations in genes that code for proteins involved in regulating cell cycle checkpoints such as p53 and the retinoblastoma protein. However, cancer cells often over express anti-apoptotic factors to suppress signals ordering the cells to undergo apoptosis [2]. This could lead to resistance of the tumour to anti-cancer treatment.

It has been shown that inhibition of transcription results in a time-dependent induction of apoptosis. Importantly, transformed cells appear to be more sensitive to disruption of RNA synthesis than corresponding normal cells [3]. It is possible that the acquired over expression of anti-apoptotic factors in cancer cells is dependent on ongoing transcription, so by inhibiting transcription, cancer cells will not be able to sustain high levels of these factors and may die. Thus, approaches to target transcription may be useful in cancer treatment. In this review we will discuss the transcription stress response, possible mechanisms of how transcription blockage results in cell death and how transcription may be a useful target for inactivation by anti-cancer therapies.

2. The transcription stress response

Our lab and others have shown that treatment of cells with agents that cause DNA damage and block transcription results in the nuclear accumulation and phosphory-
lation of p53 [4–6]. Furthermore, agents that do not cause DNA damage but arrest RNA polymerase II transcription, such as 5,6-dichloro-1-b-D-ribofuranosylbenzimidazole (DRB) [6,7], siRNA against RNA polymerase II antibodies [8] or nuclear microinjection of anti-RNA polymerase II antibodies [9], induce the nuclear accumulation of p53 suggesting that blockage of transcription is sufficient for the induction of p53. Interestingly, agents that block RNA polymerase II prior to entering the elongation phase accumulate p53 proteins that lacks phosphorylation at the ser15 site while agents that preferentially block the elongating form of RNA polymerase trigger the phosphorylation and accumulation of p53 [7–9].

RNA polymerases continuously traverse selected regions of the genome as they transcribe genes. This translocation machinery could also be used by cells as a “scanning mechanism” to monitor the DNA and to alert the cell if transcription has stalled at sites of DNA lesions [10]. In fact, a blocked RNA polymerase II transcription complex can recruit DNA repair proteins to help remove the blocking lesion and promote recovery of RNA synthesis through transcription-coupled repair (TCR) [11–13]. Furthermore, blockage of transcription is also linked to the induction of p53 [4–6,10,14] and apoptosis [5]. Through the coupling of p53 activation to blocked transcription the cell has a method to activate cell cycle checkpoints, apoptosis, or stimulate DNA repair to allow recovery of transcription. Recent results from our laboratory suggest that the ATR kinase may link blocked RNA polymerases with activation of p53 [9]. The transcription stress response may have evolved to aid cells in recognising DNA damage and to activate signal transduction pathways [10].

3. Blockage of transcription and apoptosis

Transcription is an essential process and its inhibition over a certain period of time will lead to apoptosis by both p53-dependent and p53-independent mechanisms. Following insult by UV-irradiation, the ability of cells to remove the transcription-blocking DNA lesions and recover RNA synthesis is crucial for the survival of the cells [5,15,16]. Here we will discuss four potential mechanisms by which blockage of transcription may result in apoptosis (Fig. 1).

3.1. Balance of anti- and pro-apoptotic factors

Experiments in our laboratory using the reversible transcription inhibitor DRB have suggested that there appears to be a “point of no return” following transcription inhibition at which reversal of the transcription blockage does not save the cells. We suggest that each cell has an “apoptotic clock” governing the time it takes to tip the balance of anti- and pro-apoptotic factors in favour of apoptosis. Evidence of an apoptotic clock also exists from experiments using UV light where full recovery of RNA synthesis within 6 h correlates with good survival while lack of recovery within 6 h correlates with significant induction of apoptosis [15,17–19].

The balance between cell survival and cell death is tightly regulated in all cells. Over expression of apoptosis-promoting factors such as bax or reduced expression of anti-apoptotic factors such as Bcl-2 or Mcl-1 can tip the balance in favour of apoptosis [20,21]. It is possible that inhibition of transcription preferentially reduces the level of anti-apoptotic factors relative to pro-apoptotic factors and that this is sufficient to tip the balance in favour of apoptosis. Following inhibition of transcription, the rate at which a particular protein is lost depends on the half-life of the mRNA and of the protein as well as the rate of translation. The average half-life of mRNAs is about 10 h but some transcripts are turned over in 10 min [22]. Protein half-life can range from minutes to over 100 h.

Table 1 summarises mRNA half-life for some genes encoding pro- and anti-apoptotic proteins. From this

![Fig. 1. Possible mechanisms by which blockage of transcription induces apoptosis in cells. See text for details.](image-url)
Table 1
Estimated half-lives of some mRNAs encoding pro- and anti-apoptotic factors

<table>
<thead>
<tr>
<th>Name</th>
<th>Half-life a (min)</th>
<th>Cell line</th>
<th>Inhibitor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro-apoptotic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFRSF-6/Fas/Apo-1</td>
<td>44</td>
<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>218&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HepG2</td>
<td>Act D</td>
<td>[22]</td>
</tr>
<tr>
<td>TNFSF-2/TNF-alpha</td>
<td>&lt;120</td>
<td>OCI-Ly3</td>
<td>flavopiridol</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>&gt;360</td>
<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
</tr>
<tr>
<td>TNFSF-6/FasL</td>
<td>&lt;120</td>
<td>OCI-Ly3</td>
<td>flavopiridol</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>&gt;360</td>
<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
</tr>
<tr>
<td>Bcl-2-binding protein Nip3</td>
<td>125&lt;sup&gt;c&lt;/sup&gt;</td>
<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
</tr>
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<td></td>
<td>&gt;360&lt;sup&gt;c&lt;/sup&gt;</td>
<td>T lymphocytes</td>
<td>Act D</td>
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<tr>
<td>MADD</td>
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<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
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<tr>
<td>Caspase-7 isoform beta precursor</td>
<td>128</td>
<td>T lymphocytes</td>
<td>Act D</td>
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</tr>
<tr>
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<td>TNFRSF1A</td>
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<td>Caspase-6 isoform beta</td>
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<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
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<td>723&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Programmed cell death 8/AIF</td>
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<td>T lymphocytes</td>
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<td></td>
<td>1111&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Bax</td>
<td>460&lt;sup&gt;b,d&lt;/sup&gt;</td>
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<td>Act D</td>
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<tr>
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<td>HepG2</td>
<td>Act D</td>
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<td>PIG11</td>
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<td>Act D</td>
<td>[22]</td>
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<td><strong>Anti-apoptotic</strong></td>
<td></td>
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<td></td>
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</tr>
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<td>NAIp</td>
<td>short</td>
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<td>[23]</td>
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<tr>
<td>MCL-1</td>
<td>64&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HepG2</td>
<td>Act D</td>
<td>[22]</td>
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<tr>
<td>TNFSF-5/CD40 ligand</td>
<td>74</td>
<td>T lymphocytes</td>
<td>Act D</td>
<td>[72]</td>
</tr>
<tr>
<td>c-IAP1</td>
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<td>OCI-Ly3</td>
<td>flavopiridol</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>163&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>[22]</td>
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<tr>
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<td>&lt;120</td>
<td>OCI-Ly3</td>
<td>flavopiridol</td>
<td>[23]</td>
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<td>[23]</td>
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<td>Bcl-xL</td>
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<td>HepG2</td>
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<td>[22]</td>
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<td>NF-κB1</td>
<td>268&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HepG2</td>
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<td>MAP4</td>
<td>541&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HepG2</td>
<td>Act D</td>
<td>[22]</td>
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</tbody>
</table>

<sup>a</sup> Different normalization factors for the arrays might be used; thus absolute stability comparison might not be valid between references.
<sup>b</sup> The half-life values were calculated from 1/decay rate as described in [22].
<sup>c</sup> Average of three determinations for the same gene using three different accession numbers.
<sup>d</sup> Average of two determinations for the same gene using two different accession numbers.
<sup>e</sup> Values obtained using different probes for the same gene.

It appears that the half-lives of mRNAs encoding pro-apoptotic components in general are longer than for genes encoding anti-apoptotic proteins; supporting a model in which induction of apoptosis following blockage of transcription may be solely regulated by differential stability of mRNAs [10,23]. A change in the ratio of pro- and anti-apoptotic factors following UV irradiation may in addition to their individual stabilities be differentially regulated by their gene sizes [24,25]. It is possible that the particular sizes of introns in these genes may have been selected during evolution as a mechanism to regulate apoptosis following UV light exposure, where genes with large introns would be preferentially inhibited by UV light compared to smaller genes due to their larger target size.

3.2. Role of p53 in mediating transcription block-induced apoptosis

Since p53 proteins accumulate following blockage of transcription, it is possible that p53 may contribute to the induction of apoptosis following inhibition of transcription. The role of p53 in mediating the induction of apoptosis following inhibition of transcription is not clear. Studies using human colon cancer cells have...
shown a clear trend favouring apoptosis in cells expressing wild-type p53 compared to cancer cells expressing mutant p53 following inhibition of RNA polymerase II-mediated transcription with DRB [26]. Furthermore, human colon cancer cells with both p53 genes deleted were found to be significantly more resistant to the induction of apoptosis following inhibition of transcription by α-amanitin or siRNA against RNA polymerase II than were parental cells with wt p53 [8]. Thus, it appears that p53 enhances the induction of apoptosis following RNA polymerase II inhibition at least in some cell types. However, contrasting results have been reported from other studies using murine embryonic fibroblasts (MEFs) which showed that inhibition of transcription with DRB or α-amanitin efficiently induce apoptosis in both p53+/+ and p53−/− MEF cells [3].

The transactivation activity of p53 is not expected to be involved in the induction of apoptosis following inhibition of transcription since p53 would not be able to induce expression of downstream target genes. Importantly, it has been shown that expression of a transactivation-deficient truncated p53 gene in p53−/− colon cancer cells restores the apoptosis sensitivity of these cells to inhibition of transcription, suggesting that p53 has a transactivation-independent function in enhancing the induction of apoptosis following inhibition of transcription [8]. One transactivation-independent function of p53 in stimulating the induction of apoptosis is its ability to translocate to mitochondria and bind to anti-apoptotic Bcl-2 family proteins [27–29]. In fact, p53 was found to accumulate in mitochondria following blockage of transcription. This correlated to the induction of apoptosis and suggests that p53 may contribute to the induction of apoptosis following sustained blockage of transcription by triggering mitochondria-dependent induction of apoptosis [8].

The role of p53 in the induction of apoptosis in human fibroblasts following exposure to UV light or cisplatin is not clear. In fact, studies have shown that p53 actually protects human fibroblasts and colon cancer cells from the induction of apoptosis by these agents [17–19]. Thus, it appears that the protecting effects of p53 in DNA repair and activation of cell cycle checkpoints overrides its roles in inducing apoptosis. In addition, we have found that cells with wild-type p53 recover RNA synthesis faster after UV-irradiation than cells with compromised p53 function [17–19]. Depletion of p53 by expression of the HPV16 ubiquitin ligase E6 in human cell lines with inherent defects in DNA repair revealed that loss of p53 significantly sensitised transcription-coupled repair-proficient XP-C cells [19]. These results suggest that the role of p53 in the protection against apoptosis involves enhanced recovery of transcription and that this enhancement is only operational in TCR-proficient cells.

3.3. Complications during replication by stalled transcription complexes

DNA-damaging agents, such as UV light or cisplatin, induce DNA lesions that can block the elongation of RNA polymerase complexes. In order to resume RNA synthesis, both the lesion and the stalled RNA polymerase complex must be removed. It has been shown that the largest subunit of RNA polymerase II is targeted for ubiquitylation and degradation shortly after cells are exposed to UV light or cisplatin [30–32]. The BRCA1/BARD1 complex [33] and the von Hippel-Lindau protein [34] may target RNA polymerase II for ubiquitylation and degradation. The degradation of stalled RNA polymerases appears to be dependent on the Cockayne’s syndrome factors CSA and CSB since ubiquitylation and degradation of the largest subunit of RNA polymerase is reduced in CS-A and CS-B cell lines [31,35].

It has been shown that UV-induced apoptosis is associated with the S-phase of the cell cycle [36,37]. The mechanism for this is not clear but if the stalled RNA polymerase complex is not removed prior to entry into S-phase, it is possible that the replication machinery may collide with stalled RNA polymerases [10]. Interestingly, studies using the RNA polymerase II inhibitor α-amanitin, which is thought to result in the targeting of RNA polymerase for ubiquitin-dependent degradation [38], have also shown a connection between transcription inhibition and passage through the S-phase [8]. In this case apoptosis does not seem to occur as a consequence of collision between stalled RNA polymerases and the replication machinery since the inhibition of transcription is due to the loss rather than stalling of RNA polymerases. It is possible that RNA polymerase II plays a supporting role in replication either directly or indirectly through the transcription of genes important for the replication process.

3.4. Aberrant accumulation of proteins in the cell nucleus

Nuclear import and export of proteins through nuclear pore complexes are mediated by nuclear localisation signals (NLS) and nuclear export signals (NES) [39–41]. Proteins containing leucine-rich NES domains are exported by the aid of CRM1, a member of the importin-β family of proteins [42–46]. It has been estimated that there are at least 75 proteins that have been confirmed containing NES domains [47] (Table 2).

We recently reported that nuclear export of NES-containing proteins requires ongoing synthesis and export of mRNAs [48]. In these studies, a fusion protein consisting of a NES domain fused to the green fluorescent protein (GFP) was microinjected into the nucleus of cells and the ability of this protein to export to the cytoplasm was measured within 20 min of injection. It
was found that when transcription was inhibited in cells either with drugs or microinjection of anti-RNA polymerase II antibodies, the nuclear export of the microinjected NES-tagged GFP proteins was significantly reduced [48]. Furthermore, targeting either Tap or Nup160, two components required for mRNA export, also blocked nuclear export of the fusion protein. Thus, these results suggest that general NES-dependent protein nuclear export requires ongoing nuclear export of mRNAs [48].

The p53 protein is a nucleocytoplasmic shuttling protein that contains multiple NLS and NES sequences [49–51]. The MDM2 ubiquitin ligase is important in regulating the level of p53 in cells by directing the nuclear export and degradation of p53 [52,53]. Interestingly, when transcription is inhibited by DRB, p53 accumulates in the nucleus despite the fact that MDM2 can bind to p53 and p53 proteins are ubiquitylated [54]. This suggests that inhibition of transcription blocks the ability of p53 to shuttle to the cytoplasm in an MDM2-independent manner. One possibility is that efficient nuclear export of p53 is somehow linked to the nuclear export of mRNA. In fact, similarly to the NES-GFP fusion protein mentioned above, p53 accumulates in the nucleus following specific inhibition of either RNA polymerase II-mediated transcription or Tap and Nup160-dependent nuclear export of mRNAs [9]. Furthermore, several other nucleocytoplasmic shuttling proteins such as p32 [55], VHL [56] and HIF-α [57] have been shown to accumulate in the nucleus following blockage of transcription. Thus, it appears that the nuclear export of NES-containing proteins in general depends on the continuous flow of mRNAs from the nucleus to the cytoplasm and that this protein export is blocked by inhibition of either mRNA synthesis or mRNA export. Further studies are needed to determine whether the aberrant accumulation of nucleocytoplasmic shuttling proteins in the nucleus following inhibition of transcription contributes to apoptosis.

4. Transcription blockage and anti-cancer strategies

Since inhibition of transcription induces cell death in a number of cancer cell lines [26,58] and that the induction of apoptosis has been shown to be more pronounced in transformed cells compared to their non-transformed counterparts [3], it is of interest to evaluate the potential usefulness of transcription as a cancer therapeutic target. Caution must be taken though

<table>
<thead>
<tr>
<th>Protein</th>
<th>Functional class</th>
<th>NES domains</th>
<th>Nuclear accumulation after blockage of transcription</th>
<th>Effects of nuclear accumulation by blocking export</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin B1</td>
<td>Cell cycle</td>
<td>Yes</td>
<td>?</td>
<td>Induces apoptosis [73]</td>
</tr>
<tr>
<td>NF-kB p65 subunit p53</td>
<td>Transcription factor</td>
<td>Yes</td>
<td>?</td>
<td>Inhibits apoptosis [74,75]</td>
</tr>
<tr>
<td>p73</td>
<td>Transcription factor, DNA repair, cell cycle regulation, apoptosis</td>
<td>Yes</td>
<td>Yes [4–6]</td>
<td>Enhances DNA repair, induces cell cycle arrest or apoptosis [76]</td>
</tr>
<tr>
<td>Mdm2</td>
<td>DNA repair, cell cycle, apoptosis</td>
<td>Yes</td>
<td>?</td>
<td>Induces apoptosis [77]</td>
</tr>
<tr>
<td>Cdc25B</td>
<td>Cell cycle</td>
<td>Yes</td>
<td>?</td>
<td>Promotes entry into mitosis [78]</td>
</tr>
<tr>
<td>BRCA1</td>
<td>DNA repair, DNA, damage signalling</td>
<td>Yes</td>
<td>?</td>
<td>May enhance DNA repair, activate cell cycle checkpoints and may together with BARD1 target RNA polymerase II for ubiquitylation [79,80]</td>
</tr>
<tr>
<td>VHL</td>
<td>Transcription, ubiquitin ligase complex</td>
<td>No [56]</td>
<td>Yes [56]</td>
<td>May suppress transcription elongation and promote ubiquitylation of target molecules (HIF-1 and RNA pol II) [34,81,82]</td>
</tr>
<tr>
<td>HIF-alpha</td>
<td>Transcription factor</td>
<td>Partially conserved [57,83]</td>
<td>Yes [57]</td>
<td>May promote angiogenesis, cell survival, cell invasion, and drug resistance [84]</td>
</tr>
<tr>
<td>Dsh</td>
<td>Signal transduction</td>
<td>Yes [85]</td>
<td>?</td>
<td>Affects the Wnt pathway [85] and promotes apoptosis [86]</td>
</tr>
<tr>
<td>c-Abl</td>
<td>Protein tyrosine kinase</td>
<td>Yes</td>
<td>?</td>
<td>Promotes apoptosis in a p73-dependent manner [87,88]</td>
</tr>
<tr>
<td>HDAC4&amp;5</td>
<td>Histone deacetylases</td>
<td>Yes</td>
<td>?</td>
<td>May suppress gene expression by modulating chromatin structure [89,90]</td>
</tr>
</tbody>
</table>
since long-term non-selective inhibition of transcription most likely would produce severe side effects and therefore targeted delivery of transcription inhibitors to the tumour would be preferable. One strategy that should be explored is whether transient inhibition of transcription may selectively kill tumour cells because they generally enter S-phase more frequently, a phase especially sensitive to transcription blockage [8,36,37]. Alternatively, cancer cells may be preferentially sensitive to transcription blockage because they may have less time allotted on their “apoptotic clocks” compared to normal cells before the balance of anti- and pro-apoptotic proteins will tip in favour of apoptosis.

There are many currently used chemotherapeutic agents that are known to have inhibitory effects on transcription. The topoisomerase inhibitors camptothecin and doxorubicin, the DNA-damaging agent cisplatin, the cyclin-dependent kinase-inhibitory agents flavopiridol and roscovitine and the nucleotide analogs 5-fluorouracil and fludarabine are thought to exert some of their anti-cancer activity by inhibiting transcription [6,23,59–66]. Interestingly, the combination of transcriptional inhibition with other agents such as ionising radiation [67–69] or the nuclear export inhibitor leptomycin B [70,71] have shown synergistic effects on cancer cells. These findings warrant further explorations of the potential usefulness of the transcription machinery as a therapeutic target in cancer treatment.

Conflict of interest statement

None declared.

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