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A new target for proteasome inhibitors: FOXM1

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Abstract

Importance of the field—The proteasome is responsible for ubiquitin- and ATP-dependent proteolysis of cellular proteins. The latest advances in proteasome studies led to the development of proteasome inhibitors as drugs against human cancer. It has been shown that proteasome inhibitors selectively kill cancer, but not normal cells. However, the exact mechanisms of the anticancer activity of proteasome inhibitors are not well understood. The oncogenic transcription factor Forkhead Box M1 (FOXM1) is overexpressed in a majority of human carcinomas, while its expression is usually low in normal cells. In addition, FOXM1 may also drive tumor invasion, angiogenesis, and metastasis. For these reasons, FOXM1 is an attractive target for anticancer drugs.

Areas covered in this review—My aim is to discuss the recent publications that may point out to novel mechanism of action of proteasome inhibitors. In addition, I will describe the identification of new types of proteasome inhibitors, called thiazole antibiotics. Using a cell–based screening system the thiazole antibiotics Siomycin A and thiostrepton were isolated as inhibitors of FOXM1 transcriptional activity and expression. Paradoxically, it has been showed that these drugs also stabilize the expression of other proteins and act as proteasome inhibitors in vitro. Moreover, it was found that well-known proteasome inhibitors, such as MG115, MG132 and bortezomib inhibit FOXM1 transcriptional activity and FOXM1 expression.

What the reader will gain—It has been shown that proteasome inhibitors suppress FOXM1 expression and simultaneously induce apoptosis in human tumor cell lines. This review describes the correlation between negative regulation of FOXM1 by proteasome inhibitors and apoptosis, and suggests that negative regulation of FOXM1 is a universal feature of these drugs and it may contribute to their anticancer activity.

Take home message—Oncogenic transcription factor FOXM1 is upregulated in a majority of human cancers, suggesting that growth of cancer cells may depend on FOXM1 activity. A short time ago, it has been shown that proteasome inhibitors simultaneously inhibit FOXM1 expression and induce apoptosis in human cancer cells. This effect may explain specificity of proteasome inhibitors to induce apoptosis in cancer, but not in normal cells. Now it is critical to determine the role of suppression of FOXM1 in apoptosis induced by proteasome inhibitors and to establish how significant is the inhibition of FOXM1 for the anticancer activity of proteasome inhibitors.

Keywords

proteasome inhibitors; FOXM1; apoptosis; anticancer drugs; thiazole antibiotics

Proteasome inhibitors are anticancer drugs

The proteasome is a multi-subunit protease complex that degrades proteins that are tagged with ubiquitin chains. Ubiquitin (76 amino-acid protein) is covalently linked by ubiquitinating enzymes to lysine residues of target proteins. The proteasome consists of a

cylindrical 20 S catalytic subunit that binds to one or two multi-subunit 19 S regulatory particles, forming 26 S and 30 S proteasomes and recognizes ubiquitinated proteins [1]. At the next step ubiquitinated proteins become unfold, translocated into the proteolytic chamber of the 20S proteasome and broken down into small peptides. The 19 S proteasome also has a deubiquitinating activity that removes polyubiquitin tag from the substrate protein.

Since the proteasome target ubiquitin-tagged proteins for degradation, proteasome inhibitors (PI) (Fig 1 C-E) stabilize the expression of the majority of cellular proteins and also induce apoptosis in human cancer cell lines. Six years ago PI, bortezomib (Velcade) (Fig 1E) was the first PI to be approved for the treatment of patients with multiple myeloma, suggesting that PIs could be used for treatment of human cancer. However, at this moment it is not clear how exactly PIs induce programmed cell death in cancer cells and why they selectively kill cancer, but not normal cells. It is very important to establish critical targets for PIs in human cancers of different origin. Several explanations have been presented for the proapoptotic/anticancer abilities of PIs, such as stabilization of IkB and NF-kB inhibition [2], stabilization of p53 [3] and Noxa [4], activation of JNK and Fas [5], cleavage of antiapoptotic Mcl-1 [6], induction of ROS [7], preventing the destruction of the CDK inhibitor, p27 [8], shift in the balance between pro- and antiapoptotic Bcl-2-family proteins [9, 10] and some other possibilities (reviewed in refs. [11, 12]. Abnormal NF-kB regulation has been shown in variety of cancers leading to the transcriptional activation of genes responsible for cell proliferation, inhibition of apoptosis, angiogenesis and metastasis [13]. It has been suggested that inhibition of NF-kB is one of the major mechanisms of anticancer activity of proteasome inhibitors [13, 14]. Proteasome inhibitors hinder NF-kB transcriptional activity via stabilization of IkB and sequestering of NF-kB in the cytoplasm [14]. Importance of NF-kB targeting by bortezomib was validated in multiple myeloma cells where an NF-kB signature correlated with their sensitivity to bortezomib [13, 15]. In this paper I will describe a novel target for PIs, the oncogenic transcription factor FOXM1 [16].

The role of FOXM1 in development and cancer

FOXM1 is a transcription factor of the Forkhead family that has a conserved Forkhead/winged-helix DNA-binding domain (100 amino acids) responsible for binding of Fox proteins the consensus TAAACA site in the promoters of target genes. FOXM1 is expressed in all embryonic tissues and in proliferating cells of epithelial and mesenchymal origin, but its expression is turned off in terminally differentiated, non-dividing cells [17]. In addition, it has been shown that FOXM1 plays role in development of nervous system [18] and is required for hepatoblast differentiation [19]. Following lung [20] and liver [21] injury FOXM1 expression was induced indicating that FOXM1 is essential for tissue regeneration and repair. Similarly, endothelial cell–restricted FOXM1-deficient mice displayed a significant impairment in endothelial barrier repair and a considerable increase in mortality after acute lung injury [22]. Following vascular injury, FOXM1$^{-/-}$ lungs exhibited reduced cell proliferation, diminished expression of cyclin B1 and Cdc25C and increased expression of CDK inhibitor p27 [22]. These data suggest that FOXM1 plays a essential role in the restoration of endothelial barrier function after vascular injury.

FOXM1 could be activated by oncogenic Ras-MAPK [23], Sonic Hedgehog [24], NF-kB [25] and EGFR [26] pathways, suggesting that it may act as an oncogene. In addition, as a potential oncogene FOXM1 is negatively regulated by tumor suppressor p53 [27]. When FOXM1 becomes activated, it induces cell cycle progression via transcriptional induction of genes that are involved in mitosis, including Cyclin B, Survivin, Aurora B kinase, Cdc25b phosphatase, Plk1 and some others [28]. In addition, FOXM1 transcriptionally activate Skp2 and Cks1 genes (subunits of Skp1-Cullin1-F-box ubiquitin ligase complex), thus targeting

CDK/cell cycle inhibitors $p21^{WAF1}$ and $p27^{KIP1}$ to degradation [28]. These and other data suggest that FOXM1 is required for the execution of the mitotic program [29].

FOXM1 is one of the most overexpressed genes in human solid tumors and it is upregulated in malignant mesothelioma [30], breast cancer [26, 31], non-small cell lung carcinomas [32], anaplastic astrocytomas and glioblastomas [33, 34], basal [24] and squamous [35] cell carcinomas, gastric cancer [36], colorectal cancer [37], hepatocellular carcinomas [38], pancreatic carcinomas [39], intrahepatic cholangiocarcinomas [40] and in some other human cancers. It has been shown that FOXM1 is consistently upregulated in metastatic prostate cancer cells [41] and knockdown of FOXM1 by small interfering RNAs (siRNAs) in several prostate cancer cell lines led to a significant reduction in cell proliferation and anchorage-independent cell growth on soft agar [42, 43]. Downregulation of FOXM1 in pancreatic [44] and breast [45] cancer cells by RNA interference led to inhibition of proliferation, migration and invasion of cancer cells. All these data implicate FOXM1 in human tumor growth and metastasis, and suggest that FOXM1 may be the “Achilles' heel” of cancer [46], and an attractive target for drug development [47, 48].

Thiazole antibiotics/proteasome inhibitors target FOXM1

To identify small molecule inhibitors of the transcription factor FOXM1 activity, cell–based screening system was developed and used for screening of NCI libraries of small molecules [49]. In the result of the screening thiopeptide, Siomycin A (NSC-285116) was identified as an inhibitor of FOXM1 transcriptional activity [49]. Furthermore, another thiazole antibiotic, thiostrepton with small structural differences from Siomycin A was also identified as FOXM1 inhibitor [50-52]. Thiazole compounds, Siomycin and thiostrepton are gram-positive bacteria specific, sulphur containing antibiotics [53] (Fig 1 A, B). Genetic and biochemical studies showed that thiazole antibiotics (thiostrepton, siomycin, thiopeptin, sporangiomycin, nosiheptide) have a very similar mode of action. They block the translocation step of translation by binding to the L11 binding domain of the 23S rRNA on the 50S ribosomal subunit [53], but they do not exert any inhibitory effect on eukaryotic protein synthesis (17). In addition, antitumor activities have been reported for both antibiotics. Siomycin A was identified as a strong pro-apoptotic compound in epithelial cells [54] and also as a potential anticancer drug that causes p53-independent apoptosis and induces lysosomal membrane permeabilization [55]. Reportedly, thiostrepton also possesses antitumor activity, but a synthesized fragment of thiostrepton showed even more potent antibacterial and anticancer activities than the natural substance [56].

Since FOXM1 is involved in a positive feedback loop and it activates its own transcription (Fig 2) [57], Siomycin A and thiostrepton down-regulate not only the transcriptional activity, but also the protein and mRNA levels of FOXM1 [49, 50, 52]. To evaluate the anticancer potential of the thiazole antibiotics, their effect on growth and survival of human cancer cell lines of different origin was studied. It has been shown that treatment of human cancer cells with the thiazole antibiotics resulted in downregulation of FOXM1 and potent apoptosis [49-52], suggesting that thiazole antibiotic-induced apoptosis may be linked to the suppression of FOXM1. Surprisingly, it has been discovered later that treatment of cells with thiazole antibiotics leads also to the stabilization of a variety of cellular proteins, including p21, Mcl-1, p53 and others [16]. Since these and other cellular proteins are upregulated by PIs [16, 58], it suggested that thiazole antibiotics might also act as PIs. When the thiazole antibiotics were directly tested in vitro and compared with well-known PIs MG132 (Fig 1D) and lactacystin against the 20S proteasome activity, it has been confirmed that they act as PIs in vitro [16]. Furthermore, these data implied that bona-fide PIs might also inhibit FOXM1. Additional experiments have shown that PIs strongly inhibit FOXM1 transcriptional activity and protein expression similarly to the thiazole antibiotics [16, 52].

These data suggest that down-regulation of FOXM1 may be required for the anticancer activity of PIs. Further experiments are needed to understand the importance of FOXM1 suppression for the activity of PIs as anticancer drugs.

Conclusion

In summary, recently discovered FOXM1 inhibitors, thiazole antibiotics Siomycin A and thiostrepton were identified also as PIs. In addition, bona-fide PIs such as, MG115, MG132 and bortezomib are FOXM1 inhibitors. Induction of programmed cell death by PIs correlated with the suppression of FOXM1 in human cancer cell lines of different origin. Overall, these data suggest that inhibition of FOXM1 by PIs may partially be responsible for their anticancer activity.

Expert opinion

Oncogenic transcription factor FOXM1 is upregulated in a majority of human cancers [59] and is involved in tumor growth, invasion and metastasis [41, 44]. Since cancer, but not normal cells are over-reliant on FOXM1 activity, it was suggested that potential FOXM1 inhibitors would specifically kill cancer cells. Recently, it has been shown that PIs simultaneously inhibit FOXM1 expression and induce apoptosis in human cancer cells. Suppression of FOXM1 by PIs may explain their specificity to kill cancer, but not normal cells, because FOXM1 only overexpressed in cancer cells. It is important to determine what the role FOXM1 inhibition plays in apoptosis induced by PIs in human cancer cells and how significant the inhibition of FOXM1 for the anticancer activity of PIs is. It is also essential to determine the precise mechanism of FOXM1 inhibition by PIs. Since PIs stabilize the majority of cellular proteins, it is plausible to propose that they stabilize a negative regulator of FOXM1 (NRFM) that would inhibit transcriptional activity of FOXM1 and its expression because of FOXM1 auto-regulation loop [57] (Fig 2). Additional experiments are needed to identify NRFM and to establish the mechanism of negative regulation of FOXM1 by PIs. All these data suggest that FOXM1 inhibition by PIs may be important for their anticancer activity.

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highlights

- The oncogenic transcription factor FOXM1 is overexpressed in a majority of human cancers
- Proteasome inhibitors selectively kill cancer cells, but the exact mechanisms of their anticancer activity are not well understood
- Thiazole antibiotics Siomycin A and thiostrepton were isolated as inhibitors of FOXM1 transcriptional activity and expression, and act as proteasome inhibitors
- Well-known proteasome inhibitors also inhibit FOXM1 expression and induce apoptosis in human cancer cells

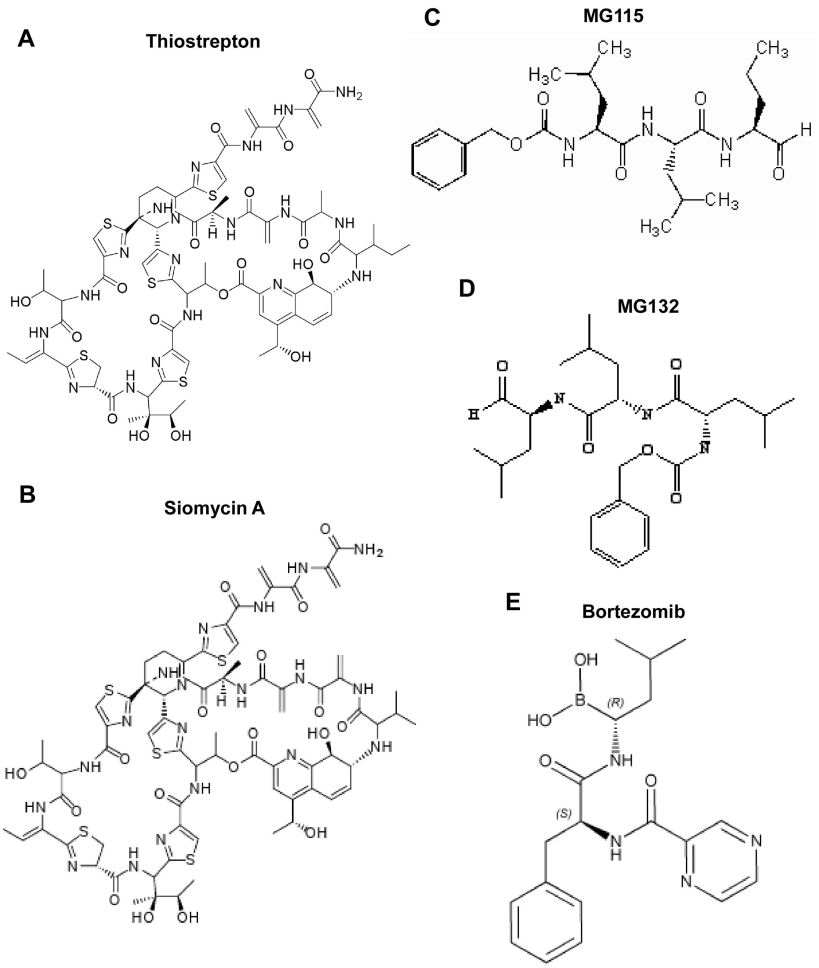

Fig 1. Structure of thiazole antibiotics (A, B) that have activity of proteasome inhibitors and bona-fide proteasome inhibitors (C-E)

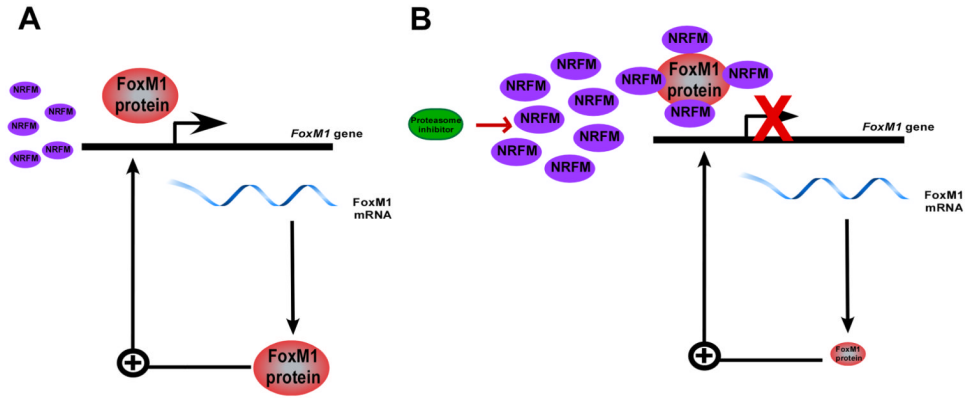

Fig 2. Proteasome inhibitors stabilize hypothetical negative regulator of FOXM1 (NRFM) that inhibits transcriptional activity of FOXM1 and its expression because of positive autoregulation of FOXM1

(A) Untreated cells where FOXM1 transcriptional activity is required for its expression **(B)** Cells treated with proteasome inhibitor, which stabilizes NRFM leading to suppression of F OXM1 transcriptional activity and expression.