The Drug-Induced Degradation of Oncoproteins: An Unexpected Achilles' Heel of Cancer Cells?

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ABSTRACT Many targeted therapies against cancer are aimed at inhibiting the enzymatic activity of kinases. Thus far, this approach has undoubtedly yielded significant clinical improvements, but has only rarely achieved cures. Other drugs, which selectively elicit proteasome-dependent degradation of oncoproteins, induce the loss of cancer cell self-renewal and promote cell differentiation and/or apoptosis. In acute promyelocytic leukemia, the cooperative degradation of PML/RARA by arsenic and retinoic acid cures most patients. In this condition and others, drug-induced proteolysis of oncoproteins is feasible and underlies improved clinical outcome. Several transcription factors, nuclear receptors, or fusion proteins driving cancer growth could be candidates for proteolysis-based drug-discovery programs.

Summary: Some cancer therapies may degrade oncoproteins. Loss of the driver oncoprotein is associated with loss of cancer cell self-renewal. Leukemia- or sarcoma-associated fusion proteins are the best candidates for small-molecule screens aimed at initiating oncoprotein degradation.
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INTRODUCTION

The past 20 years have brought an unprecedented accumulation of knowledge about cancer cells. The study of genomics has yielded a wealth of data, the analysis of which is becoming its own area of study. Signaling cascades are well-delineated, and tremendous breakthroughs have been made in stem-cell biology, the relation of which with cancer development is a field of intense investigation. Yet, patients remind us that too little progress has been achieved in the clinical management of cancer, and therapy too often remains fundamentally similar to the treatments used decades ago (surgery, radiation therapy, and inhibition of DNA replication by chemotherapy). Even though some diseases have undergone a therapeutic revolution, such as pediatric leukemia and some lymphomas, the treatment of others has improved only slightly. For example, the stage-adjusted 5-year survival of patients with head and neck cancer has remained essentially unchanged for well over 30 years (1). Clearly, one of the most urgent challenges is to translate findings in basic biology into applicable strategies for patient care.

Different biochemical means have been used to tackle directly transforming cancer-specific targets, such as inhibition of function, disruption of protein–protein or ligand–receptor interactions, misrouting within the cell, and antibody-induced neutralization. Collectively, these "targeted therapies" have undoubtedly yielded some progress. But only rare examples of cures can be unambiguously attributed to these targeted therapies. Multiple combinations have been tested (including with classic inhibitors of DNA synthesis), often with some synergy, but long-term survival benefit remains the exception rather than the rule. The most studied example of kinase inhibition in leukemia is *BCR/ABL* targeting by imatinib in chronic myeloid leukemia, which has converted a uniformly rapidly fatal disease into a chronic condition. However, disease remission in patients requires continuous inhibition of kinase activity and, with time, drug resistance frequently occurs through *BCR/ABL* mutation or amplification (2, 3), even though recent studies have suggested that a subset of patients on prolonged complete molecular remission may discontinue therapy without harm (4). Thus, solely inhibiting enzymatic activity does not seem sufficient to eradicate the leukemia-propagating cells and therefore fails to cure most patients.

In contrast, recent findings on the basis for therapy response in acute promyelocytic leukemia (APL) have demonstrated

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that full degradation of driving oncoprotein induces the loss of self-renewal and survival of the cancer-propagating cells, a feature associated with disease eradication. In this review, we discuss the importance of therapy-induced oncoprotein degradation. Indeed, although most current degradation-inducing agents were found by chance rather than by design, screens could be easily implemented to identify novel ones, and this anticancer strategy could be more generally applicable than previously anticipated.

THE ISSUE OF TARGET RELEVANCE

Many reasons may explain why most targeted therapies do not meet the high expectations they have raised. One is linked to the identification of relevant therapeutic targets. Genetic analysis of cancer cells has revealed a much greater level of gene alterations than suspected and the existence of multiple subclones within tumors (5), which harbor distinct adaptive potentials to therapies. It is thus likely that not all the different classes of events associated with cancer formation bear the same weight, with continuous proliferation and enhanced survival probably being the most important (6). In fact, as explicitly stated by the driver–passenger opposition, some alterations in cancer cells, even in growth control master genes, may occur by chance merely as the result of defects in DNA-repair pathways (5, 7). Then, the temporal sequence in which these events occur is likely to be important and may underlie a functional hierarchy in gene alterations, which was clearly established in the case of acute leukemia (8).

In line with the "oncogene addiction" model, we hypothesize that only the few initial transforming steps occur in a definite order and are absolutely and continuously needed for tumor maintenance. In contrast, subsequent hits would occur randomly and in a stochastic order, and would not be needed for the survival of cancer cells, even though they are necessary for progression to full malignancy by providing additional survival or proliferation advantages. Indeed, in the case of acute leukemias, the first hit is generally insufficient to complete the transformation process because preleukemic clones harboring the initial lesion have been detected in healthy individuals and may even persist after disease eradication (9, 10). Note that some of the progression events may be shared by very different leukemia subtypes, as demonstrated for *Ras* or *P53* mutations, *Myc* gain, or FLT3 activation (11, 12). To complicate the issue, the same signaling pathway may be an early driver in some conditions but a progression event in others. For example, *P53* alterations may occur as the initial lesion in Li-Fraumeni syndrome–associated tumors, whereas they are associated with progression for multiple other cancers (13).

Thus far, the most popular approach to targeted therapy has been to look for small molecules that inhibit the function of more or less stringently cancer-associated enzymes. Conceivably, the relative ease and availability of screening processes may have overshadowed analysis of the actual cancer relevance or specificity of these targets. For instance, histone deacetylase (HDAC) inhibitors were primarily developed to oppose transcriptional repression mediated by altered oncogenic transcription factors, which repress transcription through HDAC in many patients with acute myeloid leukemia. These have ultimately shown efficacy only in cutaneous T-cell lymphomas through poorly understood mechanisms (14). Similarly, targeting the activation of FLT3 kinase, a common progression event in many different subtypes of leukemia, failed to yield clinical benefit (15). We cannot rule out that therapeutic intervention on late secondary mutations may have some clinical efficacy, but this possibility remains to be demonstrated with *in vivo* survival as the endpoint.

IDENTIFYING THE RELEVANT TARGETS

How can this hierarchy of genetic lesions be approached in human tumors? Epidemiologic analyses, such as the link between estrogen exposure and breast cancer development (16) or the association of infections with lymphomas (17), can provide invaluable clues on the molecular pathways implicated. Genetics remains a very powerful approach: recurrent translocations, sequential analysis of cancer predisposition syndromes or pre-neoplastic lesions, presence of recurrent mutations of genes all affecting the same pathway, and the existence of strictly mutually exclusive gene alterations can all bring important pieces of information about the pathways initiating tumorigenesis. These initial alterations are most likely to be the drivers. Very powerful genetic systems using RNA interference approaches have also identified previously unsuspected key pathways (18). However, another issue comes to light: what endpoint to consider? Proliferation and/or apoptosis are the most commonly used approaches to screen for genes or small molecules. Yet, many drugs that block proliferation or induce apoptosis of cancer cells are unable to eradicate the disease because they fail to kill cancer stem cells. The ability of clonogenic cells to self-renew ("stemness") may actually be more important for tumor development and maintenance than short-term growth, and therefore may be a more relevant target, albeit technically considerably more challenging to explore. This is highlighted by the fact that several key pathways in cancer biology also control the fate of normal stem cells. Naturally, the ultimate pathway validations have to be done with survival in genetically modified mouse models and response to therapy in patients as the endpoints.

POTENTIAL TARGETS

From these considerations, a clearer image of the best pathways or disease couples to tackle starts to emerge. Fusion proteins, commonly encountered in leukemias and sarcomas where they are often the only constant genetic alteration, represent the first class of targetable cancer-driving molecules. Considerable evidence exists that they constitute the initial event of transformation (19). The presence of any given translocation actually *defines* a sarcoma or leukemia subtype (20). The pathophysiologic importance of fusion proteins together with the ability to target their function or stability places them at the pinnacle of "druggable" targets. Indeed, in murine malignancy models driven by a fusion protein, genetic or pharmacologic targeting of the leukemia-associated fusion protein is sufficient to induce rapid leukemia clearance, despite the requirement of cooperating events to yield full-blown disease (21, 22). Accordingly, among the most striking success stories

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of targeted therapy to date are diseases driven by fusion proteins (23, 24). In contrast, fusion proteins reported among innumerable other lesions in solid tumors are more likely to be associated with cancer progression (25, 26).

Transcription factors, in particular nuclear hormone receptors, constitute a second example of essential cancer-driving molecules. Although usually not amplified or mutated in tumors, transcription factors act as the final transcriptional effectors, integrating multiple signalling pathways, which are themselves targets of genetic abnormalities, particularly in breast and prostate cancers (16). Moreover, the levels of expression of the estrogen or androgen receptors are also tightly linked to therapy response (27–29; see below). The NF-κB pathway is similarly constitutively activated in many B-cell malignancies through multiple alterations of its regulatory molecules, rather than of the central effector (30).

A broader class of potential targets consists of key signaling pathways controlling stemness, as exemplified by APC or Hedgehog, which are almost always activated early in the genesis of some common varieties of skin or colon cancers. However, the key function of these pathways in the homeostasis of normal cells may ultimately impede identification of drugs with a high therapeutic index. Viral oncogenes represent a last class to consider. Among those are human T-cell lymphotropic virus, type I (HTLVI) *Tax*, hepatitis B virus (HBV) *Hbx*, and human papillomavirus (HPV) *E6/7*, which almost always play an initiating role in tumorigenesis and may also be required even at the latest stages of transformation. Clearly, these and similar viral proteins represent targets with high potential selectivity for transformed or infected cells.

PROTEOLYSIS IS HIGHLY DRUGGABLE

A novel way to target key oncoproteins by inducing their proteasome-dependent degradation was discovered largely by chance when analyzing the basis for the exquisite sensitivity of APL to retinoic acid (RA) and arsenic trioxide (arsenic) (31; see below). In parallel, it was realized that selective induction of protein catabolism may be more easily achievable than previously thought (32). Protein half-lives range from days to minutes and, importantly, for many proteins catabolism can be modulated as part of adaptive or physiologic responses, as first shown for cell-cycle proteins. The rules that predict catabolism rates and the molecular machinery involved have been largely identified (32). Globally, proteolysis is controlled by the ubiquitinylation machinery, which tags proteins for degradation and targets them to the ultimate effector, the proteasome complex (33). Changes in proteolysis rates can occur through changes in the abundance of the different proteins and/or composition of the complexes (34). In particular, the multiple E2 or E3 enzymes responsible for the conjugation of ubiquitin onto its targets undergo major transcriptional regulation during development or transformation. Some regulators, such as interferons, also appear to profoundly affect proteolysis through transcriptional control of several actors in the conjugation–degradation machinery (35). Multiple other regulatory pathways also control the binding of ubiquitin-conjugating enzymes onto their targets, notably by post-translational modification of the targets. These modifications may be influenced by an amazing variety of external signals, including hormones, stress, or various chemicals, which may inhibit or activate degradation of diverse sets of proteins, opening up a new complexity in physiologic or therapeutic biological regulations.

An example, highly relevant to the clinical situations described below, is the fact that transcriptional activation is tightly coupled to proteolysis of transcription factors and coactivators. Although modulation of transcriptional activity was considered to be the key factor underlying biological response, some recent studies have suggested that degradation may also play an important role. Indeed, as elegantly reviewed by Muratani and Tansey (36), the molecular determinants of transcriptional activation and proteolysis are highly overlapping, if not identical: the more potent a transcriptional activator, the less stable the protein. Genetic and pharmacologic studies have outlined at least 2 separate degradation pathways as part of the transcriptional activation process: one occurring prior to DNA binding, the other on DNA (37, 38). This activation–degradation coupling holds true for ligand-dependent transcriptional activation by nuclear receptors. Binding of the cognate hormone induces their rapid degradation by the proteasome, a process first uncovered for retinoic acid receptor α (RARA), which requires both DNA binding and intact transcription activating function 2 (AF2) function (39). In the case of estrogen receptor α (ERA), degradation appears to be required for transcriptional activation (38).

Finally, the links between proteolysis and cancer are underlined by the fact that several oncoproteins belong to complexes involved in proteolysis and exert their transforming activities through direct activation of tumor suppressor degradation (40). Conversely, although proteolysis is similarly enforced and regulated in cancer cells, therapeutic degradation of specific oncoproteins is feasible and has been associated to dramatic clinical responses.

This novel concept is not limited to proteasome-mediated degradation of oncoproteins. Other pathways of protein clearance, including protease-mediated cleavage or autophagy, may also operate to clear oncoproteins. For example, the Bcl-2 protein may be cleaved by caspases, transforming this oncoprotein into a death-promoting protein (41). Similarly, autophagy can modulate the abundance of a variety of proteins in response to stress. Here we discuss the settings in which therapy-driven interference with oncoprotein stability has led to clinical benefit.

CAN TARGETED THERAPIES REALLY WORK IN PATIENTS?

Acute Promyelocytic Leukemia

APL is one of the best-understood malignancies and is a rare example in which oncogene-targeted therapy has led to definitive cures (23, 24, 42). APL is caused by the expression of PML/RARA, a protein resulting from the fusion of PML, a redox-sensing protein that organizes nuclear domains, with RARA (43–47). APL has drawn much attention because of its exquisite sensitivity to RA, which induces APL cell differentiation *in vivo* or *ex vivo*. APL pathophysiology and the basis for

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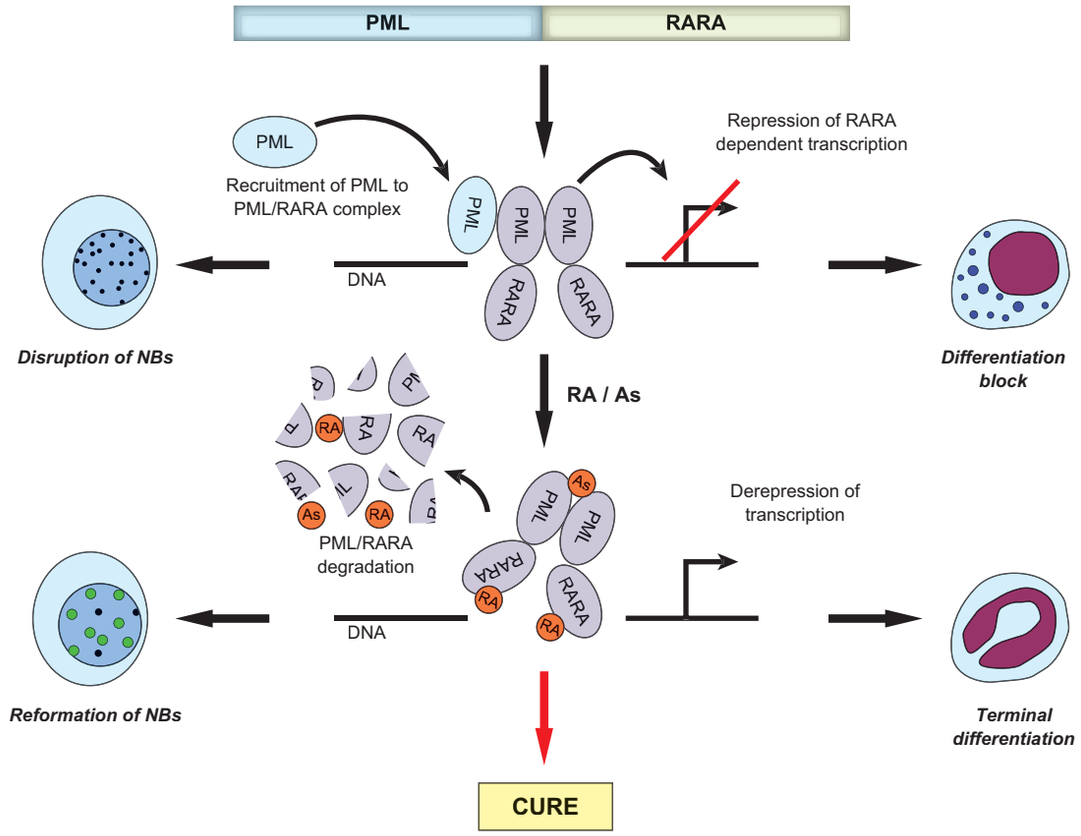

Figure 1. Model of APL cure through PML/RARA degradation. The t(15;17) chromosome translocation yields the PML/RARA fusion protein, which forms a dimer and binds DNA to repress transcription of many genes, including RARA targets, collectively resulting in the differentiation block characteristic of APL blast cells. PML/RARA complexes also recruit the PML protein, which disrupts PML nuclear bodies (NB). Combined treatment with RA and arsenic (As) induces the degradation of the PML/RARA protein and the derepression of target genes, which elicits both the terminal differentiation of leukemia cells and the reformation of NBs. This results in the definitive cure of the disease in most patients.

responsiveness to targeted therapies were recently reviewed elsewhere (23). Briefly, PML/RARA fusion has a dual action: to repress transcriptional activation by multiple nuclear receptors and to disrupt PML nuclear bodies. RARA-regulated transcription has been implicated in myeloid differentiation (48), while PML bodies play an essential role in the control of apoptosis and stem cell self-renewal (refs. 45–47, 49; Fig. 1).

The first mechanistic model of APL susceptibility to RA suggested that it resulted from the transcriptional reactivation of silenced PML/RARA target genes (50). This model has been progressively questioned by several subsequent findings. In particular, arsenic treatment, which does not directly activate PML/RARA–dependent transcription and fails to induce significant *ex vivo* differentiation, can cure up to 70% of patients when used as single agent (51–54). Similarly, although the RA–arsenic combination antagonizes differentiation (51), it is actually synergistic with regard to APL cell clearance, culminating in disease eradication in mice as well as in humans (21, 55). The only common property of the 2 agents is to induce PML/RARA degradation, with RA targeting its RARA moiety while arsenic targets its PML domain (refs. 31, 56; Figs. 2A and 2B). The similarity of the clinical responses to RA and to arsenic in APL, together with their shared ability to initiate PML/RARA degradation, suggests that the latter—and not only interference with transcriptional regulation—is an essential contributor to the response to therapy (31). Mechanistically, although the proteasome appears to play the major role, other pathways, including caspase cleavage and autophagy, also contribute to RA-induced PML/RARA degradation (39, 57, 58). Note that, in the case of RA, although transcriptional activation is tightly coupled to degradation, some cellular effects may reflect transcriptional modulation, whereas others reflect ligand-induced receptor loss. The initial proposal that oncogene proteolysis could underlie drug efficacy was received with considerable skepticism (31, 56). Yet, recent genetic and pharmacologic studies have strongly suggested that therapy-induced loss of the PML/RARA driving oncogene explains disease clearance in mice (59) and cures in patients (refs. 24, 42, 55; Fig. 1). Thus, APL probably represents the best-studied example to date in which leukemia eradication results from therapy-induced elimination of the key driver of oncogenesis (23).

Adult T-Cell Leukemia

Adult T-cell leukemia (ATL) is a rare complication of chronic infection by the oncogenic HTLVI (60). The viral regulatory protein Tax, which greatly enhances the viral long terminal repeat

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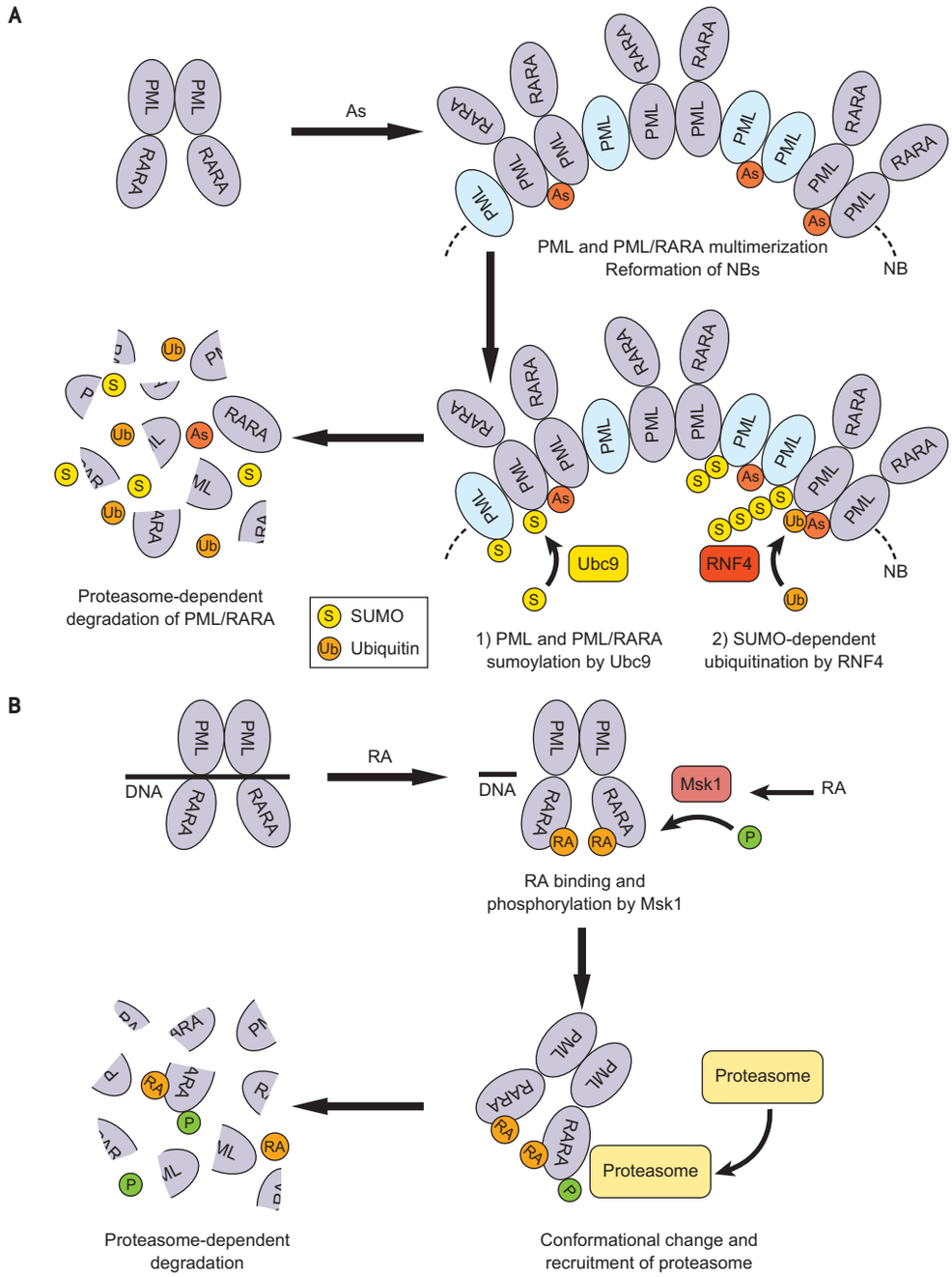

Figure 2. Therapy-induced degradation of PML/RARA. **A**, mechanism of arsenic-induced PML/RARA degradation. Arsenic directly bridges PML/RARA proteins 2 by 2, which allows formation of nuclear bodies (NB) in which the PML moiety of PML/RARA is first sumoylated by the Ubc9 conjugation enzyme and then polyubiquitinated by the SUMO-dependant E3 ligase RNF4, resulting in PML/RARA proteasome-dependent degradation. **B**, mechanism of RA-induced PML/RARA degradation. RA docks to the ligand-binding domain of the RARA moiety of PML/RARA, triggering a conformation change that is also favored by RA-induced RARA phosphorylation by Msk1. The conformation change allows subsequent recruitment of the 26S proteasome, resulting in PML/RARA degradation.

basal activity, is also a powerful transactivator of many cellular genes, including *IL2* and *IL2-R*, creating a potent autocrine loop that induces proliferation of infected T cells. Considerable controversies have arisen regarding the contribution of Tax to the initiation and maintenance of transformation in ATL, because Tax expression is usually no longer detectable in full-blown leukemia. However, transgenic mice expressing Tax in T cells develop typical ATL, demonstrating that Tax expression suffices to initiate the disease (ref. 61; Fig. 3A).

A specific drug combination, IFN-α and arsenic, has been shown to selectively induce apoptosis of HTLVI–infected cells (62). Critically, this was associated with rapid proteasome-mediated Tax degradation upon exposure to the drug combination (63, 64). The causative role of Tax degradation

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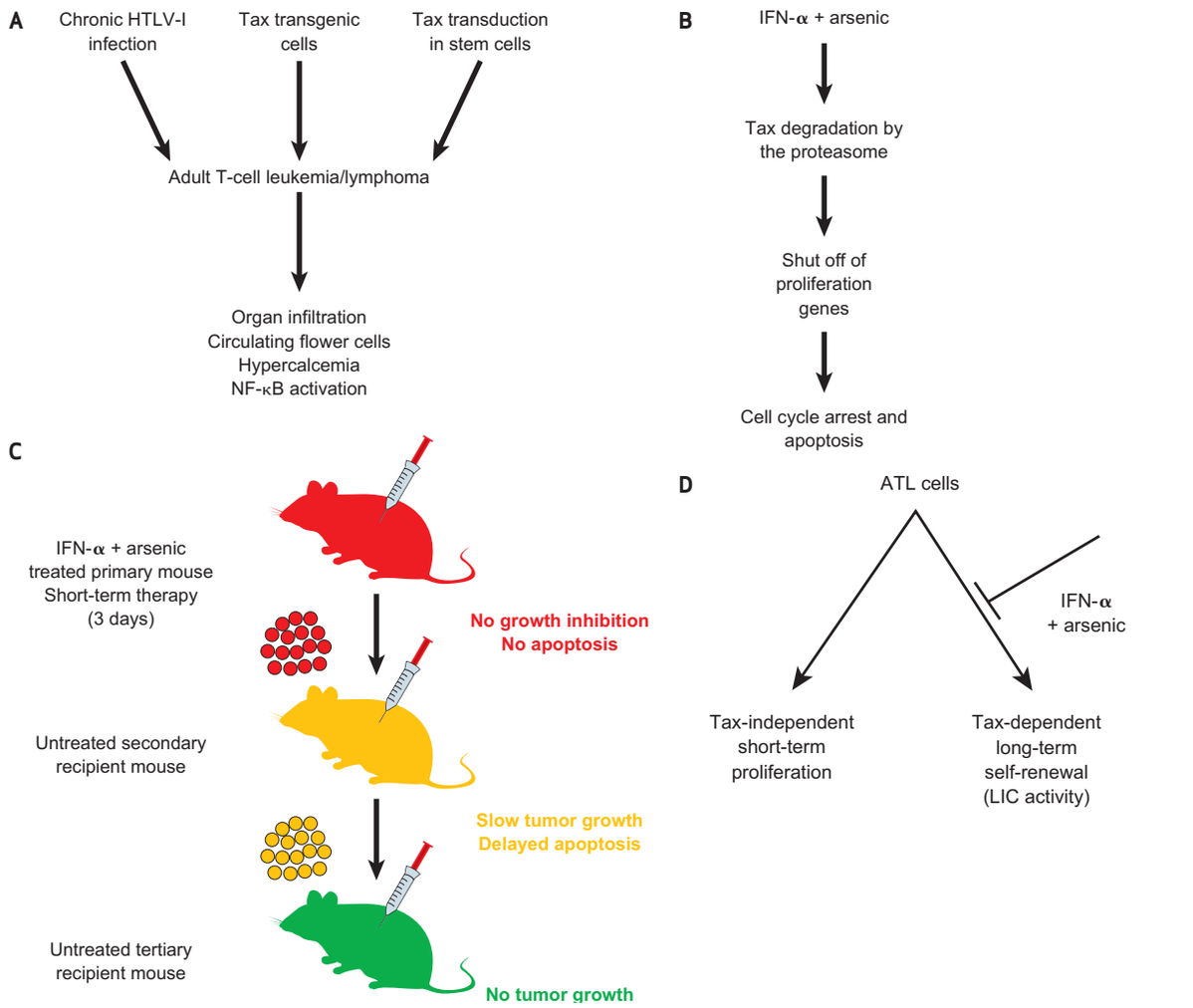

Figure 3. Role of Tax proteolysis in ATL. **A**, study models of ATL. Tax-transgenic cells or Tax-stable expression after viral transduction recapitulates the phenotype of ATL due to HTLVI infection. **B**, mechanism of action of the IFN-α/arsenic combination. This combination blocks proliferation and elicits cell-cycle arrest and apoptosis of ATL cells through the proteasome-dependent degradation of Tax oncoprotein. **C**, therapeutic efficacy of the IFN-α/arsenic combination in a preclinical model of ATL. IFN-α/arsenic treatment in primary Tax-transgenic mice does not affect tumor growth but induces delayed apoptosis and partially impairs the proliferation of leukemia cells transplanted in untreated secondary recipients, while it completely abolishes their ability to grow in recipients of tertiary transplants. **D**, proposed model of the effect of IFN-α/arsenic. Through Tax degradation, the combination inhibits the Tax-dependent sustained self-renewal capacity of ATL cells, but does not affect Tax-independent proliferation of leukemia cells. LIC, leukemia-initiating cell.

is strongly suggested by the recent report that this combination can cure murine ATL derived from Tax-transgenic mice (65). Because the action of the IFN-α/arsenic combination is very specific to both HTLVI–infected human cells and Tax-driven murine leukemia, it is most likely that therapy-induced loss of the driving oncogene underlies responsiveness to therapy (Fig. 3B). Unexpectedly, although this drug combination elicits apoptosis in cell lines, *in vivo* leukemia continued to expand for several weeks before suddenly disappearing. Transplantation studies have demonstrated that even a very brief treatment, which does not impair *in vivo* tumor growth or proliferation, abrogates the capacity of leukemia to engraft in secondary hosts, provided that the proteasome is functioning (ref. 65; Fig. 3C). This puzzling observation suggests that Tax loss abrogates "stemness," but not the short-term proliferation of leukemia cells (Fig. 3D).

Importantly, in the cutaneous form of the disease, clinical trials have provided evidence that this drug combination can induce remissions, several of which are long-lasting (66). Moreover, when used as consolidation therapy after chemotherapy, the IFN-α/arsenic combination has allowed very long-lasting remissions of the aggressive leukemic form of the disease (O. Hermine, unpublished observations), suggesting that it can efficiently target the self-renewal capacity of the remaining ATL cells in this clinically stringent condition. Although the biochemical mechanisms underlying Tax-specific degradation in this setting remain to be elucidated, the human and murine data provide a striking illustration of the clinical potency of therapy-induced oncogene clearance.

Breast Cancer

It is commonly stated that transcription factors are not readily druggable. Yet, the oldest example of targeted therapy,

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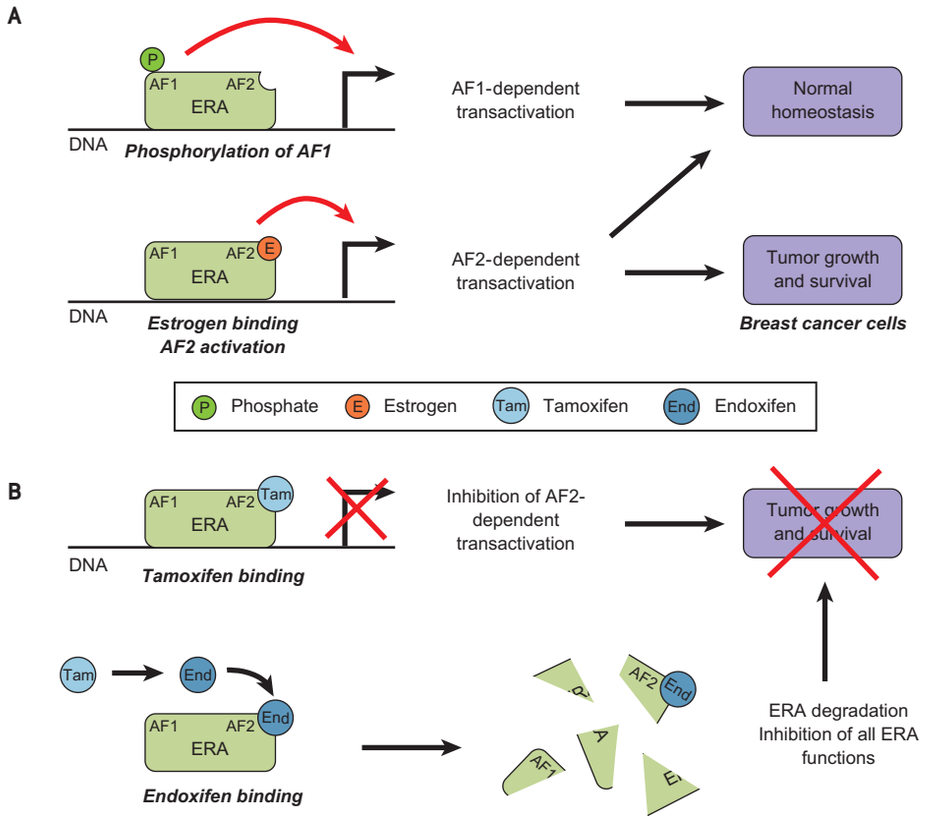

Figure 4. Potential therapeutic role of proteolysis in breast cancer. **A**, dual transcriptional function of ERA. The activation of ERA transcriptional activity resulting from phosphorylation of the AF1 domain is involved in normal homeostasis processes, whereas activation of the AF2 domain of ERA due to estrogen binding allows sustained growth and survival of breast cancer cells. **B**, tamoxifen therapeutic activity in breast cancer. Upper panel: in the classic model implicating antagonism to transactivation, tamoxifen competes with estrogens for binding to the AF2 domain of ERA and antagonizes their effect, thus inhibiting the positive effects of ERA activation on the growth and survival of cancer cells. Lower panel: proposed complementary model implicating ERA degradation. Endoxifen, a metabolite of tamoxifen, also binds to the AF2 domain of ERA and induces its degradation via the proteasome, thus abolishing all effects of ERA on cancer cells, including sustained growth and survival.

tamoxifen, targets a transcription factor, estrogen receptor α (ERA), which plays a pivotal role in the survival and proliferation of breast cancer cells. Many breast cancers are driven at least in part by ERA activation through a variety of molecular mechanisms [including local hormone production, coactivator amplification, and receptor phosphorylation (16)]. Elegant models have demonstrated that tamoxifen antagonizes transcriptional activation by the ligand-activated AF2 domain, but allows (and may actually foster) transcriptional activation by the kinase-regulated AF1 domain (67). Importantly, tumor growth and survival are AF2-dependent, while many functions of normal cells are AF1-dependent (Fig. 4A). Hence, the selective downregulation of genes required for tumor propagation, but not of genes involved in normal cellular homeostasis, results in a high therapeutic index. Note that although most studies have focused on the essential role of ERA in transcriptional activation, there is also evidence for an alternative or complementary role of ERA in promoting estrogen-regulated kinase activation (68) that may also participate in the transformation process.

Recent studies have demonstrated that the primary metabolite of tamoxifen, endoxifen, is a very potent inducer of ERA degradation (69). This finding raises the issue of the respective contribution of transcriptional repression and ERA clearance in the biological response of breast cancer cells to tamoxifen (Fig. 4B). Importantly, catabolism abrogates all functions of ERA, including kinase activation. In that respect, a potent, clinically prescribed anti-estrogen (fulvestrant) is primarily acting through ERA degradation prior to DNA binding (28). Moreover, very high doses of estrogens, which not only activate transcription but also elicit ERA degradation (70), paradoxically result in breast cancer regression with a higher efficacy (but also higher toxicity) than tamoxifen (71). Collectively, these observations raise the possibility that ERA degradation may actually play a key role in the response to fulvestran, tamoxifen, and even estrogens, with the potential to open fresh perspectives for drug discovery or new combinations.

FUTURE TARGETS?

The real successes of targeted therapy were obtained in cancers with fusion proteins (RA and arsenic with PML/RARA, imatinib with BCR/ABL), presumably because these diseases are essentially monogenic. Fusion genes associated with leukemia or sarcoma development almost always display gains of function. Cancer cells are addicted to the

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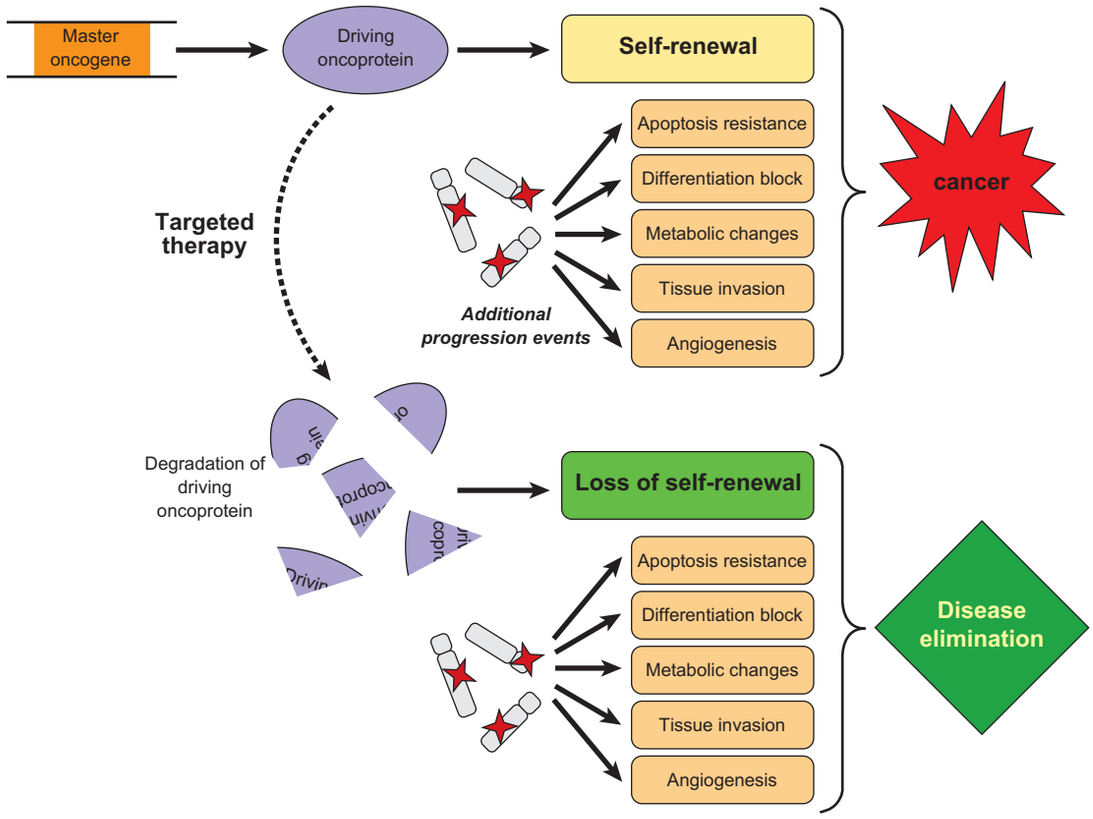

Figure 5. A general model of therapy by oncoprotein degradation. A driver oncoprotein is responsible for the abnormal self-renewal capacity of a preleukemic cell. Additional hits allow the cell to acquire other malignant features leading to the development of a full-blown tumor. Therapy-triggered degradation of the driving oncoprotein abolishes self-renewal, provoking the eradication of cancer cells and the ultimate cure of the disease.

activity (or activities) of the fusion protein, but usually not to either of the unfused constitutive moieties, which may even sometimes be dispensable for normal cells. Therefore, agents that control the degradation of one or the other of the two moieties of a transforming fusion protein should exert a very specific effect on cancer cells. Moreover, agents targeting each moiety for proteolysis should be synergistic and are not expected to display cross-resistance. This scenario is perfectly exemplified by the combination of arsenic and RA in PML/RARA–driven APL, which elicits the clearance of the malignant clone with little or no toxicity in normal cells (21, 23, 24, 55, 72). Other diseases driven by fusion oncogenes might be highly susceptible to therapies aimed at degrading the fusion protein. For example, in BCR/ABL–driven leukemia, the effect of the kinase inhibitor imatinib may be enhanced by the concomitant induction of the fusion protein degradation following arsenic treatment, via a recently discovered mechanism (73, 74).

Other fusion oncoproteins could be the targets of agents that induce their degradation, including existing drugs. For example, some thyroid cancers are associated with a *PAX8/PPARG* fusion gene, which represses PPARG- and possibly PAX8-regulated transcription (75). Binding of PPARG by its agonists not only activates transcription, but also degrades the receptor (76). Accordingly, specific PPARG agonists have been shown to induce growth arrest in thyroid carcinomas expressing *PAX8/PPARG* (77), pleading for the investigation of the *in vivo* relevance of these findings. Similarly, rare fusions involving the *PML* gene were identified in B-cell acute lymphoblastic leukemia (78). Given the ability of arsenic to degrade PML or PML-containing proteins (79–81), it is most likely that arsenic could be of therapeutic benefit in these very rare cases.

The importance of nuclear receptors in transformation (16, 50) and the magnitude of knowledge gained on ligand-dependent changes in protein conformation, interactions with other proteins, and degradation (82), makes them prime candidates for medicinal chemistry approaches aimed at uncoupling transcriptional regulation from degradation (28, 83). In this respect, genetic studies have demonstrated that RARA transcriptional activation and receptor catabolism could be uncoupled, for example, through a hormone-responsive phosphorylation site that regulates degradation (59). Conversely, RARA stabilization can be induced by a natural product without major changes in basal transcriptional regulation (84). The existence of at least two distinct proteolysis pathways (one requiring DNA binding, the other not) portends the possibility of synergistic interactions between

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agents that activate either pathway, a hypothesis that could be easily tested in pre-clinical models. It is thus conceivable that new ligands that selectively trigger nuclear receptor degradation may be discovered, with foreseeable uses in APL and in breast or prostate cancers.

CONCLUSIONS

Recent progress in cancer biology has suggested that cancers would soon be treated "*à la carte*." We do not wish to claim that drug-induced proteolysis may be a panacea applicable to all types of cancers. Yet, pharmacologic manipulation of the steady-state level of several oncoproteins is clearly feasible. In cases in which these oncoproteins were the drivers, pharmacologic manipulation has already been associated with dramatic improvements in clinical outcome. A primary function of oncoproteins is to convey immortality or "stemness." Thus, if a given target is key to stemness, its loss should be accompanied by loss of cancer cell self-renewal, a feature that is often associated with definitive cures (refs. 22, 59, 65; Fig. 5). Therefore, full degradation of oncoproteins (notably fusion proteins), when pharmacologically achievable, should be associated with a favorable long-term outcome, at least in the leukemia field where most of the seminal observations were achieved. Because protein degradation screens can be implemented using *in cellulo* imaging, drug discovery programs based on this concept should be relatively easy to do.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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