Impaired Ribosome Biogenesis and P53 Activation in Haematological Disease: Novel Therapeutic Strategies

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Abstract

Hereditary forms of bone marrow failure and aplastic anaemia (AA) manifest in rare blood syndromes (Dyskeratosis Congenita, Diamond-Blackfan Anaemia and Shwachman-Diamond Syndrome) in which genetic abnormalities directly impair ribosome biogenesis. These conditions are all associated with varying degrees of predisposition to haematological malignancy. Various studies of ribosome proteins have revealed an intimate relationship between ribosome biogenesis and p53 that governs cell fate in human haematopoietic disease.

Over 70 years ago, recognition of the bone marrow suppressive properties of nitrogen mustards led to the development of early chemotherapeutics. Since, a multitude of seemingly unrelated drugs have emerged that also provoke AA as an idiosyncratic side effect. Here we hypothesize that at least some of these bone marrow suppressive drugs target ribosome biogenesis thereby mimicking congenital forms of bone marrow failure and inducing AA. If so, these bone marrow suppressive drugs may also share the anti-cancer potential of mustard gas through targeting abnormal ribosome biogenesis in malignant haematopoietic stem cells. Targeted drug development is an arduous and time-consuming process, however, repurposing of bone marrow suppressive drugs could provide a novel, clinically applicable therapeutic strategy in haematological malignancies.

Introduction

Modern chemotherapy of leukaemia was developed during the 1940-50s following the observation that soldiers exposed to mustard gas during World War 1 suffered from aplastic anaemia [1]. In 1943, Louis Goodman et al. insightfully reasoned that mustard gas related compounds could inadvertently be used to treat leukaemia and lymphoma [2]. Successful repression of lymphoma in a xenograft mouse model led to a hurried search for related chemicals with anticancer activity culminating in the first chemotherapeutic effort to tackle childhood leukaemia in 1948, using methotrexate [3]. Since then a myriad of new drugs with alternative mechanisms of action have emerged, but common to many anti-leukaemia cell toxins is their ability to induce bone marrow suppression. Aplastic anaemia (AA) is a form of bone marrow failure in which the primary defect occurs at the level of the haematological stem cell. AA is considered the paradigm of bone marrow failure syndromes and will serve as such within the context of this review [4]. The disease is characterized by bone marrow hypocellularity, pancytopenia and is frequently associated with malignant progression. AA can be hereditary or acquired. The hereditary form manifests as or associated with a variety of rare congenital bone marrow failure syndromes including Dyskeratosis congenital (DC), Diamond-Blackfan anaemia (DBA) and Shwachman-Diamond syndrome (SDS) [5]. Interestingly these conditions are considered ribosomopathies in which genetic abnormalities directly impairing ribosome biogenesis are causative. Acquired AA is far more common and the pathophysiology of most cases is lymphocytic immune mediate destruction of hematopoietic stem cells (HSCs) [6,7]. The immune response is likely prompted by environmental exposures, including infectious agents and chemicals [8]. Idiosyncratic reactions to seemingly unrelated drug therapies are also known to provoke AA. These instances are extremely rare and restricted to a minority of patients, but are consistent among a diverse group of therapeutic agents [9].

The congenital forms of bone marrow failure described above are all associated with varying degrees of predisposition to haematological malignancies, typically transitioning to myelodysplastic syndrome (MDS) before progressing to acute myeloid leukaemia (AML) [10]. Contraction of the HSC compartment is thought to occur in bone marrow failure. As a result, a benign dysfunctional clonal or oligoclonal pool may dominate haematopoiesis in AA [11]. It is the subsequent development of this clonal pool that will dictate disease progression. Accruement of genetic defects may incite clonal expansion or continued stem cell depletion. Intriguingly, an important role for the tumour suppressor p53 further relates the disorders and may orchestrate the balance between bone marrow failure and cancer [7,12]. This review aims to discuss the continually emerging data that has established ribosome biogenesis stress response as a key p53 regulatory pathway in human disease. Understanding how this relationship operates in haematopoietic stem cells may provide great insight into the aetiology of aplastic anaemia, whilst simultaneously cultivating a novel therapeutic strategy for haematological malignancies.

Ribosome Biogenesis

Ribosome biogenesis is an energetically intensive process requiring coordination of approximately 80 core ribosomal proteins (RPs), over 150 associated proteins and around 70 small nucleolar RNAs [5]. Assembly of the ribosome takes place in the nucleolus following the generation of four ribosomal RNAs (rRNAs) that form the core constituents of the 40S and 60S subunits. The 60S subunit comprises 5.8S, 5S and 28S rRNAs, while the 40S subunit is contains a single 18S rRNA. Maturation of the rRNAs is a tightly regulated process consisting

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of various chemical modifications and nucleolytic cleavages [13]. The multifactorial and highly regulated nature of ribosome biogenesis presents a plethora of genes and products which, when mutated, may contribute to disease. Mutation of the dyskerin (DKC1) gene and its small nucleolar ribonucleoprotein (snoRNP) product, dyskerin, is thought to mitigate rRNA maturation in the cells of DC patients [13,14]. Mutations associated with DBA and SDS typically are found in the RPS19 and SBDS genes, respectively. In DBA, the defective protein products appears to impair maturation of the 40S subunit [15], whilst SBDS appears to be involved in 28S rRNA incorporation into the 60S subunit [16,17]. A simplified overview of eukaryotic ribosome biogenesis is provided in figure 1 and highlights stages associated with discussed syndromes [5,7].

Guarding the Guardian

Given the fundamental contribution of ribosomes to all cellular functions and growth, the cell requires mechanisms to safeguard the fidelity of ribosome biogenesis. Though much of the regulatory network remain ambiguous it seems clear that the tumour suppressor protein p53 plays a central role [18]. Furthermore activation of the p53 protein in the context of a ribosomal stress response appears to contribute significantly to the AA phenotype of bone marrow failure syndromes [19]. The implication of p53 in ribosomal and nucleolar stress response has led to an established p53-ribosomal stress hypothesis supported by an increasing body of literature [18]. Aberrant expression and deficiency of a variety ribosome biogenesis associated factors have been shown to promote and repress p53 activity. Perhaps the most established example of p53 regulation is through RP modification of the ubiquitin ligase mouse double minute 2 homologue (MDM2). Through binding of an internal zinc finger, RPs, RPL11, RPL23, RPL5 and RPS7 mitigate the E3 ligase activity of MDM2 and thereby stabilize p53 [20-22]. In 2011, Kim et al. further delineated the pathway by showing aberrant ribosome biogenesis can lead to activation of c-Myc and ASK1/p38 pathways resulting in p53 dependent cell cycle arrest [23]. Chakraborty et al. provide comprehensive review of the literature [18].

The varied manifestation of the p53-ribosomes biogenesis interactions may reflect and even dictate the volatile nature of the haematopoietic stem cell compartment in human disease.

Experimental Models of Haematopoietic Disease

Genetic defects in ribosomal proteins account for over 50% of DBA cases. The most frequently mutated gene is RPS19 coding for the ribosomal protein S19 [15]. In all instances S19 is rendered defective either through missense mutations or aberrant expression. As all patients are heterozygous for RPS19, haploinsufficiency appears sufficient for disease pathology. In 2011, Jaako et al. successfully generated a mouse model for haploinsufficient expression the RPS19 gene [24]. Using a transgenic RNAi approach to enable regulated and graded depletion of S19, knockdown mice developed typical DBA phenotypes including macrocytic anaemia, leukocytopenia and bone marrow failure. Interestingly haematopoietic progenitors exhibited up- regulation of p53 and critically generation of p53 null models successfully rescued the exhausted haematopoietic phenotype. The depleted haematopoietic phenotype of the model is consistent with constitutively active p53 mice models and analogous to zebrafish models of both DBA and DC [25,26]. However, bone marrow failure is not a consistent or generalized consequence of RP depletion and alternative zebrafish models of RP haploinsufficiency resulted in a predisposition to cancer. To investigate the role of critical embryonic development genes in tumorigenesis, Amsterdam et al. established a

large-scale retroviral mutagenesis screen in zebrafish [27]. Over 300 lines of fish were maintained, each heterozygote for a distinct recessive embryonic lethal mutation. In an initial screen, haploinsufficiency in 11 RP genes were observed to predispose to cancer while subsequent studies extended the number to 17 of the 28 RP heterozygotes that were characterized [27,28]. Intriguingly, lines associated with the greatest cancer incidence were significantly growth impaired presumably accountable to impeded protein translation. Tumorigenesis may therefore thrive in an environment of growth- impaired cells or simply manifest through a defect in protein translation.

These studies illustrate the variable phenotypic consequences of RP haploinsufficiencies. It seems therefore that defects in different ribosome biogenesis factors may produce a broad spectrum of disease manifestation (Figure 1). Similarly it is becoming clear that phenotypes associated with ribosome deficiency may variegate dependent on the species, tissue and even cell types. Two recent studies provide greater insight into how the RP-p53 relationship may operate in human HSCs, specifically in the context of bone marrow failure and cancer. Again implementing an RNA silencing approach, Dutt et al., were able to model haploinsufficiency of RPS19 and RPS14 in primary human haematopoietic progenitor cells [29]. RPS19 deficiency again aiming to reflect DBA, whilst RPS14 is deleted in 5q-syndrome, itself associated with severe bone marrow failure [30].

Approximately 50% knockdown of the RPs resulted accumulation of active p53 in a lineage dependent manner. CD71 positive erythroid progenitor cells contained increased levels of p53 comparable to that of gamma irradiated controls, as well as up regulation of target genes including p21 and BAX. In contrast to the Jaako et al. [24] mouse model of DBA, p53 induction was erythroid specific with myeloid (CD13+, CD33+, CD45+ and CD11b+) and megakaryocyte lineage cells failing to generate a p53 response beyond that of the shRNA controls. Crucially, blocking the transcriptional transactivation activity of p53
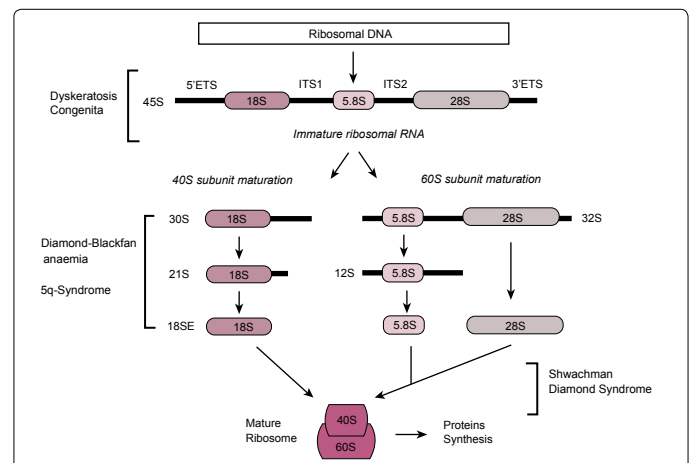

Figure 1: Schematic overview of eukaryotic ribosome biogenesis, highlighting processes defective in bone marrow failure syndromes.

Biogenesis is initiated with RNA polymerase 1 mediated transcription of a common 45S rRNA precursor. An early cleavage event at the A2 site within ITS1 separates 40S rRNA from the remaining pre-rRNA. The 40S precursor then undergoes sequential cleavage events culminating in the production of the mature 18S rRNA, ready for incorporation into the ribosome. The remaining precursor rRNA is comprises the 5.85, 28S and 5S (not shown for simplicity) and is similarly processed through cleavage within ITS2 and 3'ETS sites. Finally the mature rRNAs are combined with associated protein factors to form the mature ribosome. Labelled brackets indicate processing events associated with the bone marrow failure syndromes. ITS, Internal transcribed sequences; EST, External transcribed sequences. Adapted from Narla et al [5,7].

using pifithrin- was shown to rescue the haploinsufficient phenotype observed in haematopoietic progenitor cells.

Myelodysplastic syndrome represents a disease state that may be understood as a "middle ground" between bone marrow failure syndromes and malignant progression [31]. In a study observing 55 patients with low and intermediate risk myelodysplastic syndrome and del(5q) mutations, leukemic transformation was observed to correlate with TP53 mutation [32]. Intriguingly mutations appeared to arise early in the clinical course of the disease and surprisingly were associated with increased expression of the p53 protein. While further studies are required to understand the functional role of p53 in myelodysplastic syndrome and leukemic progression, the study further illustrates the potential for p53 to influence the fate of HSCs. It is also valuable to recognize that p53 driven depletion of the bone marrow is not restricted to ribosome biogenesis related conditions. A recent study elegantly revealed the role of exacerbated p53 response in Fanconi Anemia (FA) [33]. FA is a congenital DNA repair deficiency syndrome. Primary bone marrow samples obtained from FA patients were broadly associated with heightened p53 activation in haematopoietic stem and progenitor cells. Critically, murine models of FA could be rescued by silencing of p53. In this context p53 activation was accountable to impaired DNA damage response. However, the ostensibly significant role of p53 and bone marrow suppressive consequences of the condition are shared with the ribosomopathies discussed [33].

The studies discussed illustrate the varying and seemingly context dependent role p53 may play in HSC associated disease. As demonstrated by Dutt et al., RP haplo insufficiency induced p53 activation was restricted to human primary erythroid progenitors [29]. The authors reasoned that this lineage specificity maybe incidental of the high proliferative nature of erythroid progenitor cells. Thus highly proliferative HSCs may generally exhibit increased sensitivity to RP mediated p53 activation. Therefore while it is clear RP-p53 mediated depletion of HSC is a contributing factor in bone marrow failure syndromes, an alternative perspective could reveal RPs as a potential therapeutic target in bone marrow malignancies. Pharmacological coercion may shift the ribosomal stress-p53 balance such that leukaemia cells are killed or sensitized to traditional leukaemia therapeutics. Is ribosome biogenesis an inherent weakness in haematological cancer cells? It is valuable to consider the molecular context of a haematological cancer cell in which the ribosome stress-p53 pathway may be exploited (Figure 2). Nucleophosmin (NPM1) is an essential multifunctional nuclear-cytoplasmic chaperone implicated in a myriad of cellular process, including ribosome biogenesis [34]. Mutation and translocation of NPM1 is frequently associated with haematological malignancies. In approximately 85% of anaplastic large cell lymphomas, the t(2;5) translocation produces a NPM1-ALK fusion protein [35]. Less frequently, NPM1-RAR and NPM1-MLF1 fusion proteins are associated with acute promyelocytic leukaemia and AML/myelodysplasia respectively [36,37]. NPM1 is the single most frequently mutated gene in AML [38]. A study published in 2012 by Ånensen et al. revealed that distinct p53 biosignatures could be associated with mutated NPM1 and could further be correlated to clinical outcome in AML [39]. These heterogeneous mutations comprise - the most common being an 4 nucleotide duplication (TCTG) - a disruption of the nucleolar localization signal and the creation of an extra nuclear export signal resulting in a dramatic change in localization from a steady-state nucleus/nucleolus to cytoplasm [34]. The cytoplasmic localized NPM1 mutant maintains its ability to interact with binding partners, including wild type NPM1, thereby inflicting the same cytoplasmic restrictions upon its bound partners. It seems the varying nature of these proteins dictates the oncogenic potential of the NPM1 mutant. For example, binding of the tumour suppressor p14Arf has been shown to mitigate its p53 regulatory activity resulting in reduced cell cycle arrest in mouse embryonic fibroblasts (MEFs) [40]. Similarly, the NPM1 mutant sequestration of cMyc to the cytoplasm protects the oncoprotein from ubiquitin driven degradation leading increased cellular levels [34].
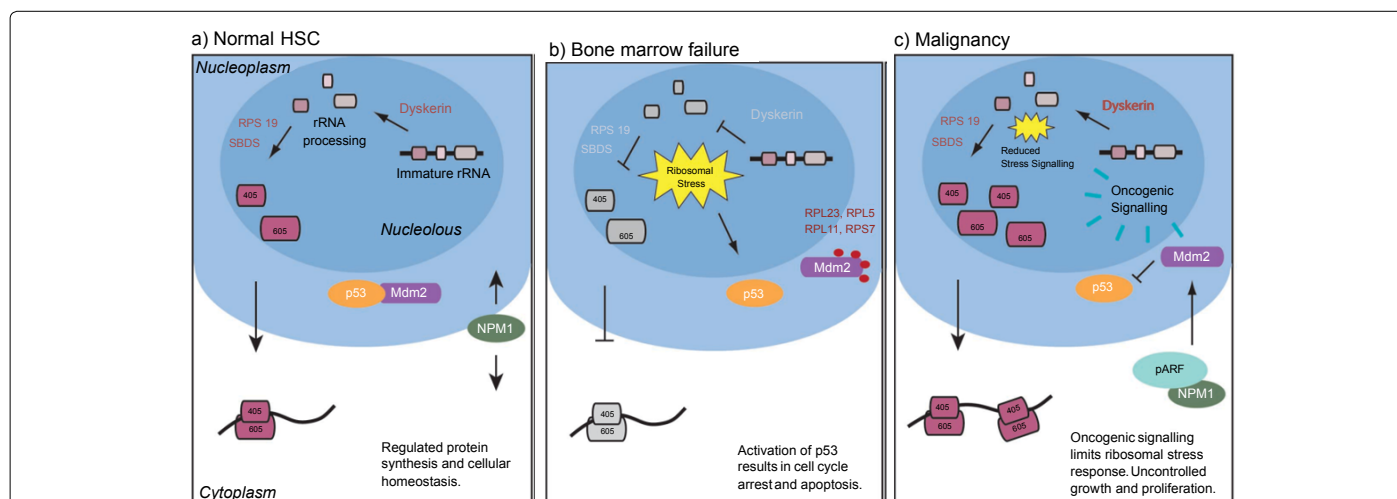

Figure 2: Comparing ribosome biogenesis and p53 activity in haematopoietic disease. a) represents a healthy haematopoietic stem cell. In the nucleolus, ribosome biogenesis is functional and regulated by proteins such Dyskerin, RPS 19 and SBDS. MDM2 regulates p53 in an appropriate manner and NPM1 nucleocytoplasmic shuttling is functional. b) HSCs in bone marrow failure syndromes contain reduced or defective copies of Dyskerin, RPS 19 and SBDS (indicated by grey colour). This leads to disrupted or reduced ribosome biogenesis culminating in a ribosomal stress response. Ribosomal proteins (RPL23, RPL5, RPL11 and RPS7) bind MDM2 and liberate p53. Constitutive activation of p53 may lead cell death and bone marrow aplasia. c) Represents a typical cancerous HSC. Accumulation of malignant mutations means oncogenic signalling dominates the cell. Ribosome biogenesis is abnormal but stress signalling to p53 is largely nullified by growth and proliferation signals. These signals may also accelerate ribosome biogenesis and protein synthesis. Mutated NPM1 is restricted to the cytoplasm further contributing to oncogenic signalling and inhibition of p53.

NPM1 Mouse Models and Ribosome Biogenesis

Much focus has been placed upon elucidating the functional consequences of the delocalized NPM1 mutants. However, in the context of leukaemia, the potential effect on ribosome biogenesis has been somewhat neglected. In vitro studies have shown that NPM1 interacts directly with multiple RPs and functions as an endoribonuclease for the maturing rRNA transcript [41,42]. A heterozygote mouse model of NPM1 (NPM1±) provided great insight into NPM1's ability to influence haematopoietic disease [43]. Initially mice exhibited characteristic features of myelodysplastic syndrome including dyserythropoiesis and megakaryocytic dysplasia. However, in a follow up study published 2 years later, the same NPM1± mice displayed high propensity to myeloid and lymphoid malignancies [44]. The model candidly reflects human disease progression from myelodysplastic syndrome to AML. The original publication from Grisendi et al. also demonstrated accumulation of activated p53 in NPM1± and hypomorphic mutant (NPM1hy/hy) MEF cells [43]. This was attributed to genomic instability; however, defective ribosome biogenesis was also observed and may have been a contributing factor. NPM1+/- cells exhibited reduced levels of the 80S subunit relative to wild type controls whilst NPM1hy/hy cells contained relatively less of all three subunits (40S, 60S and 80S) [43]. It may be possible that the dual tumour suppression/oncogenic potential of NPM1 are reflected in the mouse models described above and perhaps in human disease. Initially, dysfunctional or haploinsufficiency of NPM1 drives a genomic and ribosomal stress response, provoking p53 activation in proliferating haematopoietic cells. Over expression of p53 may initially manifest as aplasia or MDS-like conditions in the bone marrow compartment. However, accruement of additional mutation could release the oncogenic potential of NPM1 (and associated factors) thereby nullifying the initial p53 response and leading to malignant transformation. The spectrum of aplasia to malignancy observed in the NPM1 deficient mice may further reflect the variable haematopoietic dysfunction observed in the RP knockdown models described previously [34].

Targeting Ribosome Biogenesis

In toto, the studies discussed reveal a capricious balance of ribosome biogenesis and p53 stress that may have an important role in determining the fate of haematopoietic cells. As such, abnormal ribosome biogenesis may represent a therapeutically targetable weakness in cancer cells. Vast and heterogenic remodeling of cell signaling pathways are critical for cancer cell survival [45]. Pharmacological coercion of the ribosome-p53 balance to reactivate p53 against the wave of oncogenic signaling may provide a novel mechanism to induce cell death. Such a therapeutic strategy is particularly attractive in the context of haematological malignancies such as AML where more than 90% of patients comprise wild type p53 [46,47].

In 2010, Burger et al. conducted an insightful study of 36 unrelated chemotherapeutics in order to assess their ability to target ribosome biogenesis. Human sarcoma cells (2fTGH) were metabolically labelled with [32P] orthophosphate, enabling quantification of detectable rRNA forms following drug incubations [48]. Ten of the compounds inhibited rRNA transcription whilst another eleven appeared to target early or late rRNA processing. Furthermore, reduction of rRNA processing inversely correlated with p53 levels. The study illustrated the value of seeking new and old compounds that effectively target ribosome biogenesis in cancer cells.

Among the 36 compounds examined was the pyrimidine analogue, fluorouracil (5-FU). 5-FU's potential to incite irreversible DNA damage in an S-phase specific manner has been utilized against cancers for over 40 years [49]. However, it has become increasingly clear that 5-FU affects multiple facets of ribosome biogenesis including rRNA processing and pseudouridylation [50,51]. Intriguingly, bone marrow suppression is a frequent side effect associated with 5-FU and the compound has even been used to induce bone marrow aplasia in animal models [52]. Various therapeutic compounds have been associated with AA induction [9]. Some of these compounds, such as 5-FU, appear to inflict AA in a dose dependent manner, while other associations appear to be idiosyncratic. It is reasonable to hypothesise that, like 5-FU, some of these compounds target ribosome biogenesis in HSCs and effectively mimic the RP deficient congenital forms of AA discussed previously. The anticancer capacity of these ribosome-targeting compounds may even exceed p53 dependency.

Pharmacological repression of anthracycline induced protein synthesis in p53 negative models of AML was shown to significantly enhance cell death. Intriguingly, accumulation of ribosomal protein RPP2 was observed following daunorubicin treatment and may contribute to leukemic cell resistance to anthrycycline treatment [53]. Can abnormal ribosome biogenesis sensitize cancer cells to available Aplastic Anaemia inducing pharmaceuticals? Drug induced AA accounts for a small fraction of disease cases and is attributed to a range of functionally and structurally distinct compounds [4]. Idiosyncratic drug responses are exceptional and restricted to a small minority of patients. However, compounds associated with these events are consistent despite such responses being rare [8]. The idiosyncratic nature of drug induced AA obstructs mechanistic studies to reveal any underlying relationship and only limited information can be gathered through controlled case studies [54]. The bacteriostatic chloramphenicol exhibits the strongest epidemiological correlation with drug induced AA [55]. Chloramphenicol is directly myelosuppressive at high doses, however, at regular dosing levels the tendency to develop AA increases to 25- fold that of the general population [56]. An inherited sensitivity to toxic drug intermediates may be causative [55]. However, it is also conceivable that chloramphenicol exercises its bone marrow inhibitory effect by binding and disrupting human ribosomes in a manner analogous to its prokaryotic function. A twisted pharmacogenetic perspective may help explain the scarcity yet consistency of such side effects.

Genes encoding ribosomal proteins within a human population contain many polymorphisms. Individuals who develop AA following unrelated medication may have genetic polymorphisms predisposing to the condition [57]. Furthermore if these polymorphisms result in altered or limited ribosome biogenesis, drugs associated with idiosyncratic AA may target ribosome biogenesis thereby revealing the underlying genetic disposition. It is possible that haematological cancer cells share the same inherent weakness due to abnormal ribosome function and may be targetable with AA inducing compounds. Table 1 provides an incomprehensive list of candidate drugs illustrating the variety of compounds associated with AA and or bone marrow suppression [9,58]. These drugs should be screened for anticancer activity and ribosomal reactivation of p53. Yeast studies with 5-FU provide an in vitro analogy of how the relationship may operate. 5-FU coated rRNAs are subject to exosome degradation and yeast strains haploinsufficient for exosome components accumulate rRNAs [59]. This initiates a ribosomal stress response rendering them hypersensitive to 5-FU treatment [60]. An inherent version of this ribosome haploinsufficient synthetic lethality may be operational in patients suffering from idiosyncratic drug induced AA. Similarly haematological cancer cells, particularly those containing dysfunctional or haploinsufficient NPM1, may be sensitive to pharmacological targeting of ribosome biogenesis and reactivation of p53.

In conclusion, hereditary forms of AA manifest as rare bone marrow failure syndromes (DC, DBA and SDS) in which genetic abnormalities directly impair ribosome biogenesis. Interestingly, these conditions are all associated with varying degrees of predisposition to haematological malignancies [5]. *In vitro* and *in vivo* knockdown studies of RPs have revealed an intimate relationship between ribosome biogenesis and p53 that appears to govern cell fate in human haematopoietic disease. Since the aplasia inducing properties of nitrogen mustards were exploited to treat leukaemia and lymphoma [2], a plethora of seemingly unrelated drugs have emerged that also provoke AA as a side effect (Table 1). These compounds may target important ribosomal process thereby mimicking congenital forms of bone marrow failure and inducing AA. If so, the AA inducing drugs may also share the anti-cancer potential of mustard gas through targeting abnormal ribosome biogenesis in malignant HSC (Figure 3). Targeting of ribosome biogenesis is emerging as an important therapeutic strategy in cancer; the studies discussed in this review reveal this may be especially true of haematological malignancies. Targeted drug development is an arduous, expensive and time-consuming process. Repurposing of AA inducing drugs could provide a novel, clinically applicable therapeutic strategy in haematological malignancies.

Primary use	Drug (s)
Antibacterial	Chloramphenicol, Co-trimoxazole
	Sulphonamides, Tetracyclines
Anti-inflammatory agents	Benoxaprofen, Fenbufen, Indomethacin
	Oxyphenbutazone, Penicillamine
	Phenylbutazone, Piroxicam
Anti-thyroid Agents	Carbimazole,Thiouracil
Anti-Malarial Agents	Amodiaquine, Mepacrine, Pyrimethamine
Anticonvulsants	Phenytoin
Antidepressants	Chlorpromazine, Dothiepin
	3,4-Methylenedioxymethamphetamine
Anti-hypertension agents	Lisinopril
Anti-diabetic agents	Chlorpropamide, Tolbutamide
Other	Acetazolamide, Ticlopidine

Table 1: Drugs implicated in the development of AA and/or bone marrow failure.

A multitude of mechanistically diverse drugs have been associated with AA and bone marrow failure. These compounds may harbour untapped therapeutic potential in haematological malignancies. The table provides a diverse selection of drugs implicated in bone marrow suppression but is does not comprise of all associated compounds [9,58].
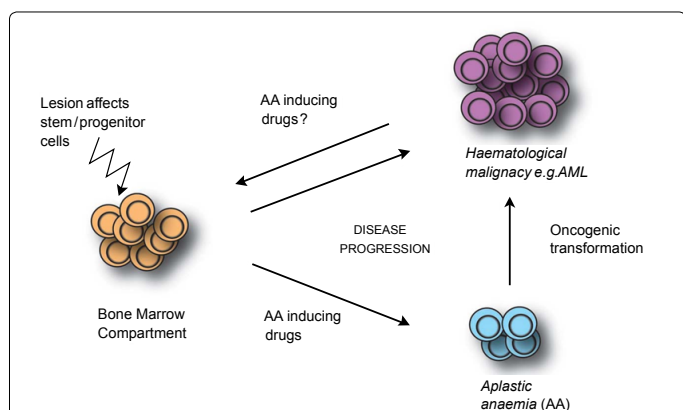

Figure 3: Haematological disease progression in the bone marrow compartment. Lesions in the form of inherited genetic defects or acquired mutations drive haematopoietic disease in the form of aplastic anaemia or malignant transformation. Unrelated drugs may also damage the bone marrow compartment leading acquisition of AA. Whilst progression to oncogenic transformation is frequently associated with AA, treatment with AA inducing drugs may induce regression of the cancer through targeting ribosome biogenesis.

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