bjh review

Mechanisms and clinical applications of chromosomal instability in lymphoid malignancy

Maxwell M. Krem,[1,2]* Oliver W. Press,[2] Marshall S. Horwitz[3] and Timothy Tidwell[3]

[1]Department of Medicine and Institute for Stem Cell and Regenerative Medicine, University of Washington School of Medicine, [2]Clinical Research Division, Fred Hutchinson Cancer Research Center, and [3]Department of Pathology and Institute for Stem Cell and Regenerative Medicine, University of Washington School of Medicine, Seattle, WA, USA

Summary

Lymphocytes are unique among cells in that they undergo programmed DNA breaks and translocations, but that special property predisposes them to chromosomal instability (CIN), a cardinal feature of neoplastic lymphoid cells that manifests as whole chromosome- or translocation-based aneuploidy. In several lymphoid malignancies translocations may be the defining or diagnostic markers of the diseases. CIN is a cornerstone of the mutational architecture supporting lymphoid neoplasia, though it is perhaps one of the least understood components of malignant transformation in terms of its molecular mechanisms. CIN is associated with prognosis and response to treatment, making it a key area for impacting treatment outcomes and predicting prognoses. Here we will review the types and mechanisms of CIN found in Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma and the lymphoid leukaemias, with emphasis placed on pathogenic mutations affecting DNA recombination, replication and repair; telomere function; and mitotic regulation of spindle attachment, centrosome function, and chromosomal segregation. We will discuss the means by which chromosome-level genetic aberrations may give rise to multiple pathogenic mutations required for carcinogenesis and conclude with a discussion of the clinical applications of CIN and aneuploidy to diagnosis, prognosis and therapy.

Keywords: lymphoma, leukaemia, chromosomal instability, aneuploidy, translocations.

Cancers are characterized by intrinsic genetic derangements and may evolve additional mutations that confer a pathogenic survival advantage. Genetic instability, an increased propensity towards mutations, is a requirement for malignant transformation (Loeb, 1991). Two classes of genetic instability occur at the chromosomal level: gains or losses of whole chromosomes and chromosome translocations (Lengauer *et al*, 1998). Chromosomal aberrations are the most frequent mutations in lymphoid malignancies (Küppers, 2005; Nussenzweig & Nussenzweig, 2010). The mechanisms behind chromosomal instability (CIN) in lymphoid malignancies fit within several definable patterns. We will describe the molecular pathogenesis of CIN and explore contemporary hypotheses for how chromosome-level errors of DNA handling predispose to cancer.

The terminology relevant to chromosomal mutations is potentially confusing. Pfau and Amon (2012) provide a detailed discussion of 'ploidy' terminology. 'Aneuploid' is Greek for 'not correct fold', or a chromosome number that is an incorrect multiple of the haploid content. 'Aneuploidy' is used in a less strict sense to refer to partial chromosomal gains or losses, i.e. translocations (abnormal fusions between heterologous chromosomes). The terms aneuploidy and CIN are not interchangeable. The former refers to a state of an erroneous chromosomal content, whereas the latter connotes a dynamic mutator state characterized by a heightened rate of chromosomal losses or gains. Aneuploidy is therefore a likely outcome of CIN, but the presence of one does not conclusively establish the presence of the other (Lengauer *et al*, 1998; Bakhoum & Compton, 2012). Relevant terminology and abbreviations are further defined in Table I.

Mechanisms of CIN

Mechanisms

The major areas of vulnerability to chromosomal defects are the '3 Rs' of DNA processing (recombination, replication and repair); telomere function; and mitotic spindle function (regulation of spindle attachment, centrosome function, chromosomal segregation and cytokinesis). Several other processes, most notably infections, are additionally implicated in contributing to errors of chromosomal content.

Relative contributions of different mechanisms vary based on disease subtype and cellular origin, determining the pre-

Correspondence: Maxwell M. Krem, James Graham Brown Cancer Center, University of Louisville, Louisville, KY 40202, USA.
E-mail: mkrem@u.washington.edu
**Present address*: Department of Medicine and Division of Blood and Bone Marrow Transplantation, University of Louisville School of Medicine, Louisville, KY, USA

First published online 26 May 2015
doi: 10.1111/bjh.13507

Table I. Definitions and frequently used abbreviations.

ALL	Acute lymphoblastic leukaemia/lymphoma
BL	Burkitt lymphoma
Aneuploidy	State of erroneous chromosomal content, literally 'not correct fold' or multiple of the haploid chromosomal content
CIN	Chromosomal instability, a dynamic mutator state characterized by a heightened rate of chromosomal losses or gains
CLL	Chronic lymphocytic leukaemia/small lymphocytic lymphoma
DLBCL	Diffuse large B cell lymphoma
DSB	Double-strand break
FL	Follicular lymphoma
HL	Hodgkin lymphoma
HR	Homologous recombination
MCL	Mantle cell lymphoma
MM	Multiple myeloma
NHEJ	Non-homologous end joining
NHL	Non-Hodgkin lymphoma

dominant chromosomal aberrations in each disease. Errors of mitotic function are primarily responsible for changes in chromosome number, which have the highest prevalence in Hodgkin lymphoma (HL) and are frequent in paediatric B-cell acute lymphoblastic leukaemia (ALL) (Küppers, 2005); those diseases arise from lineages that rely less on gene rearrangements (pre- or pro-B cells) or have lost gene-rearranging capability (Reed-Sternberg cells). Translocation-generating errors of DNA processing and telomere function, by contrast, account for the high prevalence of translocations in non-Hodgkin lymphoma (NHL), with approximately 12 breakpoints per case of diffuse large B-cell lymphoma (DLBCL) (Nanjangud *et al*, 2002); NHL disease subtypes primarily arise from immature and maturing lymphocytes, which rely heavily on gene rearrangements.

Recombination, replication and repair

Lymphocyte function depends upon generation of variability at immunoglobulin (B cells) and T-cell receptor (TCR, T cells) loci, making lymphocytes heavily reliant upon DNA processing. We will describe how programmed cellular processes and their associated repair mechanisms (Recombination and Double-strand breaks) and spontaneous DNA breakages (DNA fragility and Replication) account for the high prevalence of translocations in lymphomas (Fig 1). Normal functions that predispose to translocations are summarized in Table II.

DNA fragility

DNA fragile sites are chromosomal regions with an increased risk of breakage in the setting of partial DNA replication inhibition and confer an underlying susceptibility to translocations (Fig 1A). They originate from DNA repeat sequences

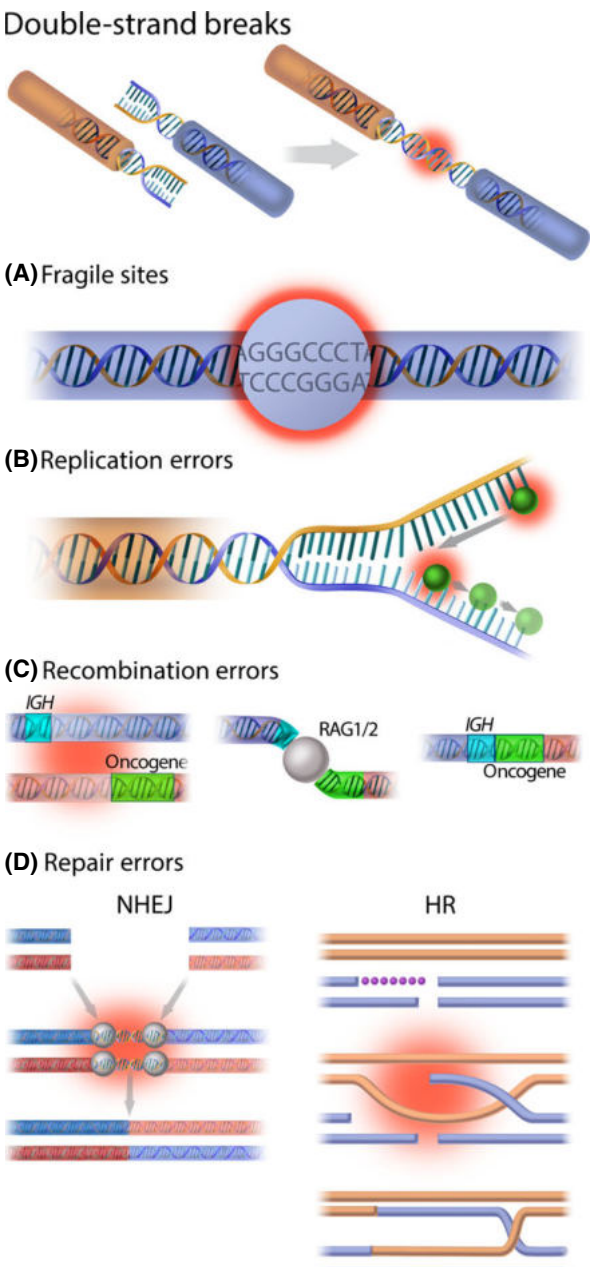

Fig 1. Processes that can lead to chromosomal translocations. (A) Fragile sites. The consequences of these repeat sequences are higher torsional flexibility, ability to form non-B DNA structures, and interference with chromatin folding. (B) Replication errors. Regulation of replication origins and replicative helicases protects against chromosomal abnormalities. (C) Recombination is mediated in large part by the RAG1/2 recombinases; errors frequently place proto-oncogenes under the regulation of strong promoters for immunoglobulin genes. (D) Double strand break repair takes place through the closely related functions homologous recombination (HR) and non-homologous end-joining (NHEJ), crucial players in protecting against chromosomal instability and lymphomagenesis.

in polymorphic CCG/CGG trinucleotide repeats (folate sensitive) or AT-rich minisatellite repeats (non-folate sensitive), causing higher torsional flexibility, ability to form non-B

Table II. Physiological lymphocyte functions that predispose to pathological translocations.

Cell	Process	Product
B lymphocyte	V(D)J recombination Somatic hypermutation Class switch recombination	*IGH*
	VJ recombination Somatic hypermutation	*IGK* and *IGL*
T lymphocyte	V(D)J recombination	T-cell receptor genes

DNA structures and interference with chromatin folding (Durkin & Glover, 2007). Fragile sites have been mapped to the sites of chromosomal translocation breakpoints, tumour suppressor genes, high-level amplifications and oncogenes in mantle cell lymphoma (MCL) (Bea *et al*, 2009), multiple myeloma (MM) (Lukusa & Fryns, 2008) and ALL (Gümüş *et al*, 2002). B cells, which experience high replicative stress, are subject to a specialized type of genomic hotspot, the early replication fragile site (ERFS). ERFSs are triggered by replicative stress, including S phase arrest (induced by hydroxycarbamide), high transcriptional activity, or oncogene expression (such as *MYC* activation). ERFSs may trigger replication fork collapse and are probably permissive to double-strand breaks (DSBs), which may lead to translocations. More than half of recurrent amplifications or deletions in human DLBCL map to ERFSs (Barlow *et al*, 2013).

Replication

Damage to the machinery of DNA replication (Fig 1B) is associated with chromosomal abnormalities and lymphoma in humans, and murine models provide corroboration (Table SI). MCM4 forms part of the MCM2-7 complex that helps license DNA replication origins and serves as the core of the helicase that unwinds DNA at replication forks. Loss of the RecQ helicase BLM leads to Bloom Syndrome, characterized by small stature, male infertility, predisposition to leukaemia and lymphoma, and immunodeficiency. Another two regulators of replication origins, CDT1 and CDC6, are overexpressed in a subset of MCL, with associated increases in chromosomal abnormalities as measured by comparative genomic hybridization (CGH); the additional prevalence of TP53 alterations potentiated the rate of chromosomal aberrations (Pinyol *et al*, 2006).

Recombination

Lymphocytes are unique in that they undergo programmed DNA breakage and rejoining. B and T lymphocytes achieve functional flexibility through immunoglobulin and TCR class switching, respectively, which requires recombination among the **V**ariable, **D**iversity, and **J**oining [V(D)J] regions of immunoglobulin genes. Heavy usage of recombination places the lymphocyte at greater risk of pathological translocations; analogous to the hero's flaw in classical tragedy, V(D)J recombination is the *hamartia* ('flaw' or 'error' in Greek) that generates both the lymphocyte's greatness and downfall.

V(D)J recombination permits diverse antigen presentation and recognition by lymphocytes. Immunoglobulin and TCR genes are constructed by recombinational selection of single V, D, and J regions from multiple, tandem-arrayed V, D, and J region choices along the loci. Beyond performing V(D)J recombination, B cells utilize somatic hypermutation and class switching to augment antibody affinity and broaden range of function, respectively (Küppers, 2005; Nussenzweig & Nussenzweig, 2010; Lin *et al*, 2012; Alt *et al*, 2013). Mistakes in V gene recombination, class switching, and somatic hypermutation are features of translocations in B-cell lymphomas; the *IGH* locus on chromosome 14 is a primary 'hotspot' for translocations in B-cell malignancies, which probably take place in the bone marrow, early in B cell development (Küppers, 2005; Nussenzweig & Nussenzweig, 2010; Bouamar *et al*, 2013). Aberrant somatic hypermutation, taking place during the germinal centre reaction, creates DSB-induced translocations in DLBCL-related proto-oncogenes (Pasqualucci *et al*, 2001). Erroneous V(D)J recombination during the development of immature B cells is centrally involved in the generation of *IGH* locus breaks that result in t(11;14) associated with MCL (Küppers, 2005). By contrast, T cells do not perform class-switching and somatic hypermutation, and their rearrangements are primarily confined to the TCR loci on chromosomes 7 and 14 (Ong & Le Beau, 1998). Compared to T cells, B cells' increased reliance on translocation-predisposing mechanisms for DNA editing and breakage accounts for the the vast majority of lymphomas being of B-cell origin.

V(D)J recombination requires a complex molecular machinery, at the centre of which is the RAG1/2 recombinase. Multiple lines of evidence support the theory that RAG1/2 nicks DNA to facilitate recombination, with the unintended side-effect of generating translocation-prone lesions in or near oncogenes, leading to their activation (Nussenzweig & Nussenzweig, 2010). *In vitro* data suggests that proto-oncogenes contain cryptic sequences that attract illegitimate V(D)J recombination events in both the TCR and *IGH* loci (Marculescu *et al*, 2002).

Double-strand breaks

Double-strand breaks may lead directly to translocations and occur both inside and outside the context of generating diverse antigen presenters via V(D)J recombination (Fig 1D). DSB repair takes place through the related functions homologous recombination (HR) and non-homologous end-joining (NHEJ), crucial players in protecting against CIN and lymphomagenesis.

Double-strand breaks originate from RAG1/2 or activation-induced cytidine deaminase (AICDA). AICDA is essential for class-switch recombination and somatic hypermutation during

germinal centre maturation of B cells. AICDA destabilizes the B-cell genome by producing U:G mismatches, causing DSBs, which then require NHEJ pathways for repair. Regulated AICDA expression leads to Ig class switching, but deregulated expression causes chromatid breaks and translocations throughout the genome (Nussenzweig & Nussenzweig, 2010). Sequencing of human lymphomas suggests that AICDA-induced breaks at CpG dinucleotides and WGCW (W = A or T) motifs cause t(11;14) and t(8;14) rearrangements in MCL and Burkitt lymphoma (BL), respectively (Greisman *et al*, 2012). Deregulated AICDA expression leads to point mutations in oncogenes in B lymphocytes; non-immunoglobulin gene mutations may be correlated with the presence of DSBs (Nussenzweig & Nussenzweig, 2010).

Activation-induced cytidine deaminase is also responsible for the phenomenon of clustered hypermutation, or kataegis. AICDA targets highly transcribed super-enhancers, resulting in clusters of deamination sites, especially the immunoglobulin loci (Qian *et al*, 2014). B cells are more prone to AICDA-related kataegis, marked by elevated genomic uracil content, than non-lymphoma cancers (Pettersen *et al*, 2015). AICDA-induced kataegis partially explains why the highly-transcribed *IGH* region is a translocational hotspot.

Double-strand breaks may originate iatrogenically due to alkylator drugs, demonstrated with nitrogen mustard, vincristine, procarbazine and prednisone-treated patients in HL (Salas *et al*, 2012) and chemotherapy-treated ALL survivors (Brassesco *et al*, 2009). Radiation exposure can cause DSBs, and translocations may result from ensuing DSB misrepair (Allan & Travis, 2005).

Homologous recombination utilizes the sequence on the homologous sister chromatid as a repair template for DSBs. Generation of a single-stranded 3′ end makes homologous pairing and strand invasion possible; in this manner, HR restores the original sequence prior to a mutagenic event. NHEJ functions through direct reconnection of the ends of DSBs, with the potential for loss of genetic material, as extended sequence homology is not utilized. HR is more accurate but is only available during S and G2 phases of the cell cycle. NHEJ is the less accurate but more readily available method of DSB repair.

Lymphoid malignancy-related genes involved in HR include *ATM* and *NBN*. ATM, the DNA-damage Ser-Thr kinase whose autosomal recessive mutation causes ataxia-telangiectasia, repairs RAG-induced locus breaks during V(D)J recombination (Shiloh, 2003). ATM may play an additional role in protecting against cyclin-induced DSBs (Aggarwal *et al*, 2007). Nijmegen breakage syndrome is an autosomal recessive disorder caused by mutation of *NBN*, a downstream substrate of ATM that locates to DSB sites and participates in DNA damage repair. Manifestations include microcephaly, mild growth retardation, intellectual disability and strong predisposition to lymphoid malignancies, notably DLBCL and T-cell ALL (Chrzanowska *et al*, 2012).

As NHEJ confers the risk of loss of genetic material, it is more likely to contribute to mutagenesis events and translocations, compared with HR. Translocation reporter experiments demonstrate that HR is less proficient at mediating translocations due to crossover suppression. The core factors in NHEJ (XRCC4-6, PRKDC, DCLRE1C, and LIG4) perform the steps of binding, processing and ligating DNA ends, are essential to immune function and ultimately protect against translocations (Nussenzweig & Nussenzweig, 2010). Mutation of *DCLRE1C* attenuates NHEJ and is accompanied by lymphopenias, immunodeficiency, CIN and Epstein-Barr virus (EBV)-associated lymphomas (Moshous *et al*, 2003). The majority of data regarding the oncogenic potential of NHEJ core factor loss comes from murine knockout models in which dual loss of a NHEJ core factor and *TP53* leads to lymphoma (Table SII). A recurring theme is that concurrent knockout of *TP53* is required for malignant phenotypes.

TP53 binding protein 1, TP53BP1, beyond interacting with TP53, plays a key role in regulating DSB repair. TP53BP1, a DNA damage repair protein, limits accumulation of BRCA1 at DSB sites and inhibits HR (Bunting *et al*, 2010), tipping the balance of DSB repair in favour of NHEJ. When the lymphocyte requires rapid and less restrictive DSB repair capacity, TP53BP1 turns on the switch favouring NHEJ. *TP53BP1* copy loss has been demonstrated in cases of DLBCL (Takeyama *et al*, 2008).

From DSBs to translocations

The chance of DSBs progressing to translocations is from 0·4% to 1% (McCord & Dekker, 2011). Several factors favour translocation formation. The spatial positioning of chromosomes may play a role. Physical proximity of loci prone to breakage may increase the frequency of translocation, as observed with *MYC* and *IGH* (Nussenzweig & Nussenzweig, 2010). Deep sequencing of translocation sites in B cells reveals that active transcription start sites, class-switch recombination sites and the presence of AICDA activity also favour translocation formation (Chiarle *et al*, 2011; Klein *et al*, 2011).

Telomere dysfunction

Breakage-fusion-bridge cycles

Telomeres are physiological DSBs that protect against end-to-end fusions (Fig 2): the sparing of chromosomal end-caps from breakages and ensuing breakage-fusion-bridge (BFB) cycles led to the discovery of telomeres. Telomere loss is linked to infertility, impaired haematopoiesis, chromosome fusions and aneuploidy. Telomere dysfunction and BFB cycles are strongly implicated as sources of CIN in lymphoid malignancies. Telomere loss may be a mechanism for CIN in Reed-Sternberg cells and HL by leading to disruption of the standard three-dimensional distribution of chromosomes within the nucleus (Knecht *et al*, 2009; Guffei *et al*, 2010). BFB cycles amplify oncogenic translocation events and provide a partial explanation why DSBs cause CIN. In murine

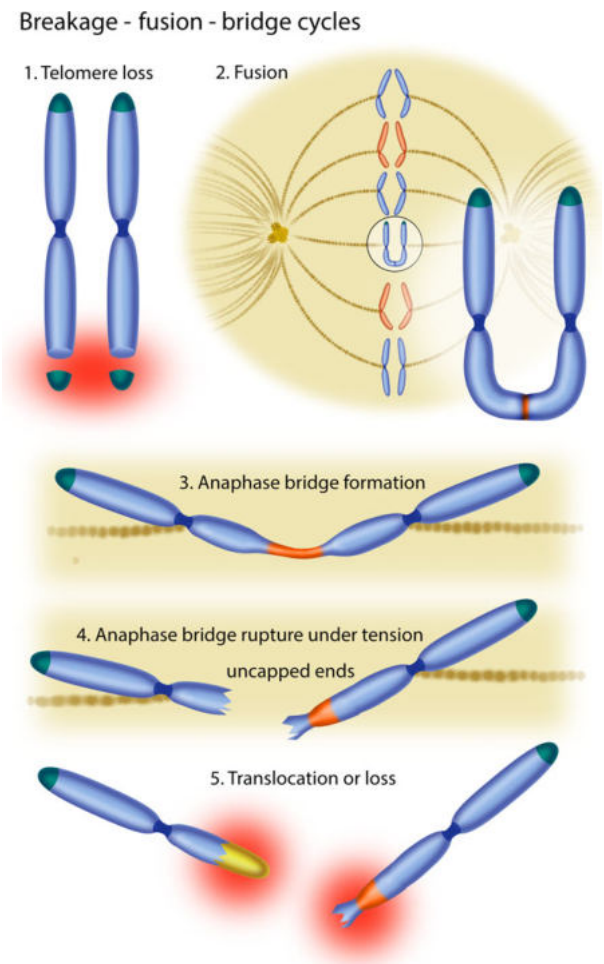

Fig 2. Telomere dysfunction and breakage-fusion-bridge (BFB) cycles. Telomere dysfunction or absence (panel 1) leads to BFB cycles, in which sister chromatids fuse to each other (panel 2) and subsequently form internuclear DNA bridges during anaphase (panel 3). These 'anaphase bridges' ultimately rupture due to forces of tension (panel 4), leaving uncapped ends, which are free to repeat the cycle again, resulting in translocations and aneuploid nuclei (panel 5). BFBs can be considered a variant of abnormal recombination.

models, BFB cycles amplify the *IGH-MYC* fusion (Gladdy *et al*, 2003). The amplification may result from the absence of NHEJ or the inability to maintain telomere length, possibly from inadequate telomerase recruitment (Fisher & Zakian, 2005). BFB cycles are responsible for intrachromosomal amplification of chromosome 21, a cytogenetic marker for a poor-prognosis subset of precursor B-cell ALL that contains *RUNX1*, which encodes a haematopoietic transcription factor necessary for haematopoiesis and is strongly implicated in leukaemogenesis (Sinclair *et al*, 2011; Heerema *et al*, 2013).

Telomere structure and function

Telomere protection and length homeostasis rely upon the shelterin complex, consisting of TERF1, TBPL1, TERF2IP, TINF2, TPP1 and POT1 (de Lange, 2005). Disruption of the complex by altering expression or mutating one of its components may be oncogenic (Begemann *et al*, 2009). ATM, known as a V(D)J recombination cofactor, also regulates telomere length (Qi *et al*, 2003). Maintenance of telomere length prevents CIN, and telomerase (TERT) plays perhaps the most crucial role in preventing telomere shortening. Expression of telomerase (and XRCC5) is reduced in chronic lymphocytic leukaemia (CLL) (Poncet *et al*, 2008). By contrast, mutation of the shelterin component ACD in human cells causes telomere *elongation* (de Lange, 2005). Down-regulation and dysfunction of ACD and TINF2 are associated with decreased telomere function in CLL (Augereau *et al*, 2011).

Telomere length correlates with clinical syndromes and, occasionally, prognosis. Compared with age-matched healthy controls, patients with aggressive NHL had T cells, B cells and granulocytes with telomere shortening; the predominant malignancies were DLBCL and follicular lymphoma (FL) (Widmann *et al*, 2007). Among NHL patients, telomere length was shortest for MCL and CLL at 3–6 kB; germinal centre-derived lymphomas (FL, DLBCL, and BL) possessed the longest telomeres at 6–8 kB (Lobetti-Bodoni *et al*, 2010). A separate study confirmed shorter telomere length in MCL but found no correlations among telomere length, clinical characteristics, morphology, or karyotype (Cottliar *et al*, 2009). The dependence of telomere length on lymphoma subtype may be related to differing expression levels of telomerase during B-cell development. Germinal centre B cells are unique in their expression of telomerase and ability to elongate their telomeres, which may explain why post-germinal centre B cells and germinal centre-derived lymphomas have longer telomeres. Nevertheless, a definitive mechanism leading from telomere loss to CIN remains to be delineated (Lobetti-Bodoni *et al*, 2010). Shorter telomeres in HL have been associated with refractory disease (Knecht *et al*, 2012) and predisposition to second malignancies (M'kacher *et al*, 2007). Telomere length in CLL also correlates strongly with outcome, with telomere length shorter than 5 kB predicting reduced treatment-free and overall survival and increased risk of Richter transformation (Lobetti-Bodoni *et al*, 2010).

Spindle attachment, centrosomes, and mitotic regulation

The integrity of cellular chromosomal content depends on the mitotic spindle, the structure that pulls condensed chromosomes to respective daughter cells, and the centrosomes, the organelles responsible for establishing and orienting the mitotic spindle (Vitre & Cleveland, 2012). Spindle and centrosome function guard against chromosome missegregation and CIN (Fig 3).

Spindle and microtubule attachment

Mutation and dysregulation of kinetochore components are linked to chromosomal missegregation in lymphoid malig-

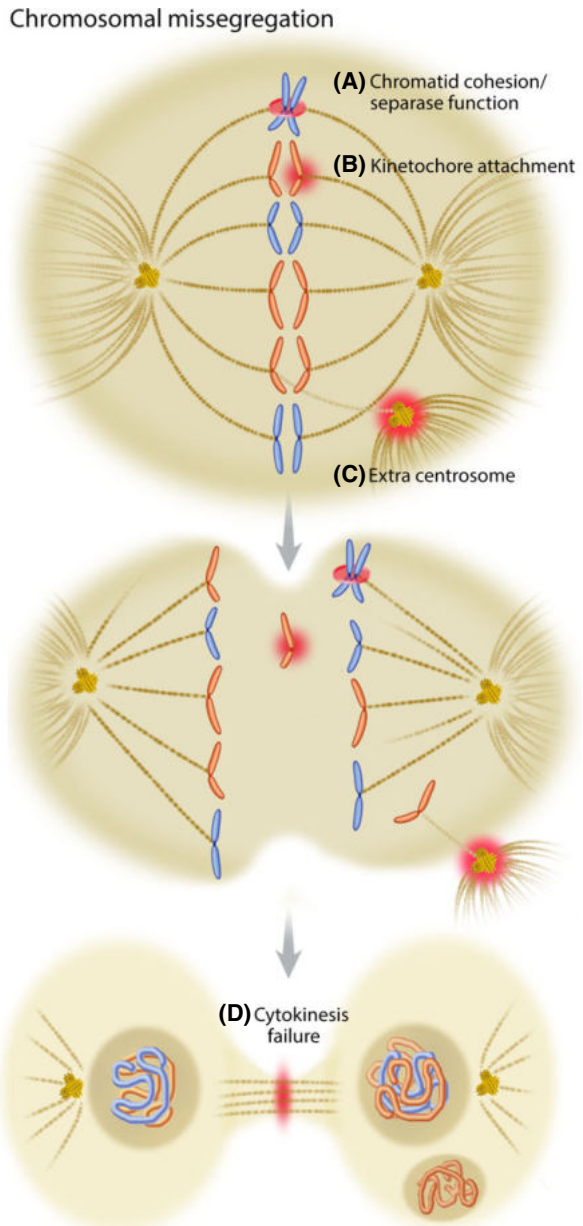

Fig 3. Errors of chromosome segregation and mitotic function. (A) The protease separase is required for chromatid separation and chromosomal stability. (B) Chromosomes attach to the mitotic spindle via the kinetochore, a multifunctional protein complex that connects centromeric DNA to the microtubule components of the spindle. Incorrect or inadequate kinetochore attachment creates a predisposition to chromosomal segregation errors at anaphase. (C) The centrosome cycle is closely linked to the cell cycle; duplication of the single centrosome takes place during G1 and S phase, with the mother and daughter centrosomes separating during mitosis, leaving the daughter cells once again with a single centrosome. Extra centrosomes trigger aneuploidy primarily through disruption of one-to-one kinetochore-to-spindle pole attachments, as opposed to causing multipolar mitoses. (D) Cytokinesis involves the formation of a cleavage furrow between the dividing daughter cells, leading to the formation of the midbody, an intracellular protein complex that serves as the last point of contact between the dividing cells. Failure to complete cytokinesis may disrupt the normal segregation of chromosomes.

nancy (Fig 3). Deletions in the kinetochore protein BUB1 have been demonstrated in T lymphoblastic lymphoma cell lines and in tumour cells from ALL and HL patients (Ru *et al*, 2002); mutations of *BUB1* and the related *BUB1B* are associated with complex chromosomal abnormalities in T cell lymphoma cases (Ohshima *et al*, 2000).

The germinal centre-expressed gene *LMO2*, associated with improved survival in DLBCL (Lossos *et al*, 2004), is a DNA-binding protein that regulates expression of kinetochore proteins, centromere proteins and other mitotic regulators. LMO2 provides convincing evidence that regulation of chromosomal segregation impacts both DLBCL pathogenesis and prognosis. Bioinformatic analysis of genes implicated in pathogenesis of cutaneous T-cell lymphoma suggests that kinetochore proteins are implicated in the pathogenesis of mycosis fungoides (van Kester *et al*, 2012).

Faithful segregation

Regulation of sister chromatid separation at the metaphase-to-anaphase transition protects against aneuploidy. Deregulation of ubiquitination is associated with chromosome missegregation. Overexpression of the deubiquitinase USP44 triggers prolonged mitotic checkpoint activity, leading to anaphase bridges, chromosome segregation errors and aneuploidy; furthermore, USP44 is overexpressed in a subset of T-cell ALL and is believed to regulate cyclin expression (Zhang *et al*, 2011). A microarray study of DNA from MCL cases demonstrated recurrent impact of chromosomal alterations on *MAP2*, *MAP6* and *TP53*, all of which are associated with microtubule function (Vater *et al*, 2009). Similarly, aurora A overexpression and gene polymorphisms may occur in sporadic cases of MCL, contributing to numerical chromosome aberrations (Camacho *et al*, 2006). PTTG1 is a vertebrate homolog of yeast securins, which regulate synchronous sister chromatid separation at the metaphase-to-anaphase transition. PTTG1 appears correlated with cells that are highly proliferative, and overexpression has been linked to aneuploidy (Yu *et al*, 2003). PTTG1 is highly expressed in plasma cell tumours, DLBCL, FL and Reed-Sternberg cells (Saez *et al*, 2002).

Centrosomal amplification

Centrosome amplification is present in nearly all solid and haematological malignancies (Zyss & Gergely, 2009). Dysregulation of the centrosome cycle is strongly linked to lymphoid malignancy. The leucine zipper transcription factor MYC may function oncogenically by upregulating aurora kinases, causing centrosomal amplification and CIN (den Hollander *et al*, 2010). In a murine model of large granular lymphocyte leukaemia (LGL), overexpression of interluekin 15 (IL15) stimulates MYC, in turn upregulating aurora kinases, leading to centrosomal amplification and aneuploidy (Mishra *et al*, 2012). Centrosomal amplification can initiate

leukaemic transformation in lymphoid lineages early in haematopoiesis. Activating mutations of the centrosomal protein PTPN11 cause centrosomal amplification and aneuploidy, resulting in murine ALL (Xu *et al*, 2011). *PTPN11* mutation is causative of Noonan syndrome, which predisposes patients to ALL (Pauli *et al*, 2012). Clinical correlates of centrosome dysfunction are found in HL (Martin-Subero *et al*, 2003) and NHL, in which disease aggressiveness is associated with the presence of centrosomal abnormalities (Krämer *et al*, 2003).

Cytokinesis failure

Inability to complete cytokinesis is a cause of CIN in B-cell neoplasms. Haploinsuffiency for the kelch domain-containing 8B protein, KLHDC8B, which localizes to the midbody, has been linked to familial HL; functional studies of KLHDC8B demonstrate markedly delayed cytokinesis as the cause of mitotic errors and aneuploidy (Krem *et al*, 2012). Video microscopic observation of HL cell lines confirms that multinucleated Reed-Sternberg cells arise from incomplete cytokinesis of mitotic daughter cells that remain joined via the midbody bridge (Rengstl *et al*, 2013). The tumour suppressor RASSF1 regulates several mitotic functions, including cytokinesis. Murine knockout of *Rassf1a* together with *Tp53* caused increased predisposition to lymphoma. Video microscopy of embryonic fibroblasts from the mice demonstrated cytokinetic failure and CIN, with a significant fraction of tetraploid cells (Tommasi *et al*, 2011). Cytokinesis and abscission failure represent attractive, though relatively new, explanations for CIN in lymphoid malignancy.

Other pathogenic mechanisms

Structural chromosomal abnormalities in lymphoid malignancies may arise from pathogenic processes such as infections, epigenetic changes and oxidative stress.

Infections

Infections of lymphocytes may contribute substantially to CIN. The human T-cell lymphotrophic virus type 1 (HTLV-1) contributes to CIN via the Tax oncoprotein, which promotes generation of reactive oxygen species (ROS) and centrosomal amplification (Chlichlia & Khazaie, 2010). EBV infection, linked to HL and BL, promotes CIN via multiple mechanisms. EBV impairs DSB repair, telomere function, spindle checkpoint function and TP53 expression; it may also upregulate AICDA (Bornkamm, 2009; Gruhne *et al*, 2009). Kaposi sarcoma-associated herpesvirus causes CIN by suppressing TP53 function (Si & Robertson, 2006). Chlamydia psittaci, which is thought to be the causative infectious agent of ocular mucosa-associated lymphoid tissue lymphomas, may contribute to CIN by triggering DNA oxidative damage and interfering with the mitotic checkpoint by causing centrosome abnormalities, spindle defects, multinucleation and abscission failure (Brown *et al*, 2012; Collina *et al*, 2012).

Epigenetics

Epigenetic alterations are linked to CIN and lymphoid malignancy. In FL and DLBCL, defects in histone acetylation lead to activation of *BCL6* and inactivation of *TP53* (Pasqualucci *et al*, 2011). These acetylation errors may also play a role in FL transformation (Pasqualucci *et al*, 2014). In the previously described murine model of LGL (Mishra *et al*, 2012), IL15 expression downregulates *MIR29B*, leading to increased DNMT3B expression, enhanced genomic methylation and CIN. In fact, DNA methylation and modulation of chromatin structure favour translocations (Lin *et al*, 2012). Epigenetic deregulation has prognostic impact and is associated with aggressiveness and chemotherapy-responsiveness of DLBCL (Jiang & Melnick, 2015).

Oxidative stress

Reactive oxygen species are associated with both CIN and malignancy; the mechanisms are not fully elucidated, though free radical generation leading to DNA damage is a plausible explanation. The antioxidant manganese superoxide dismutase (SOD2) appears to be protective; murine haploinsufficiency for *Sod2* predisposes to T-cell lymphomas (Van Remmen *et al*, 2003). In a murine T-cell lymphoma model, suppression of ROS by antioxidant enzymes may protect against CIN by suppressing chromosome breakage and thus translocations (van de Wetering *et al*, 2008).

Cellular and molecular consequences of CIN

The molecular consequences of aneuploidy and CIN that lead to malignancy are only partially delineated. Effects of aneuploidy include cellular stress, progression of aneuploidy to CIN and chromothripsis (Gordon *et al*, 2012; Pfau & Amon, 2012). We will review key mechanisms, with an emphasis on lymphoid cells.

Ubiquity

Lymphoma- or leukaemia-associated aneuploidies are insufficient for disease. Translocations occur in healthy lymphocytes and increase with age. There are 0·024 chromosomal aberrations per cell in the elderly, *versus* 0·0043 per cell in non-elderly controls (Mladinic *et al*, 2010). Likewise, the t(11;14)(q13;q32)/*IGH-CCND1* associated with MCL has a 1–2% prevalence in the blood of healthy individuals (Hirt *et al*, 2004), and the t(14;18)(q32;q21)/*IGH-BCL2* of FL is present in 36% of studied healthy controls and approximately 1–100 per 10^6 peripheral blood cells; in FL patients the t(14;18) is more prevalent, upwards of 3000 per 10^6 cells (Schuler *et al*, 2003). Thus, secondary genomic alterations

are required for malignant transformation, in concordance with data from murine models of FL (McDonnell & Korsmeyer, 1991) and MCL (Gladden *et al*, 2006). Aneuploidy is a phenomenon of even 'healthy' lymphoid cells.

Resolution

Cells have preexisting mechanisms in place to resolve aneuploidies to prevent a state of CIN. The TP53 pathway plays a central role and induces cell-cycle arrest and apoptosis in human cells in response to aneuploidy (Thompson & Compton, 2010). Minor aneuploidies trigger cell-cycle arrest, whereas substantial aneuploidies trigger apoptosis (Pfau & Amon, 2012). Chronic aneuploidy has negative effects on cellular physiology, including slowed proliferation, altered gene transcription, proteotoxic stress and metabolic stress; proteotoxic stress leads to ROS generation, which activates ATM and stimulates DSB repair (Gordon *et al*, 2012; Pfau & Amon, 2012). Hyperploid cells have been shown to induce an endoplasmic reticulum stress response and become immunogenic, making them susceptible to attack and elimination by the immune system (Senovilla *et al*, 2012).

Progression

Aneuploidy may progress with accumulation of additional chromosomal gains or losses. Expression of the *BCR-ABL1* gene product in Philadelphia chromosome-positive ALL in three separate murine cell lines induced conserved clonal chromosomal aberrations (Rudolph *et al*, 2005). BCR-ABL1 may cause additional chromosomal abnormalities by influencing the proteolytic activity of separase, a required component for chromatid separation and chromosomal stability. MCL demonstrates accumulation of chromosome structural-level mutations beyond the characteristic IGH-CCND1 product, including uniparental disomies of 17p, resulting in TP53 disruption (Bea *et al*, 2009). The accumulation of new, malignancy-promoting genetic alterations is called clonal evolution. In a study of 336 cases of FL, investigators used principle components analysis to identify cytogenetic evolutionary markers for particular evolutionary subgroups, namely 6q-, +7, and der(18)t(14;18). Del(17p) and +12 were markers for poor prognosis (Höglund *et al*, 2004).

Chromosomal instability appears to be part of a multistep pathway of tumour initiation in both solid and haematological malignancies, though aneuploidy-generating events that disable the TP53 pathway may be sufficient for tumour formation (Bakhoum & Compton, 2012). Numerous models of CIN require concomitant TP53 dysfunction to generate lymphoid malignancy (Table SIII). The TP53 pathway induces cell-cycle arrest and apoptosis in response to aneuploidy, functioning as the central component of the aneuploidy surveillance system, and when mutated is a 'second hit' that allows CIN to progress to lymphoid cancer.

Micronuclei and chromothripsis

Micronucleus formation, leading to subsequent chromothripsis, provides a mechanism by which aneuploidy can lead to multiple malignancy-inducing mutation events in lymphoid malignancy (Fig 4). Chromothripsis (*thripsis* means 'pulverization' in Greek), the phenomenon of a single chromosome pieced together from tens to hundreds of rearranged fragments, gives insight into how aneuploidy causes multiple new mutations over a brief time span (Stephens *et al*, 2011;

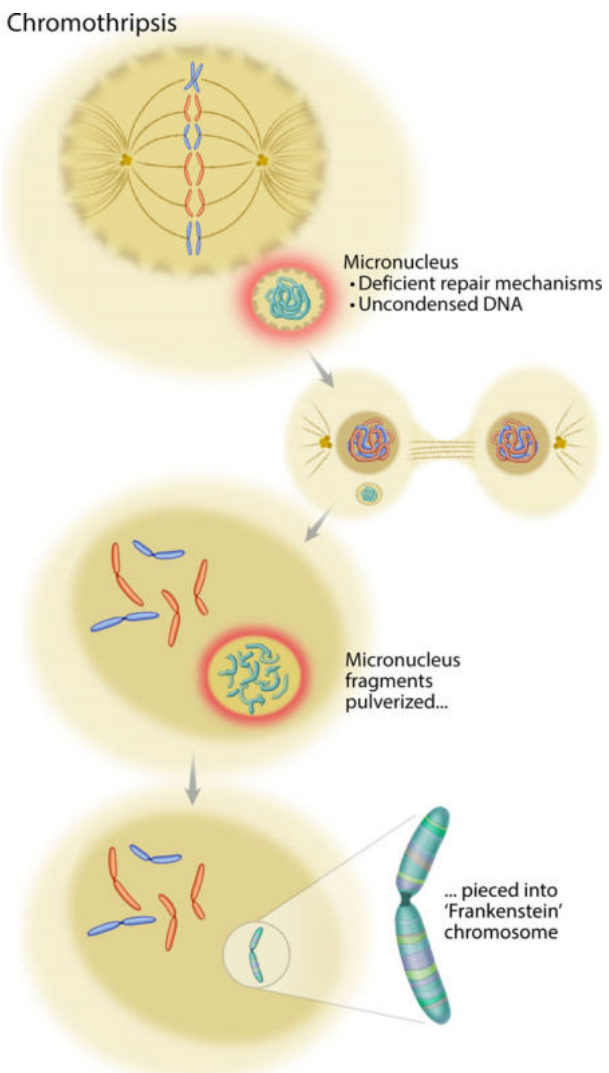

Fig 4. Aneuploidy gives rise to chromosome shattering, or chromothripsis. Micronuclei originate from chromosome fragments that arise due to DNA damage, such as double strand breaks or missegregated chromosomes. The whole or partial chromosomes are sequestered into structures similar to but much smaller than normal nuclei. The DNA of chromosomes or chromosome fragments in micronuclei does not appropriately condense at the G2/M cell cycle checkpoint, and the chromosomes are then pulverized during mitosis. The DNA is subsequently reassembled into patchwork (or Frankenstein) chromosomes that are ultimately reincorporated into the main cellular nucleus.

Crasta *et al*, 2012). Chromothripsis has been documented in DLBCL (Morin *et al*, 2013), CLL (Stephens *et al*, 2011; Edelmann *et al*, 2012; Bassaganyas *et al*, 2013), MCL (Moncunill *et al*, 2014) and MM (Magrangeas *et al*, 2011); in CLL and MM, the presence of chromothripsis is correlated with aggressive disease and poor outcome. Chromothripsis has also been described in the HL-derived cell lines L-1236, HDLM-2, and L-428 (Nagel *et al*, 2013).

Clinical application of CIN

Chromosome-level mutations play a prominent role in the diagnosis and treatment of lymphoid malignancies. This may be related to the relative ease with which diagnostic genetic material is obtained from most haematological malignancies.

Diagnosis and prognosis

Several lymphoid malignancies carry characteristic, though not pathognomonic, chromosomal alterations (Fig 5 and Table SIV). Two phenomena are of special clinical relevance. One is the impact of whole-chromosome gains *versus* losses on the prognosis of B-cell ALL. Losses correlate with poor prognosis (long-term survival of 40% or less), whereas gains of 5–20 chromosomes (hyperdiploidy) confer more favourable prognoses (up to 90% long-term survival). In fact, the degree of negative prognostic impact from hypodiploidy correlates with the number of chromosomes lost, as demonstrated by two studies. A study of adults and children demonstrated that ALLs bearing from 42 to 44 or 45 chromosomes had markedly better outcomes than ALLs bearing fewer than 42 chromosomes, termed low hypodiploidy or near-haploidy (Harrison *et al*, 2004). A paediatric study similarly showed that leukaemias with 44 chromosomes had markedly better outcomes (69% long-term survival) than leukaemias with fewer than 44 chromosomes (38% long-term survival) (Nachman *et al*, 2007). This dose-dependent effect may occur because mono- or oligo-chromosomal losses are more likely to eliminate essential tumour suppressors than gains are likely to cause overexpression of deleterious oncogenes.

The second phenomenon is double-hit NHL. *IGH*-oncogene fusions are insufficient to cause FL and MCL in murine models and occur benignly in patients (*IGH-MYC* fusions are notable exceptions). However, 'double-hit' lymphoma, characterized by expression of two *IGH*-oncogene fusions, is an aggressive variant of DLBCL with a refractory disease course and an extremely poor prognosis. The most common pair of transactivated genes is *BCL2* and *MYC*, though *MYC/BCL6* combinations and *MYC/BCL2/BCL6* 'triple-hit lymphomas' have been described (Aukema *et al*, 2011).

Chromosomal instability is associated with adverse outcomes in both B- and T-cell malignancies. In DLBCL, anaphase fixation of tumour cells showed that the extent of chromosome missegregation predicts survival; a doubling of segregation errors led to a 24% decrease in overall survival and a 48% decrease in relapse-free survival (Bakhoum *et al*, 2011). Loss or mutation of *TP53* confers poor outcomes in multiple lymphoid malignancies. *TP53* mutations group with poor prognosis and low hypodiploidy in ALL (Stengel *et al*, 2014), shorter survival in MM (Chng *et al*, 2007), and poor prognosis in CLL, FL, and DLBCL, though not in HL (Cheung *et al*, 2009). TP53 dysfunction may exacerbate CIN and accumulation of additional cytogenetic abnormalities, notably amplification of 2p and del(6q) in CLL (Rudenko *et al*, 2008).

Comparative genomic hybridization measures chromosomal aberrations and copy number alterations (CNAs), indirect measures of CIN that provide prognostic and pathological insights. Increased CNAs confer higher risk in CLL (Edelmann *et al*, 2012). Transformed FL has higher genetic complexity (measured by whole genome sequencing and copy number analysis) than FL, implicating a role for CIN (Pasqualucci *et al*, 2014). In DLBCL, CNAs that decrease TP53 activity and perturb cell cycle regulation lead to higher genomic complexity and worse prognosis (Monti *et al*, 2012). Increased numbers of chromosomal aberrations confer poor prognosis in HTLV-1-induced adult T-cell leukaemia-lymphoma (Tsukasaki *et al*, 2001). However, CNAs are not correlated with survival in MCL (Halldorsdottir *et al*, 2011).

Numerous human genes that protect against or contribute to aneuploidy or CIN are clinically linked to lymphoid malignancy. In Table SV lists genes associated with CIN; that list may warrant consideration for inclusion in diagnostic and prognostic platforms.

Therapeutics

Several currently marketed therapeutic agents may affect CIN in lymphoid malignancies. DNA methylation status impacts proteins that regulate chromosomal stability. Hypomethylating agents, specifically 5-azacitidine and decitabine, may have the effect of unsilencing tumour suppressors that protect against CIN. 5-azacitidine has been shown to enhance the toxicity of standard chemotherapy towards lymphoid cell lines (Valdez *et al*, 2012), and decitabine reprogrammed chemoresistant DLBCL lines to become doxorubicin-sensitive, probably by reactivation of the transcription factor SMAD1 (Clozel *et al*, 2013); the same study included a phase I trial in which 5-azacitidine was administered as a priming agent to sensitize high-risk DLBCL to standard chemoimmunotherapy. An alternative mechanism of action for hypomethylating agents is suggested by the ability of decitabine to downregulate MYC expression (Guan *et al*, 2013); as discussed above, MYC induces DSBs and disrupts telomere function.

The proteasome inhibitors bortezomib and carfilzomib take advantage of proteotoxic stress and upregulation of the unfolded protein response induced by chronic aneuploidy. Proteasome inhibitors are theorized to negatively impact

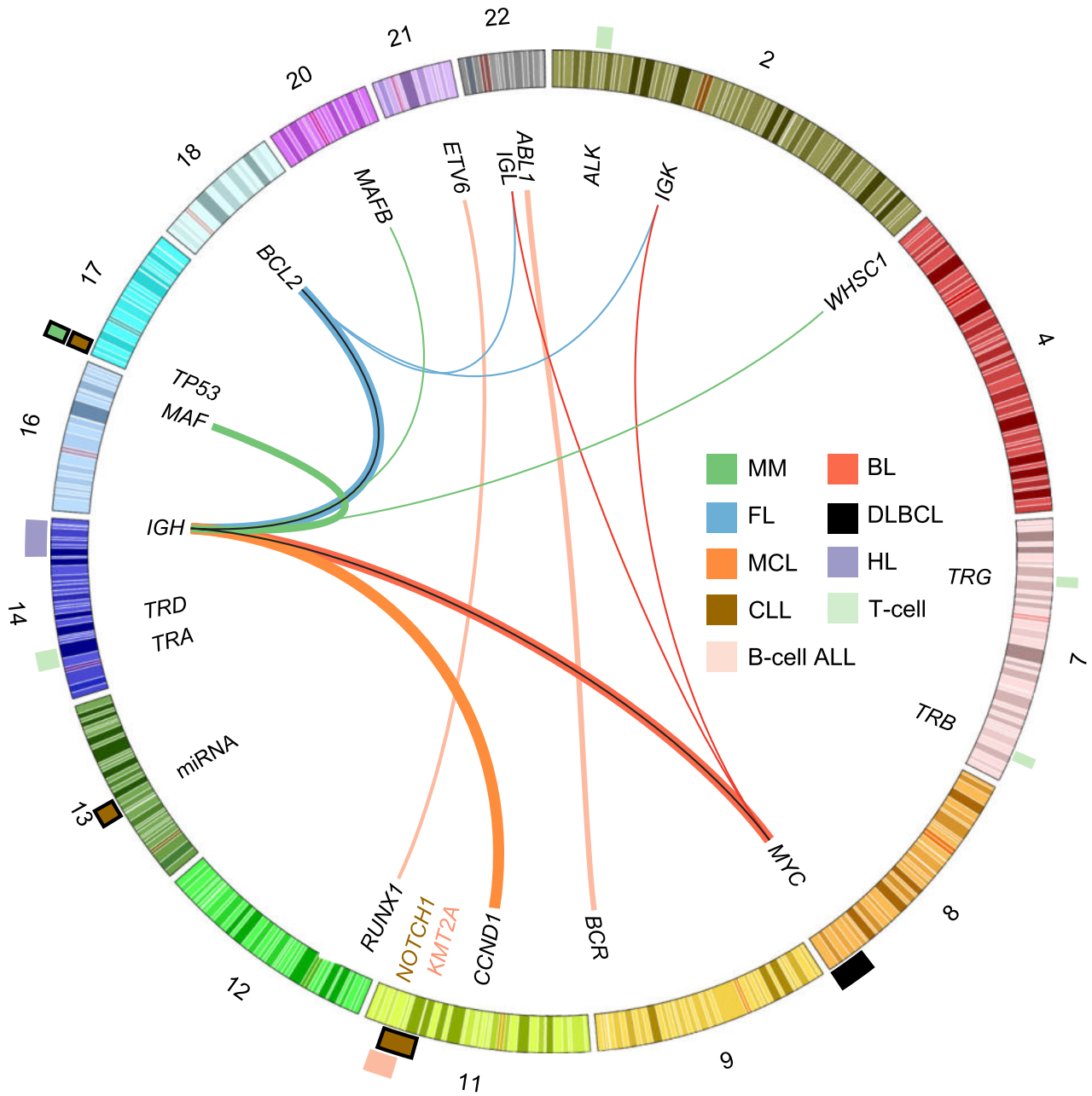

Fig 5. Disease-specific cytogenetic associations. This Circos-generated (Krzywinski *et al*, 2009; http://circos.ca) representation of lymphoid cancer-associated rearrangements includes clinically notable associations and is not intended to be exhaustive. Chromosomes are labelled by number. Boxes with black borders indicate deletions, and boxes without borders represent rearrangement 'hotspots'. Translocations are indicated by connections within the circle. Boxes and connections are colour-coded by disease per the legend within the circle. Key trends include *IGH* on chromosome 14 as a translocation partner for oncogenes in several malignancies, loss of *TP53* on chromosome 17 as a poor prognostic indicator and *MYC* overexpression as a marker for aggressive malignancies. Please see Table S4 for a more detailed listing and relevant citations.

chromosomally unstable cell lines by exaggerating stress energy phenotypes, rendering cells more susceptible to apoptosis. Supporting data for this mechanism of action is currently limited to preclinical cell line and animal studies (Nawrocki *et al*, 2005; Neznanov *et al*, 2011; Gordon *et al*, 2012).

Several new classes of pharmaceutical agents exploit the CIN of malignant lymphoid cells. CIN makes tumour cells prone to attack by a variety of mechanisms. CIN induces cellular energy and proteotoxic stress responses, requiring activation of heat shock protein (HSP) chaperone and autophagy pathways for cell survival; compounds specifically interfering with those pathways may have differential toxicity towards aneuploid cells and thus therapeutic potential (Pfau & Amon, 2012). HSP90AA1 (also termed HSP90) inhibitors demonstrated efficacy against primary effusion lymphoma

cells in a murine preclinical model (Nayar *et al*, 2013), and a phase I trial of an HSP90AA1 inhibitor induced stabilization and a partial response in a patient with MM and a patient with transformed lymphoma, respectively (Reddy *et al*, 2013). Preclinical studies in DLBCL cell lines show that the checkpoint kinase inhibitor PF-0477736 causes DNA damage accumulation and apotptosis. It is thought that DSBs accumulate, leading to CIN (Derenzini *et al*, 2015).

Kinesin spindle protein (KSP), a kinesin motor superfamily member, is an ATP hydrolase that regulates microtubule movement during mitosis and governs centrosome separation and normal bipolar spindle assembly. Inhibition of KSP causes cell cycle arrest and cell death (Sarli & Giannis, 2008). KSP inhibitors probably exaggerate the predisposition of chromosomally unstable cells to make chromosome segregation errors, inducing catastrophic aneuploidies that are incompatible with survival. Preliminary trials of KSP inhibitors in lymphoid malignancy patients are underway. Initial data indicate efficacy in refractory MM (Lee *et al*, 2013), an ability to induce disease stabilization in refractory DLBCL and a favourable toxicity profile (Gerecitano *et al*, 2013). Preclinical studies show that knockdown of *KIFC1* (also termed *HSET*), a kinesin motor family member, is selectively toxic to cells with supernumerary centrosomes; KIFC1 inhibition represents an attractive molecular target to stress and eliminate malignant cells with centrosomal amplification or abnormal spindle architecture (Gordon *et al*, 2012).

Chromosomal instability itself can be a therapeutic goal, with *AURKA* and *AURKB* serving as enticing molecular targets (Bakhoum & Compton, 2012). Pharmaceuticals that introduce a substantial level of CIN are capable of inducing apoptosis. AURKB is the catalytic component of the chromosome passenger complex, promotes alignment of chromosomes at metaphase, ensures proper microtubule-kinetochore connections, and is necessary for cytokinesis. Overexpression of AURKB is associated with aneuploidy, yet AURKB inhibition stabilizes microtubules and increases chromosome missegregation (Farag, 2011); either too much or too little AURKB activity is deleterious. Early-phase clinical trials of aurora kinase inhibitors in lymphoid malignancies show promise of efficacy in T315I-mutated Philadelphia-positive ALL (Giles *et al*, 2007; Cortes-Franco *et al*, 2009). The AURKA substrate TACC3, a motor spindle protein that stabilizes the mitotic spindle and prevents tripolar mitoses, shows promise as a therapeutic target in lymphoid malignancies. Preclinical studies demonstrate that conditional *Tacc3* knockout causes regression of thymic lymphomas in mice and that TACC3 is required for cell proliferation in BL and T-cell ALL cells (Yao *et al*, 2012).

Telomeres and telomerase are also potential targets for the induction of therapeutic CIN, though progress in solid tumours has outpaced that in lymphoid malignancies (Giles *et al*, 2007; Cortes-Franco *et al*, 2009). The telomerase inhibitor BIBR1532 has shown growth-inhibitory and pro-apoptotic effects against CLL and MM cell lines (El-Daly *et al*, 2005) and rapid cell death in pre-B ALL cells (Bashash *et al*, 2013). The anti-telomerase oligonucleotide GRN163 showed similar effects in NHL and MM cell lines (Wang *et al*, 2004). *In vivo* studies of an antisense oligonucleotide against telomerase demonstrated efficacy against a hepatic lymphoma model in mice (Yang *et al*, 2012). Initial clinical trials have explored adoptive immunotherapy against telomerase. A telomerase-targeting adoptive immunotherapy was developed that successfully exerted specific tumouricidal activity of cytotoxic T cells against autologous adult T cell leukaemia tumour cells in 10 patients (Miyazaki *et al*, 2013). A phase I/II two-arm trial of tumour antigen vaccination against telomerase and survivin in MM patients pre- and post-autologous stem cell transplantation showed a 36% immune response rate to the vaccination, but there was no impact of vaccination on 3-year overall survival (83%) compared with pneumococcal conjugate control (Rapoport *et al*, 2011).

Therapeutic agents that manipulate CIN offer a novel and promising field of study, but their mechanism of action raises the hypothetical but significant concern for long-term toxicity; exacerbating CIN poses risk for chromosome-level mutagenesis and thus secondary malignancies. CIN-targeting therapeutics are in early-phase trials; later-phase studies will need to monitor for potential malignant adverse effects of agents that directly impact chromosomal dynamics.

Concluding thoughts

Accumulating data from study of lymphoid malignancies supports the view that translocations and chromosome segregation errors are tumourigenic, though other oncogenic molecular events, such as *TP53* loss and chromothripsis, may be necessary to cause lymphoma or leukaemia. There is a substantial body of literature establishing the concept that chromosomal translocations are not random, but instead the sequelae of discrete oncogenic or epigenetic molecular events (Lin *et al*, 2012). The non-random nature of translocations and the association of CIN with poor outcomes corroborate a pathogenic role. Chromosome-level mutations have initially served as keys to diagnosis and prognosis, and they are becoming increasingly important to unravelling the pathophysiology of lymphoid diseases and designing treatment approaches.

Acknowledgements

This work was supported by a CureSearch Young Investigator Award (MMK); NIH R01CA076287, R01CA109663, PO1CA044991, and a gift from the David and Patricia Giuliani Family Foundation (OWP); and NIH R01DK58161 (MSH). The authors thank Kate Sweeney for expert assistance with illustrations. Heidi Back assisted with manuscript preparation. The authors apologize to those whose studies were omitted from the main text due to space limitations; the data supplement contains additional relevant citations.

Conflict of interest

The authors declare no competing financial interests.

Author contributions

MMK performed literature searching, designed figures and wrote the manuscript; OWP wrote the manuscript; MSH wrote the manuscript; TT designed figures and wrote the manuscript. All of the authors participated in the discussion and reviewed and approved the current version of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Murine lymphoma models based on aberrant DNA replication.

Table SII. Murine lymphoma knockout models based on deficient NHEJ in V(D)J recombination and DSB repair.

Table SIII. Dysregulated murine genes requiring concomitant p53 knockout for lymphoma phenotype. *Myc* and *Bax* are upregulated; all other models result from losses of function.

Table SIV. Disease-specific cytogenetic associations. The table includes clinically notable associations and breakpoints, and for practical purposes it cannot be exhaustive.

Table SV. Human genes linked to CIN in lymphoid malignancies.

Table SVI. Relevant citations for novel therapeutics exploiting CIN in lymphoid cancers. ATL, HTLV-1-induced adult T cell leukemia-lymphoma; HSP90, heat shock protein 90; KSP, kinesin spindle protein; Ph-ALL, Philadelphia chromosome-positive ALL; PR, partial response; SD, stable disease.

References

Aggarwal, P., Lessie, M., Lin, D., Pontano, L., Gladden, A., Nuskey, B., Goradia, A., Wasik, M.A., Klein-Szanto, A.J.P., Rustgi, A.K., Bassing, C.H. & Diehl, J.A. (2007) Nuclear accumulation of cyclin D1 during S phase inhibits Cul4-dependent Cdt1 triggers proteolysis and p53-dependent DNA rereplication. *Genes and Development*, **21**, 2908–2922.

Allan, J.M. & Travis, L.B. (2005) Mechanisms of therapy-related carcinogenesis. *Nature Reviews Cancer*, **5**, 943–955.

Alt, F.W., Zhang, Y., Meng, F.L., Guo, C. & Schwer, B. (2013) Mechanisms of programmed DNA lesions and genomic instability in the immune system. *Cell*, **152**, 417–429.

Augereau, A., T'kint de Roodenbeke, C., Simonet, T., Bauwens, S., Horard, B., Callanan, M., Leroux, D., Jallades, L., Salles, G., Gilson, E. & Poncet, D. (2011) Telomeric damage in early stage of chronic lymphocytic leukemia correlates with shelterin dysregulation. *Blood*, **118**, 1316–1322.

Aukema, S.M., Siebert, R., Schuuring, E., van Imhoff, G.W., Kluin-Nelemans, H.C., Boerma, E.J. & Kluin, P.M. (2011) Double-hit B-cell lymphomas. *Blood*, **117**, 2319–2331.

Bakhoum, S.F. & Compton, D.A. (2012) Chromosomal instability and cancer: a complex relationship with therapeutic potential. *Journal of Clinical Investigation*, **122**, 1138–1143.

Bakhoum, S.F., Danilova, O.V., Kaur, P., Levy, N.B. & Compton, D.A. (2011) Chromosomal instability substantiates poor prognosis in patients with diffuse large B-cell lymphoma. *Clinical Cancer Research*, **17**, 7704–7711.

Barlow, J.H., Faryabi, R.B., Callén, E., Wong, N., Malhowski, A., Chen, H.T., Gutierrez-Cruz, G., Sun, H.W., McKinnon, P., Wright, G., Casellas, R., Robbiani, D.F., Staudt, L., Fernandez-Capetillo, O. & Nussenzweig, A. (2013) Identification of early replicating fragile sites that contribute to genome instability. *Cell*, **152**, 620–632.

Bashash, D., Ghaffari, S.H., Mirzaee, R., Alimoghaddam, K. & Ghavamzadeh, A. (2013) Telomerase inhibition by non-nucleosidic compound BIBR1532 causes rapid cell death in pre-B acute lymphoblastic leukemia cells. *Leukemia and Lymphoma*, **54**, 561–568.

Bassaganyas, L., Beà, S., Escaramís, G., Tornador, C., Salaverria, I., Zapata, L., Drechsel, O., Ferreira, P.G., Rodriguez-Santiago, B., Tubio, J.M., Navarro, A., Martín-García, D., López, C., Martínez-Trillos, A., López-Guillermo, A., Gut, M., Ossowski, S., López-Otín, C., Campo, E. & Estivill, X. (2013) Sporadic and reversible chromothripsis in chronic lymphocytic leukemia revealed by longitudinal genomic analysis. *Leukemia*, **27**, 2376–2379.

Bea, S., Salaverria, I., Armengol, L., Pinyol, M., Fernández, V., Hartmann, E.M., Jares, P., Amador, V., Hernandez, L., Navarro, A., Ott, G., Rosenwald, A., Estivill, X. & Campo, E. (2009) Uniparental disomies, homozygous deletions, amplifications, and target genes in mantle cell lymphoma revealed by integrative high-resolution whole-genome profiling. *Blood*, **113**, 3059–3069.

Begemann, S., Galimi, F. & Karlsreder, J. (2009) Moderate expression of TRF2 in the hematopoietic system increases development of large cell blastic T-cell lymphomas. *Aging*, **1**, 122–130.

Bornkamm, G.W. (2009) Epstein-Barr virus and its role in the pathogenesis of Burkitt's lymphoma: an unresolved issue. *Seminars in Cancer Biology*, **19**, 351–365.

Bouamar, H., Abbas, S., Lin, A.P., Wang, L., Jiang, D., Holder, K.N., Kinney, M.C., Huncike-Smith, S. & Aguiar, R.C.T. (2013) A capture-sequencing strategy identifies *IRF8*, *EBF1*, and *APRIL* as novel *IGH* fusion partners in B-cell lymphoma. *Blood*, **122**, 726–733.

Brassesco, M.S., Montaldi, A.P., Gras, D.E., Camparoto, M.L., Martinez-Rossi, N.M., Scrideli, C.A., Tone, L.G. & Sakamoto-Hojo, E.T. (2009) Cytogenetic and molecular analysis of MLL rearrangements in acute lymphoblastic leukaemia survivors. *Mutagenesis*, **24**, 153–160.

Brown, H.M., Knowlton, A.E. & Grieshaber, S.S. (2012) Chlamydial infection induces host cytokinesis failure at abscission. *Cellular Microbiology*, **14**, 1554–1567.

Bunting, S.F., Callén, E., Wong, N., Chen, H.T., Polato, F., Gunn, A., Bothmer, A., Feldhahn, N., Fernandez-Capetillo, O., Cao, L., Xu, X., Deng, C.X., Finkel, T., Nussenzweig, M., Stark, J.M. & Nussenzeig, A. (2010) 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. *Cell*, **141**, 243–254.

Camacho, E., Beà, S., Salaverría, I., López-Guillermo, A., Puig, X., Benavente, Y., de Sanjose, S., Campo, E. & Hernandez, L. (2006) Analysis of Aurora-A and hMPS1 mitotic kinases in mantle cell lymphoma. *International Journal of Cancer*, **118**, 357–363.

Cheung, K.J., Horsman, D.E. & Gascoyne, R.D. (2009) The significance of *TP53* in lymphoid malignancies: mutation prevalence, regulation, prognostic impact and potential as a therapeutic target. *British Journal of Haematology*, **146**, 257–269.

Chiarle, R., Zhang, Y., Frock, R.L., Lewis, S.M., Molinie, B., Ho, Y.J., Myers, D.R., Choi, V.W., Compagno, M., Malkin, D.J., Neuberg, D., Monti, S., Giallourakis, C.C., Gostissa, M. & Alt, F.W. (2011) Genome-wide translocation sequencing reveals mechanisms of chromosome breaks and rearrangements in B cells. *Cell*, **147**, 107–119.

Chlichlia, K. & Khazaie, K. (2010) HTLV-1 Tax: linking transformation, DNA damage and apoptotic T-cell death. *Chemico-Biological Interactions*, **188**, 359–365.

Chng, W.J., Price-Troska, T., Gonzalez-Paz, N., Van Wier, S., Jacobus, S., Blood, E., Henderson, K., Oken, M., Van Ness, B., Greipp, P., Rajkumar, S.V. & Fonseca, R. (2007) Clinical significance of TP53 mutation in myeloma. *Leukemia*, **21**, 582–584.

Chrzanowska, K.H., Gregorek, H., Dembowska-Bagińska, B., Kalina, M.A. & Digweed, M. (2012) Nijmegen breakage syndrome (NBS). *Orphanet Journal of Rare Diseases*, **7**, 13.

Clozel, T., Yang, S., Elstrom, R.L., Tam, W., Martin, P., Kormaksson, M., Banerjee, S., Vasanthakumar, A., Culjkovic, B., Scott, D.W., Wyman, S., Leser, M., Shaknovich, R., Chadburn, A., Tabbo, F., Godley, L.A., Gascoyne, R.D., Borden, K.L., Inghirami, G., Leonard, J.P., Melnick, A. & Cerchietti, L. (2013) Mechanism-based epigenetic chemosensitization therapy of diffuse large B-cell lymphoma. *Cancer Discovery*, **3**, 1002–1019.

Collina, F., De Chiara, A., De Renzo, A., De Rosa, G., Botti, G. & Franco, R. (2012) Chlamydia psittaci in ocular adnexa MALT lymphoma: a possible role in lymphomagenesis and a different geographical distribution. *Infectious Agents and Cancer*, **7**, 8.

Cortes-Franco, J., Dombret, H., Schafhausen, P., Brummendorf, T.H., Boissel, N., Latini, F., Capolongo, L., Laffranchi, B. & Comis, S. (2009) Danusertib hydrochloride (PHA-739358), a multi-kinase aurora inhibitior, elicits clinical benefit in advanced chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia. *Blood*, **114**, 356 (abstract 864).

Cottliar, A.S., Panero, J., Pedrazzini, E., Noriega, M.F., Narbaitz, M., Rodríguez, A. & Slavutsky, I. (2009) Analysis of telomere length in mantle cell lymphoma. *European Journal of Haematology*, **83**, 433–438.

Crasta, K., Ganem, N.J., Dagher, R., Lantermann, A.B., Ivanova, E.V., Pan, Y., Nezi, L., Protopopov, A., Chowdhury, D. & Pellman, D. (2012) DNA breaks and chromosome pulverization from errors in mitosis. *Nature*, **482**, 53–58.

Derenzini, E., Agostinelli, C., Imbrogno, E., Iacobucci, I., Casadei, B., Brighenti, E., Righi, S., Fuligni, F., Di Rora, A.G.L., Ferrari, A., Martinelli, G., Pileri, S. & Zinzani, P.L. (2015) Constitutive activation of the DNA damage response pathway as a novel therapeutic target in diffuse large B-cell lymphoma. *Oncotarget*, **6**, 6553–6569.

Durkin, S.G. & Glover, T.W. (2007) Chromosome fragile sites. *Annual Review of Genetics*, **41**, 169–192.

Edelmann, J., Holzmann, K., Miller, F., Winkler, D., Bühler, A., Zenz, T., Bullinger, L., Kühn, M.W., Gerhardinger, A., Bloehdorn, J., Radtke, I., Su, X., Ma, J., Pounds, S., Hallek, M., Lichter, P., Korbel, J., Busch, R., Mertens, D., Downing, J.R., Stilgenbauer, S. & Döhner, H. (2012) High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. *Blood*, **120**, 4783–4794.

El-Daly, H., Kull, M., Zimmermann, S., Pantic, M., Waller, C.F. & Martens, U.M. (2005) Selective cytotoxicity and telomere damage in leukemia cells using the telomerase inhibitor BIBR1532. *Blood*, **105**, 1742–1749.

Farag, S.S. (2011) The potential role of Aurora kinase inhibitors in haematological malignancies. *British Journal of Haematology*, **155**, 561–579.

Fisher, T.S. & Zakian, V.A. (2005) Ku: a multifunctional protein involved in telomere maintenance. *DNA Repair*, **4**, 1215–1226.

Gerecitano, J.F., Stephenson, J.J., Lewis, N.L., Osmukhina, A., Li, J., Wu, K., You, Z., Huszar, D., Skolnik, J.M. & Schwartz, G.K. (2013) A Phase I trial of the kinesin spindle protein (Eg5) inhibitor AZD4877 in patients with solid and lymphoid malignancies. *Investigational New Drugs*, **31**, 355–362.

Giles, F.J., Cortes, J., Jones, D., Bergstrom, D., Kantarjian, H. & Freedman, S.J. (2007) MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. *Blood*, **109**, 500–502.

Gladden, A.B., Woolery, R., Aggarwal, P., Wasik, M.A. & Diehl, J.A. (2006) Expression of constitutively nuclear cyclin D1 in murine lymphocytes induces B-cell lymphoma. *Oncogene*, **25**, 998–1007.

Gladdy, R.A., Taylor, M.D., Williams, C.J., Grandal, I., Karaskova, J., Squire, J.A., Rutka, J.T., Guidos, C.J. & Danska, J.S. (2003) The RAG-1/2 endonuclease causes genomic instability and controls CNS complications of lymphoblastic leukemia in p53/Prkdc-deficient mice. *Cancer Cell*, **3**, 37–50.

Gordon, D.J., Resio, B. & Pellman, D. (2012) Causes and consequences of aneuploidy in cancer. *Nature Reviews Genetics*, **13**, 189–203.

Greisman, H.A., Lu, Z., Tsai, A.G., Greiner, T.C., Yi, H.S. & Lieber, M.R. (2012) IgH partner breakpoint sequences provide evidence that AID initiates t(11;14) and t(8;14) chromosomal breaks in mantle cell and Burkitt lymphomas. *Blood*, **120**, 2864–2867.

Gruhne, B., Sompallae, R. & Masucci, M.G. (2009) Three Epstein-Barr virus latency proteins independently promote genomic instability by inducing DNA damage, inhibiting DNA repair and inactivating cell cycle checkpoints. *Oncogene*, **28**, 3997–4008.

Guan, H., Xie, L., Klapproth, K., Weitzer, C.D., Wirth, T. & Ushmorov, A. (2013) Decitabine represses translocated MYC oncogene in Burkitt lymphoma. *Journal of Pathology*, **229**, 775–783.

Guffei, A., Sarkar, R., Klewes, L., Righolt, C., Knecht, H. & Mai, S. (2010) Dynamic chromosomal rearrangements in Hodgkin lymphoma are due to ongoing three-dimensional nuclear remodeling and breakage-bridge fusion cycles. *Haematologica*, **95**, 2038–2046.

Gümüş, G., Sunguroğlu, A., Tükün, A., Sayin, D.B. & Bökesoy, I. (2002) Common fragile sites associated with the breakpoints of chromosomal aberrations in hematologic neoplasms. *Cancer Genetics and Cytogenetics*, **133**, 168–171.

Halldorsdottir, A.M., Sander, B., Goransson, H., Isaksson, A., Kimby, E., Mansouri, M., Rosenquist, R. & Ehrencrona, H. (2011) High-resolution genomic screening in mantle cell lymphoma—specific changes correlate with genomic complexity, the proliferation signature and survival. *Genes, Chromosomes and Cancer*, **50**, 113–121.

Harrison, C.J., Moorman, A.V., Broadfield, Z.J., Cheung, K.L., Harris, R.L., Reza Jalali, G., Robinson, H.M., Barber, K.E., Richards, S.M., Mitchell, C.D., Eden, T.O., Hann, I.M., Hill, F.G., Kinsey, S.E., Gibson, B.E., Lilleyman, J., Vora, A., Goldstone, A.H., Franklin, I.M., Durrant, J. & Martineau, M.; Childhood and Adult Leukaemia Working Parties. (2004) Three distinct groups of hypodiploidy in acute lymphoblastic leukaemia. *British Journal of Haematology*, **125**, 552–559.

Heerema, N.A., Carroll, A.J., Devidas, M., Loh, M.L., Borowitz, M.J., Gastier-Foster, J.M., Larsen, E.C., Mattano, L.A., Maloney, K.W., Willman, C.L., Wood, B.L., Winick, N.J., Carroll, W.L., Hunger, S.P. & Raetz, E.A. (2013) Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. *Journal of Clinical Oncology*, **31**, 3397–3402.

Hirt, C., Schuler, F., Dolken, L., Schmidt, C.A. & Dolken, G. (2004) Low prevalence of circulating t(11;14)(q13;q32)-positive cells in the peripheral blood of healthy individuals as detected by real-time quantitative PCR. *Blood*, **104**, 904–905.

Höglund, M., Sehn, L., Connors, J.M., Gascoyne, R.D., Siebert, R., Säll, T., Mitelman, F. & Horsman, D.E. (2004) Identification of cytogenetic subgroups and karyotypic pathways of clonal evolution in follicular lymphomas. *Genes, Chromosomes and Cancer*, **39**, 195–204.

den Hollander, J., Rimpi, S., Doherty, J.R., Rudelius, M., Buck, A., Hoellein, A., Kremer, M., Graf, N., Scheerer, M., Hall, M.A., Goga, M.A., von Bubnoff, N., Duyster, J., Peschel, C., Cleveland, J.L., Nilsson, J.A. & Keller, U. (2010) Aurora kinases A and B are up-regulated by Myc and are essential for maintenance of the malignant state. *Blood*, **116**, 1498–1505.

Jiang, Y. & Melnick, A. (2015) The epigenetic basis of diffuse large B-cell lymphoma. *Seminars in Hematology*, **52**, 86–96.

van Kester, M.S., Borg, M.K., Zoutman, W.H., Out-Luiting, J.J., Jansen, P.M., Dreef, E.J., Vermeer, M.H., van Doorn, R., Willemze, R. & Tensen, C.P. (2012) A meta-analysis of gene expression data identifies a molecular signature characteristic for tumor-stage mycosis fungoides.

Journal of Investigative Dermatology, **132**, 2050–2059.

Klein, I.A., Resch, W., Jankovic, M., Oliveira, T., Yamane, A., Nakahashi, H., Di Virgilio, M., Bothmer, A., Nussenzweig, A., Robbiani, D.F., Casellas, R. & Nussenzweig, M.C. (2011) Translocation-capture sequencing reveals the extent and nature of chromosomal rearrangements in B lymphocytes. *Cell*, **147**, 95–106.

Knecht, H., Sawan, B., Lichtensztejn, D., Lemieux, B., Wellinger, R.J. & Mai, S. (2009) The 3D nuclear organization of telomeres marks the transition from Hodgkin to Reed-Sternberg cells. *Leukemia*, **23**, 565–573.

Knecht, H., Kongruttanachok, N., Sawan, B., Brossard, J., Prévost, S., Turcotte, E., Lichtensztejn, Z., Lichtensztejn, D. & Mai, S. (2012) Three-dimensional telomere signatures of Hodgkin- and Reed-Sternberg cells at diagnosis identify patients with poor response to conventional chemotherapy. *Translational Oncology*, **5**, 269–277.

Krämer, A., Schweizer, S., Neben, K., Giesecke, C., Kalla, J., Katzenberger, T., Benner, A., Muller-Hermelink, H.K., Ho, A.D. & Ott, G. (2003) Centrosome aberrations as a possible mechanism for chromosomal instability in non-Hodgkin's lymphoma. *Leukemia*, **17**, 2207–2213.

Krem, M.M., Luo, P., Ing, B.I. & Horwitz, M.S. (2012) The kelch protein KLHDC8B guards against mitotic errors, centrosomal amplification, and chromosomal instability. *Journal of Biological Chemistry*, **287**, 39083–39093.

Krzywinski, M., Schein, J.E., Birol, I., Connors, J., Gascoyne, R., Horsman, D., Jones, S.J. & Marra, M.A. (2009) Circos: an information aesthetic for comparative genomics. *Genome Research*, **19**, 1639–1645.

Küppers, R. (2005) Mechanisms of B-cell lymphoma pathogenesis. *Nature Reviews Cancer*, **5**, 251–262.

de Lange, T. (2005) Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes and Development*, **19**, 2100–2110.

Lee, H.C., Shah, J.J. & Orlowski, R.Z. (2013) Novel approaches to treatment of double-refractory multiple myeloma. *American Society of Clinical Oncology Education Book*, **2013**, 302–306.

Lengauer, C., Kinzler, K.W. & Vogelstein, B. (1998) Genetic instabilities in human cancers. *Nature*, **396**, 643–649.

Lin, C., Yang, L. & Rosenfeld, M.G. (2012) Molecular logic underlying chromosomal translocations, random or non-random? *Advances in Cancer Research*, **113**, 241–279.

Lobetti-Bodoni, C., Bernocco, E., Genuardi, E., Boccadoro, M. & Ladetto, M. (2010) Telomeres and telomerase in normal and malignant B-cells. *Hematological Oncology*, **28**, 157–167.

Loeb, L.A. (1991) Mutator phenotype may be required for multistage carcinogenesis. *Cancer Research*, **51**, 3075–3079.

Lossos, I.S., Czerwinski, D.K., Alizadeh, A.A., Wechser, M.A., Tibshirani, R., Botstein, D. & Levy, R. (2004) Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. *New England Journal of Medicine*, **350**, 1828–1837.

Lukusa, T. & Fryns, J.P. (2008) Human chromosome fragility. *Biochimica Biophysica Acta*, **1779**, 3–16.

Magrangeas, F., Avet-Loiseau, H., Munshi, N.C. & Minvielle, S. (2011) Chromothripsis identifies a rare and aggressive entity among newly diagnosed multiple myeloma patients. *Blood*, **118**, 675–678.

Marculescu, R., Le, T., Simon, P., Jaeger, U. & Nadel, B. (2002) V(D)J-mediated translocations in lymphoid neoplasms: a functional assessment of genomic instability by cryptic sites. *Journal of Experimental Medicine*, **195**, 85–98.

Martin-Subero, J.I., Knippschild, U., Harder, L., Barth, T.F., Riemke, J., Grohmann, S., Gesk, S., Hoppner, J., Moller, P., Parwaresch, R.M. & Siebert, R. (2003) Segmental chromosomal aberrations and centrosome amplifications: pathogenetic mechanisms in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma? *Leukemia*, **17**, 2214–2219.

McCord, R.P. & Dekker, J. (2011) Translocation mapping exposes the risky lifestyle of B cells. *Cell*, **147**, 20–22.

McDonnell, T.J. & Korsmeyer, S.J. (1991) Progression from lymphoid hyperplasia to high-grade malignant lymphoma in mice transgenic for the t(14;18). *Nature*, **349**, 254–256.

Mishra, A., Liu, S., Sams, G.H., Curphey, D.P., Santhanam, R., Rush, L.J., Schaefer, D., Falkenberg, L.G., Sullivan, L., Jaroncyk, L., Yang, X., Fisk, H., Wu, L.C., Hickey, C., Chandler, J.C., Wu, Y.Z., Heerema, N.A., Chan, K.K., Perrotti, D., Zhang, J., Porcu, P., Racke, F.K., Garzon, R., Lee, R.J., Marcucci, G. & Caligiuri, M.A. (2012) Aberrant overexpression of IL-15 initiates large granular lymphocyte leukemia through chromosomal instability and DNA hypermethylation. *Cancer Cell*, **22**, 645–655.

Miyazaki, Y., Fujiwara, H., Asai, H., Ochi, F., Ochi, T., Azuma, T., Ishida, T., Okamoto, S., Mineno, J., Kuzushima, K., Shiku, H. & Yasukawa, M. (2013) Development of a novel redirected T-cell-based adoptive immunotherapy targeting human telomerase reverse transcriptase for adult T-cell leukemia. *Blood*, **121**, 4894–4901.

M'kacher, R., Bennaceur-Griscelli, A. & Girinsky, T. (2007) Telomere shortening and associated chromosomal instability in peripheral blood lymphocytes of patients with Hodgkin's lymphoma prior to any treatment are predictive of second cancers. *International Journal of Radiation Oncology, Biology, Physics*, **68**, 465–471.

Mladinic, M., Kopjar, N., Milic, M., Dasovic, A.B., Huzak, M. & Zeljezic, D. (2010) Genomic instability in a healthy elderly population: a pilot study of possible cytogenetic markers related to ageing. *Mutagenesis*, **25**, 455–462.

Moncunill, V., Gonzalez, S., Beà, S., Andrieux, L.O., Salaverria, I., Royo, C., Martinez, L., Puiggròs, M., Segura-Wang, M., Stütz, A.M., Navarro, A., Royo, R., Gelpí, J.L., Gut, I.G., López-Otín, C., Orozco, M., Korbel, J.O., Campo, E., Puente, X.S. & Torrents, D. (2014) Comprehensive characterization of complex structural variations in cancer by directly comparing genome sequence reads. *Nature Biotechnology*, **32**, 1106–1112.

Monti, S., Chapuy, B., Takeyama, K., Rodig, S.J., Hao, Y., Yeda, K.T., Inguilizian, H., Mermel, C., Currie, T., Dogan, A., Kutok, J.L., Beroukhim, R., Neuberg, D., Habermann, T.M., Getz, G., Kung, A.L., Golub, T.R. & Shipp, M.A. (2012) Integrative analysis reveals an outcome-associated and targetable pattern of p53 and cell cycle deregulation in diffuse large B cell lymphoma. *Cancer Cell*, **22**, 359–372.

Morin, R.D., Mungall, K., Pleasance, E., Mungall, A.J., Goya, R., Huff, R.D., Scott, D.W., Ding, J., Roth, A., Chiu, R., Corbett, R.D., Chan, F.C., Mendez-Lago, M., Trinh, D.L., Bolger-Munro, M., Taylor, G., Hadj Khodabakhshi, A., Ben-Neriah, S., Pon, J., Meissner, B., Woolcock, B., Farnoud, N., Rogic, S., Lim, E.L., Johnson, N.A., Shah, S., Jones, S., Steidl, C., Holt, R., Birol, I., Moore, R., Connors, J.M., Gascoyne, R.D. & Marra, M.A. (2013) Mutational and structural analysis of diffuse large B-cell lymphoma using whole genome sequencing. *Blood*, **122**, 1256–1265.

Moshous, D., Pannetier, C., de Chasseval, R., le Deist, F., Cavazzana-Calvo, M., Romana, S., Macintyre, E., Canioni, D., Brousse, N., Fischer, A., Casanova, J.L. & de Villartay, J.P. (2003) Partial T and B lymphocyte immunodeficiency and predisposition to lymphoma in patients with hypomorphic mutations in Artemis. *Journal of Clinical Investigation*, **111**, 381–387.

Nachman, J.B., Heerema, N.A., Sather, H., Camitta, B., Forestier, E., Harrison, C.J., Dastugue, N., Schrappe, M., Pui, C.H., Basso, G., Silverman, L.B. & Janka-Schaub, G.E. (2007) Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. *Blood*, **110**, 1112–1115.

Nagel, S., Meyer, C., Quentmeier, H., Kaufmann, M., Drexler, H.G. & MacLeod, R.A. (2013) Chromothripsis in Hodgkin lymphoma. *Genes, Chromosomes and Cancer*, **52**, 741–747.

Nanjangud, G., Rao, P.H., Hegde, A., Teruya-Feldstein, J., Donnelly, G., Qin, J., Jhanwar, S.C., Zelenetz, A.D. & Chaganti, R.S. (2002) Spectral karyotyping identifies new rearrangements, translocations, and clinical associations in diffuse large B-cell lymphoma. *Blood*, **99**, 2554–2561.

Nawrocki, S.T., Carew, J.S., Dunner, Jr, K., Boise, L.H., Chiao, P.J., Huang, P., Abbruzzese, J.L. & McConkey, D.J. (2005) Bortezomib inhibits PKR-like endoplasmic reticulum (ER) kinase and induces apoptosis via ER stress in human pancreatic cancer cells. *Cancer Research*, **65**, 11510–11519.

Nayar, U., Lu, P., Goldstein, R.L., Vider, J., Ballon, G., Rodina, A., Taldone, T., Erdjument-Bromage, H., Chomet, M., Blasberg, R., Melnick, A., Cerchietti, L., Chiosis, G., Wang, Y.L. & Ce-

sarman, E. (2013) Targeting the Hsp90-associated viral oncoproteome in gammaherpesvirus-associated malignancies. *Blood*, **122**, 2837–2847.

Neznanov, N., Komarov, A., Neznanova, L., Stanhope-Baker, P. & Gudkov, A. (2011) Proteotoxic stress targeted therapy (PSTT): induction of protein misfolding enhances the antitumor effect of the proteasome inhibitor bortezomib. *Oncotarget*, **2**, 209–221.

Nussenzweig, A. & Nussenzweig, M.C. (2010) Origin of chromosomal translocations in lymphoid cancer. *Cell*, **141**, 27–38.

Ohshima, K., Haraoka, S., Yoshioka, S., Hamasaki, M., Fujiki, T., Suzumiya, J., Kawasaki, C., Kanda, M. & Kikuchi, M. (2000) Mutation analysis of mitotic checkpoint genes (hBUB1 and hBUBR1) and microsatellite instability in adult T-cell leukemia/lymphoma. *Cancer Letters*, **158**, 141–150.

Ong, S.T. & Le Beau, M.M. (1998) Chromosomal abnormalities and molecular genetics of non-Hodgkin's lymphoma. *Seminars in Oncology*, **25**, 447–460.

Pasqualucci, L., Neumeister, P., Goossens, T., Nanjangud, G., Chaganti, R.S., Küppers, R. & Dalla-Favera, R. (2001) Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. *Nature*, **412**, 341–346.

Pasqualucci, L., Dominguez-Sola, D., Chiarenza, A., Fabbri, G., Grunn, A., Trifonov, V., Kasper, L.H., Lerach, S., Tang, H., Ma, J., Rossi, D., Chadburn, A., Murty, V.V., Mullighan, C.G., Gaidano, G., Rabadan, R., Brindle, P.K. & Dalla-Favera, R. (2011) Inactivating mutations of acetyltransferase genes in B-cell lymphoma. *Nature*, **471**, 189–195.

Pasqualucci, L., Khiabanian, H., Fangazio, M., Vasishtha, M., Messina, M., Holmes, A.B., Ouillette, P., Trifonov, V., Rossi, D., Tabbò, F., Ponzoni, M., Chadburn, A., Murty, V.V., Bhagat, G., Gaidano, G., Inghirami, G., Malek, S.N., Rabadan, R. & Dalla-Favera, R. (2014) Genetics of follicular lymphoma transformation. *Cell Reports*, **6**, 130–140.

Pauli, S., Steinemann, D., Dittmann, K., Wienands, J., Shoukier, M., Möschner, M., Burfeind, P., Manukjan, G., Gohring, G. & Escherich, G. (2012) Occurrence of acute lymphoblastic leukemia and juvenile myelomonocytic leukemia in a patient with Noonan syndrome carrying the germline PTPN11 mutation p. E139D. *American Journal of Medical Genetics Part A*, **158A**, 652–658.

Pettersen, H.S., Galashevskaya, A., Doseth, B., Sousa, M.M., Sarno, A., Visnes, T., Aas, P.A., Liabakk, N.B., Slupphaug, G., Sætrom, P., Kavli, B. & Krokan, H.E. (2015) AID expression in B-cell lymphomas causes accumulation of genomic uracil and a distinct AID mutational signature. *DNA Repair*, **25**, 60–71.

Pfau, S.J. & Amon, A. (2012) Chromosomal instability and aneuploidy in cancer: from yeast to man. *EMBO Reports*, **13**, 515–527.

Pinyol, M., Salaverria, I., Bea, S., Fernández, V., Colomo, L., Campo, E. & Jares, P. (2006) Unbalanced expression of licensing DNA replication factors occurs in a subset of mantle cell lymphomas with genomic instability. *International Journal of Cancer*, **119**, 2768–2774.

Poncet, D., Belleville, A., T'kint de Roodenbeke, C., Roborel de Climens, A., Ben Simon, E., Merle-Beral, H., Callet-Bauchu, E., Salles, G., Sabatier, L., Delic, J. & Gilson, E. (2008) Changes in the expression of telomere maintenance genes suggest global telomere dysfunction in B-chronic lymphocytic leukemia. *Blood*, **111**, 2388–2391.

Qi, L., Strong, M.A., Karim, B.O., Armanios, M., Huso, D.L. & Greider, C.W. (2003) Short telomeres and ataxia-telangiectasia mutated deficiency cooperatively increase telomere dysfunction and suppress tumorigenesis. *Cancer Research*, **63**, 8188–8196.

Qian, J., Wang, Q., Dose, M., Pruett, N., Kieffer-Kwon, K.R., Resch, W., Liang, G., Tang, Z., Mathé, E., Benner, C., Dubois, W., Nelson, S., Vian, L., Oliveira, T.Y., Jankovic, M., Hakim, O., Gazumyan, A., Pavri, R., Awasthi, P., Song, B., Liu, G., Chen, L., Zhu, S., Feigenbaum, L., Staudt, L., Murre, C., Ruan, Y., Robbiani, D.F., Pan-Hammarström, Q., Nussenzweig, M.C. & Casellas, R. (2014) B cell super-enhancers and regulatory clusters recruit AID tumorigenic activity. *Cell*, **159**, 124–1537.

Rapoport, A.P., Aqui, N.A., Stadtmauer, E.A., Vogl, D.T., Fang, H.B., Cai, L., Janofsky, S., Chew, A., Storek, J., Akpek, G., Badros, A., Yanovich, S., Tan, M.T., Veloso, E., Pasetti, M.F., Cross, A., Philip, S., Murphy, H., Bhagat, R., Zheng, Z., Milliron, T., Cotte, J., Cannon, A., Levine, B.L., Vonderheide, R.H. & June, C.H. (2011) Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma. *Blood*, **117**, 788–797.

Reddy, N., Voorhees, P.M., Houk, B.E., Brega, N., Hinson, Jr, J.M. & Jillela, A. (2013) Phase I trial of the HSP90 inhibitor PF-04929113 (SNX5422) in adult patients with recurrent, refractory hematologic malignancies. *Clinical Lymphoma, Myeloma, and Leukemia*, **13**, 385–391.

Rengstl, B., Newrzela, S., Heinrich, T., Weiser, C., Thalheimer, F.B., Schmid, F., Warner, K., Hartmann, S., Schroeder, T., Kuppers, R., Rieger, M.A. & Hansmann, M.L. (2013) Incomplete cytokinesis and re-fusion of small mononucleated Hodgkin cells lead to giant multinucleated Reed-Sternberg cells. *Proceedings of the National Academy of Sciences of the United States of America*, **110**, 20729–20734.

Ru, H.Y., Chen, R.L., Lu, W.C. & Chen, J.H. (2002) hBUB1 defects in leukemia and lymphoma cells. *Oncogene*, **21**, 4673–4679.

Rudenko, H.C., Else, M., Dearden, C., Brito-Babapulle, V., Jones, C., Dexter, T., Fenwick, K., Mackay, A., Ashworth, A., Matutes, E., Gonzalez, D., Catovsky, D. & Morgan, G.J. (2008) Characterising the TP53-deleted subgroup of chronic lymphocytic leukemia: an analysis of additional cytogenetic abnormalities detected by interphase fluorescence in situ hybridisation and array-based comparative genomic hybridization. *Leukemia and Lymphoma*, **49**, 1879–1886.

Rudolph, C., Hegazy, A.N., von Neuhoff, N., Steinemann, D., Schröck, E., Stripecke, R., Klein, C. & Schlegelberger, B. (2005) Cytogenetic characterization of a BCR-ABL transduced mouse cell line. *Cancer Genetics and Cytogenetics*, **161**, 51–56.

Saez, S., Pereda, T., Borrero, J.J., Espina, A., Romero, F., Tortolero, M., Pintor-Toro, J.A., Sequra, D.I. & Japon, M.A. (2002) Expression of *hpttg* proto-oncogene in lymphoid neoplasias. *Oncogene*, **21**, 8173–8177.

Salas, C., Niembro, A., Lozano, V., Gallardo, E., Molina, B., Sánchez, S., Ramos, S., Carnevale, A., Perez-Vera, P., Rivera Luna, R. & Frias, S. (2012) Persistent genomic instability in peripheral blood lymphocytes from Hodgkin lymphoma survivors. *Environmental and Molecular Mutagenesis*, **53**, 271–280.

Sarli, V. & Giannis, A. (2008) Targeting the kinesin spindle protein: basic principles and clinical indications. *Clinical Cancer Research*, **14**, 7583–7587.

Schuler, F., Hirt, C. & Dolken, G. (2003) Chromosomal translocation t(14;18) in healthy individuals. *Seminars in Cancer Biology*, **13**, 203–209.

Senovilla, L., Vitale, I., Martins, I., Tailler, M., Pailleret, C., Michaud, M., Galluzzi, L., Adjemian, S., Kepp, O., Niso-Santano, M., Shen, S., Mariño, G., Criollo, A., Boilève, A., Job, B., Ladoire, S., Ghiringhelli, F., Sistigu, A., Yamazaki, T., Rello-Varona, S., Locher, C., Poirier-Colame, V., Talbot, M., Valent, A., Berardinelli, F., Antoccia, A., Ciccosanti, F., Fimia, G.M., Piacentini, M., Fueyo, A., Messina, N.L., Li, M., Chan, C.J., Sigl, V., Pourcher, G., Ruckenstuhl, C., Carmona-Gutierrez, D., Lazar, V., Penninger, J.M., Madeo, F., López-Otín, C., Smyth, M.J., Zitvogel, L., Castedo, M. & Kroemer, G. (2012) An immunosurveillance mechanism controls cancer cell ploidy. *Science*, **337**, 1678–1684.

Shiloh, Y. (2003) ATM and related protein kinases: safeguarding genome integrity. *Nature Reviews Cancer*, **3**, 155–168.

Si, H. & Robertson, E.S. (2006) Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen induces chromosomal instability through inhibition of p53 function. *Journal of Virology*, **80**, 697–709.

Sinclair, P.B., Parker, H., An, Q., Rand, V., Ensor, H., Harrison, C.J. & Strefford, J.C. (2011) Analysis of a breakpoint cluster reveals insight into the mechanism of intrachromosomal amplification in a lymphoid malignancy. *Human Molecular Genetics*, **20**, 2591–2602.

Stengel, A., Schnittger, S., Weissman, S., Kuznia, S., Kern, W., Kohlmann, A., Haferlach, T. & Haferlach, C. (2014) TP53 mutations occur in 15.7% of ALL and are associated with MYC-rearrangement, low hypodiploidy, and a poor prognosis. *Blood*, **124**, 251–258.

Stephens, P.J., Greenman, C.D., Fu, B., Yang, F., Bignell, G.R., Mudie, L.J., Pleasance, E.D., Lau,

K.W., Beare, D., Stebbings, L.A., McLaren, S., Lin, M.L., McBride, D.J., Varela, I., Nik-Zainal, S., Leroy, C., Jia, M., Menzies, A., Butler, A.P., Teague, J.W., Quail, M.A., Burton, J., Swerdlow, H., Carter, N.P., Morsberger, L.A., Iacobuzio-Donahue, C., Follows, G.A., Green, A.R., Flanagan, A.M., Stratton, M.R., Futreal, P.A. & Campbell, P.J. (2011) Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *Cell*, **144**, 27–40.

Takeyama, K., Monti, S., Manis, J.P., Dal Cin, P., Getz, G., Beroukhim, R., Dutt, S., Aster, J.C., Alt, F.W., Golub, T.R. & Shipp, M.A. (2008) Integrative analysis reveals 53BP1 copy loss and decreased expression in a subset of human diffuse large B-cell lymphomas. *Oncogene*, **27**, 318–322.

Thompson, S.L. & Compton, D.A. (2010) Proliferation of aneuploid human cells is limited by a p53-dependent mechanism. *Journal of Cell Biology*, **188**, 369–381.

Tommasi, S., Besaratinia, A., Wilczynski, S.P. & Pfeifer, G.P. (2011) Loss of Rassf1a enhances p53-mediated tumor predisposition and accelerates progression to aneuploidy. *Oncogene*, **30**, 690–700.

Tsukasaki, K., Krebs, J., Nagai, K., Tomonaga, M., Koeffler, H.P., Bartram, C.R. & Jauch, A. (2001) Comparative genomic hybridization analysis in adult T-cell leukemia/lymphoma: correlation with clinical course. *Blood*, **97**, 3875–3881.

Valdez, B.C., Nieto, Y., Murray, D., Li, Y., Wang, G., Champlin, R.E. & Andersson, B.S. (2012) Epigenetic modifiers enhance the synergistic cytotoxicity of combined nucleoside analog-DNA alkylating agents in lymphoma cell lines. *Experimental Hematology*, **40**, 800–810.

Van Remmen, H., Ikeno, Y., Hamilton, M., Pahlavani, M., Wolf, N., Thorpe, S.R., Alderson, N.L., Baynes, J.W., Epstein, C.J., Huang, T.T., Nelson, J., Strong, R. & Richardson, A. (2003) Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging. *Physiological Genomics*, **16**, 29–37.

Vater, I., Wagner, F., Kreuz, M., Berger, H., Martín-Subero, J.I., Pott, C., Martinez-Climent, J.A., Klapper, W., Krause, K., Dyer, M.J., Gesk, S., Harder, L., Zamo, A., Dreyling, M., Hasenclever, D., Arnold, N. & Siebert, R. (2009) GeneChip analyses point to novel pathogenetic mechanisms in mantle cell lymphoma. *British Journal of Haematology*, **144**, 317–331.

Vitre, B.D. & Cleveland, D.W. (2012) Centrosomes, chromosomal instability, and aneuploidy. *Current Opinion in Cell Biology*, **24**, 809–815.

Wang, E.S., Wu, K., Chin, A.C., Chen-Kiang, S., Pongracz, K., Gryaznov, S. & Moore, M.A. (2004) Telomerase inhibition with an oligonucleotide telomerase template antagonist: in vitro and in vivo studies in multiple myeloma and lymphoma. *Blood*, **103**, 258–266.

van de Wetering, C.I., Coleman, M.C., Spitz, D.R., Smith, B.J. & Knudson, C.M. (2008) Manganese superoxide dismutase gene dosage affects chromosomal instability and tumor onset in a mouse model of T cell lymphoma. *Free Radical Biology and Medicine*, **44**, 1677–1686.

Widmann, T.A., Herrmann, M., Taha, N., König, J. & Pfreundschuh, M. (2007) Short telomeres in aggressive non-Hodgkin's lymphoma as a risk factor in lymphomagenesis. *Experimental Hematology*, **35**, 939–946.

Xu, D., Liu, X., Yu, W.M., Meyerson, H.J., Guo, C., Gerson, S.L. & Qu, C.K. (2011) Non-lineage/stage-restricted effects of a gain-of-function mutation in tyrosine phosphatase Ptpn11 (Shp2) on malignant transformation of hematopoietic cells. *Journal of Experimental Medication*, **208**, 1977–1988.

Yang, B., Yu, R.L., Tuo, S., Tuo, C.W., Liu, Q.Z., Zhang, N., Lu, X.C., Chi, X.H., Lv, S.B. & Cai, L.L. (2012) Antisense oligonucleotide against hTERT (Cantide) inhibits tumor growth in an orthotopic primary hepatic lymphoma mouse model. *PLoS ONE*, **7**, e41467.

Yao, R., Natsume, Y., Saiki, Y., Shioya, H., Takeuchi, K., Yamori, T., Toki, H., Aoki, I., Saga, T. & Noda, T. (2012) Disruption of Tacc3 function leads to in vivo tumor regression. *Oncogene*, **31**, 135–148.

Yu, R., Lu, W., Chen, J., McCabe, C.J. & Melmed, S. (2003) Overexpressed pituitary tumor-transforming gene causes aneuploidy in live human cells. *Endocrinology*, **144**, 4991–4998.

Zhang, L., Reynolds, T.L., Shan, X. & Desiderio, S. (2011) Coupling of V(D)J recombination to the cell cycle suppresses genomic instability and lymphoid tumorigenesis. *Immunity*, **34**, 163–174.

Zyss, D. & Gergely, F. (2009) Centrosome function in cancer. Guilty or innocent? *Trends in Cell Biology*, **19**, 334–346.