

REVIEW

Effect of Environmental Factors on Nuclear Organization and Transformation of Human B Lymphocytes

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Abstract—Chromosomal translocations have long been known for their association with malignant transformation, particularly in hematopoietic disorders such as B-cell lymphomas. In addition to the physiological process of maturation, which creates double strand breaks in immunoglobulin gene loci, environmental factors including the Epstein–Barr and human immunodeficiency viruses, malaria-causing parasites (*Plasmodium falciparum*), and plant components (*Euphorbia tirucalli* latex) can trigger a reorganization of the nuclear architecture and DNA damage that together will facilitate the occurrence of deleterious chromosomal rearrangements.

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In humans, malignant transformation is often associated with specific chromosomal translocations. Those result from two DNA double strand breaks (DSBs) erroneously repaired through non-homologous end joining (NHEJ). Proximity (colocalization) of the two translocation partners in the 3D nuclear space is necessary for translocations to take place.

DSBs can be generated by a variety of exogenous factors including ionizing radiations, chemotherapeutic drugs, and infectious agents or toxins. The production of

reactive oxygen species (ROS) or enzyme-dependent physiological processes such as the chromosomal rearrangements that occur during the normal maturation of B and T lymphocytes also generate DNA breakage.

DYNAMICS OF NUCLEAR ORGANIZATION, DNA DAMAGE, AND TRANSLOCATIONS

With chromosomes nonrandomly arranged in the nuclear space and occupying so-called chromosome territories [1], genomes are spatially organized in tissue- and cell type-specific ways [2, 3]. In general and regardless of the proliferation status of the cell, gene-rich and smaller chromosomes tend to be located in central areas of the nucleus, while gene-poor and larger chromosomes mostly lie in the nuclear periphery [2, 4-6]. Gene loci also exhibit nonrandom and gene-specific distribution patterns in the interphase nucleus [7]. The interaction between distinct chromosomes can activate genes in *trans*

Abbreviations: AICDA, activation-induced cytosine deaminase; BL, Burkitt lymphoma; CSR, class switch recombination; DSBs, DNA double strand breaks; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; NHEJ, non-homologous end joining; RAG1(2), recombination activating gene 1(2); ROS, reactive oxygen species; SHM, somatic hypermutation.

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resulting in colocalization of actively transcribed gene loci on different chromosomes [8]. The precise positioning of genes in the nuclear space, which is important for essential DNA transactions including transcription, replication, and repair [9, 10], reviewed in [11], evolves during development, differentiation, and aging, and during cellular responses to stress and various stimuli. The molecular factors that control this 3D (re)positioning remain largely unknown.

Chromosomal movements are known to accompany DNA repair, creating the possibility that two loci normally located away from each other are brought together [12–14]. Two alternative models have been proposed. In the “contact-first” model, both chromosomal partners lie in the vicinity of each other at the time of DNA damage. Live imaging analysis has shown that more than 80% of the translocations are created when DNA breaks are produced on two different chromosomes within a distance less than 2.5 μm [15]. Translocations are less frequent if the breaks are separated by 5 μm or more [15]. Usually, neither damaged nor intact chromatin fibers undergo extensive movements [12, 16]. However, the “break-first” model postulates that chromosomes are first broken away from each other and then move in the nuclear space and find their translocation partner. Indeed, under certain circumstances (e.g. large scale DNA damage or the intervention of the DNA repair factors) an enhanced mobility has been demonstrated for damaged DNA [13, 17]. As often, “break-first” and “contact-first” mechanisms can combine to produce a translocation. In this respect, we reported recently that inducing DSBs in the *MYC* locus in peripheral B-cells incubated in the presence of an HIV protein results in *MYC* relocating proximal to *IGH* gene loci (see further below) [18].

Recently, epigenetic modifications have been shown to have an impact on the susceptibility of chromatin to undergo DNA DSBs and on the movements of broken chromosomes [19]. Histone posttranslational modifications that regulate gene transcription have such an impact on chromosome breakages and ensuing translocations [20]. It has been reported that the methylation of K4 and K36 on histone H3 facilitates chromatin decondensation and also DSB formation [21]. In addition, chromosomal regions enriched in H3K4me3 constitute preferential targets for two enzymes, Recombination Activating Gene (RAG) 2 and Activation-Induced Cytosine Deaminase (AICDA) involved in V(D)J recombination and Class Switch Recombination (CSR) in normal B cells [22, 23]. That DSBs occur predominantly in transcriptionally active regions [24–26] comes as no surprise, since the recruitment of transcription factors further opens the chromatin structure. In turn, such sites become more susceptible to DNA damage and prone to translocations [27, 28].

Transcription is also regulated by the methylation/demethylation of genomic DNA within

CpG islands present in as much as 70% of gene promoters [29]. Interestingly, 40 to 70% of the breakpoints specifically associated with pro-B and/or pre-B leukemias and lymphomas are found in the vicinity of such CpG-rich regions [30]. Moreover, independently of their methylation status, the cytosine residues in the CpG islands are potential targets for AICDA, which can induce their deamination resulting in single-nucleotide mismatches that in turn become targets for nucleases including RAG1/2 [31].

Transcription is not the only process that leads to chromatin decondensation. Local chromatin structures can be modified by many chromatin remodeling complexes involved in different DNA transactions [32, 33]. Along with these changes, large-scale chromatin motions occur due to the increased flexibility of the chromatin fiber [33]. All together, these findings suggest the existence of a functional relationship between mechanisms of epigenetic regulation, the occurrence of DSBs, and the deleterious production of chromosomal rearrangements.

BURKITT LYMPHOMA AND NUCLEAR GENE RELOCALIZATION

Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma with three clinically distinct presentations [34, 35]. The endemic form is observed in children in Central Africa, particularly in areas with holoendemic malaria where it is virtually always associated with an infection by the Epstein–Barr virus (EBV) [36, 37]. The sporadic form of BL seen all over the world in patients usually in their teens, has an EBV prevalence of ~10–20% [34]. The third form, which occurs in HIV-infected patients, exhibits an intermediary level (~40–50%) of EBV prevalence [34, 36, 38]. What is constant in all three forms, is the existence of one among three possible chromosomal translocations, all involving the *MYC* oncogene on chromosome 8 rearranged either with the immunoglobulin (Ig) heavy chain gene locus (*IGH*) on chromosome 14, or with one of the two chromosomes carrying the Ig light chain genes *IGK* on chromosome 2 or *IGL* on chromosome 22. The t(8;14) translocation is the most frequent, being found in ~80% of the cases. The resulting juxtaposition of *MYC* and *IGH* leads to hyperactivation of *MYC* [38–40] via its relocalization from the periphery towards a perinucleolar region [41] in a more central position in the nucleus [42]. Similarly to *MYC*, *IGK* is often found near the nuclear periphery, but not *IGL*, which resides closer to the nuclear center while *IGH* is mostly found in regions located in-between [43]. Thus, the frequency of *MYC* rearrangement with either one of the three *Ig* gene loci could be directly related to its relative proximity with each of them [18, 43, 44].

In normal peripheral blood B-cells, the *IGH* and *MYC* gene loci are separated by approximately 40% of the nuclear diameter [18, 41, 43]. At the time of Somatic

Hypermethylation (SHM) and CSR in both human and murine B-cells, *MYC* relocalizes close to an *IGH* locus [41, 45] in the vicinity of the so-called “recombination compartment”, which is enriched in AICDA [46], one enzyme absolutely required for *Ig* gene maturation [47, 48]. Through its enzymatic activity, AICDA deaminates cytidines and produces U:G mismatches [49]. It can also target and modify regions outside *IGH*, as demonstrated when overexpressed in murine activated B-cells [47, 48, 50]. Indeed, proximity to *IGH* predisposes to AICDA targeting with 90% of the AICDA hotspots being found in gene loci located in the vicinity of the *IGH* locus [50]. AICDA can thus induce chromosomal breaks in the *MYC* region [47, 48], which in turn increases the probability of *IGH/MYC* translocations. Below, we will briefly review various environmental factors that have been shown to increase the risk of occurrence of a BL-associated chromosomal translocation.

BL-ASSOCIATED ENVIRONMENTAL FACTORS AND NUCLEAR ORGANIZATION

Viruses (EBV and HIV), the malaria parasite *Plasmodium falciparum*, and the latex of the plant *Euphorbia tirucalli* are some of the etiological factors that have been associated with the endemic form of BL, but the mechanism whereby these factors contribute to lymphomagenesis remain largely unknown. Their ability to affect the nuclear organization could play a role in BL oncogenesis. Here we will describe and summarize their impact on B-cells nuclear organization and the consequences in terms of lymphomagenesis.

EBV. BL was the first human tumor associated with a virus [51]. The Epstein–Barr virus (EBV) is a human gamma-herpesvirus with a tropism for B lymphocytes and an ability to establish long term persistence in memory B-cells. The EBV life cycle includes two phases: viral particles are produced in the lytic phase; in the latent phase, extrachromosomal episome persists in the nucleus [52].

EBV can remodel the nuclear organization, changing the positioning of chromosomes in infected cells [53]. EBV-positive cells also exhibit additional chromosomal aberrations such as dicentric chromosomes, chromosome fragments, and chromatid gaps, suggesting that chromosome breaks are produced along with defects in DNA repair [54, 55].

EBV latency. The latent phase of EBV infection is characterized by expression of several nuclear antigens (Epstein–Barr Nuclear Antigen [EBNA]-1, -2, -3A, -3B, -3C, and -LP), membrane proteins (Latent Membrane Protein [LMP]-1, -2A, and -2B), and noncoding RNA (EBER-1 and -2) [56]. The EBV Nuclear Antigen-1 (EBNA-1), expressed in both the latent and lytic phases of EBV infection [57], was found to induce DSBs via production of ROS with consequent chromosomal instabili-

ty [55]. Its expression leads to the deregulation of several genes involved in the maintenance of chromatin organization [58]. EBNA-1 can also induce chromatin decondensation [59]. EBNA-2, a transcriptional activator of both viral and cellular genes, is expressed during latent infection of B lymphocytes and is necessary for B-cell immortalization [60]. It can interact with histone acetyltransferases (HATs) and the SWI/SNF chromatin remodeler complex, thus disturbing the chromatin organization including in the upstream region of *MYC* [61]. EBNA-3 proteins also play an important role in B-cell immortalization [62]. EBNA-3C can activate the expression of AICDA by directly binding to upstream regulatory elements, where it provokes increased H3K4 trimethylation [63]. The latent protein LMP-1 participates in epigenetic regulation of the host genome by modulating the expression of three DNA methyltransferases – DNMT1, DNMT3A, and DNMT3B [64].

EBV reactivation from latency. The activation of *BZLF1* gene transcription leads to the switch from the latent to the lytic phases. The BZLF1 protein (Zebra or Zta) is a transcriptional transactivator that promotes transcription of viral genes inducing the viral lytic cycle [65]. The Zta protein also induces oxidative stress-mediated DNA damage by interacting with p53 [66, 67]. Inducing the EBV lytic cycle distorts the nuclear architecture, resulting in chromatin condensation at the nuclear periphery and formation of transcription factories in the nuclear center [68]. BGLF4 kinase, another key protein for EBV reactivation, phosphorylates and activates BZLF1 [69]. BGLF4 may play a role in marginal chromatin condensation by activating DNA topoisomerase II and phosphorylating condensin [70]. This could increase the risk of DNA breaks, as premature chromatin condensation is associated with a high risk of chromosomal breaks at common fragile sites [71].

The genome of the EBV resembles a small human chromosome in many ways. During latency, the EBV genome interacts with repressive heterochromatin, but upon spontaneous reactivation when EBV transcription drastically increases, the episome leaves the repressive environment and surrounds itself with active chromatin, leading to rearrangement of neighboring gene loci [72]. EBV can also integrate into the host genome [73] in sites located inside or in the vicinity of regions that harbor potential genome structural variations [74]. Thus, EBV integration can induce genome instability.

HIV-1. Infection by HIV-1 is associated with a significantly elevated incidence of cancer, particularly B-cell lymphomas [75, 76]. In Europe and in the US, the BL incidence is significantly higher in HIV-infected individuals compared with healthy subjects [18, 77]. This is also true for BL endemic zones where BL patients are 10–12 times more prone to be HIV-positive than healthy people [78]. Intriguingly, HIV cannot infect B-cells. Thus, the elevated risk of BL in HIV patients can be

caused either by immunodeficiency induced by AIDS or by HIV having a lymphomagenic role by itself.

According to one hypothesis, HIV induces chronic B-cell activation through an immune dysfunction leading to a deregulated clonal expansion of B lymphocytes [79]. Uncontrolled persistent stimulation of B lymphocytes may favor the uncontrolled monoclonal proliferation with as a consequence an increased risk of acquiring critical genetic alterations, ultimately leading to lymphoma development [79]. As already mentioned, AICDA is overexpressed in hyperactivated B-cells [48, 80]. Moreover, in EBV-infected patients, HIV infection can lead to EBV lytic cycle reactivation [34]. In these conditions of immunodepression induced by HIV, EBV-induced cell proliferation fails to be fully controlled by the immune system, resulting in an increased number of latently infected B-cells [34, 81].

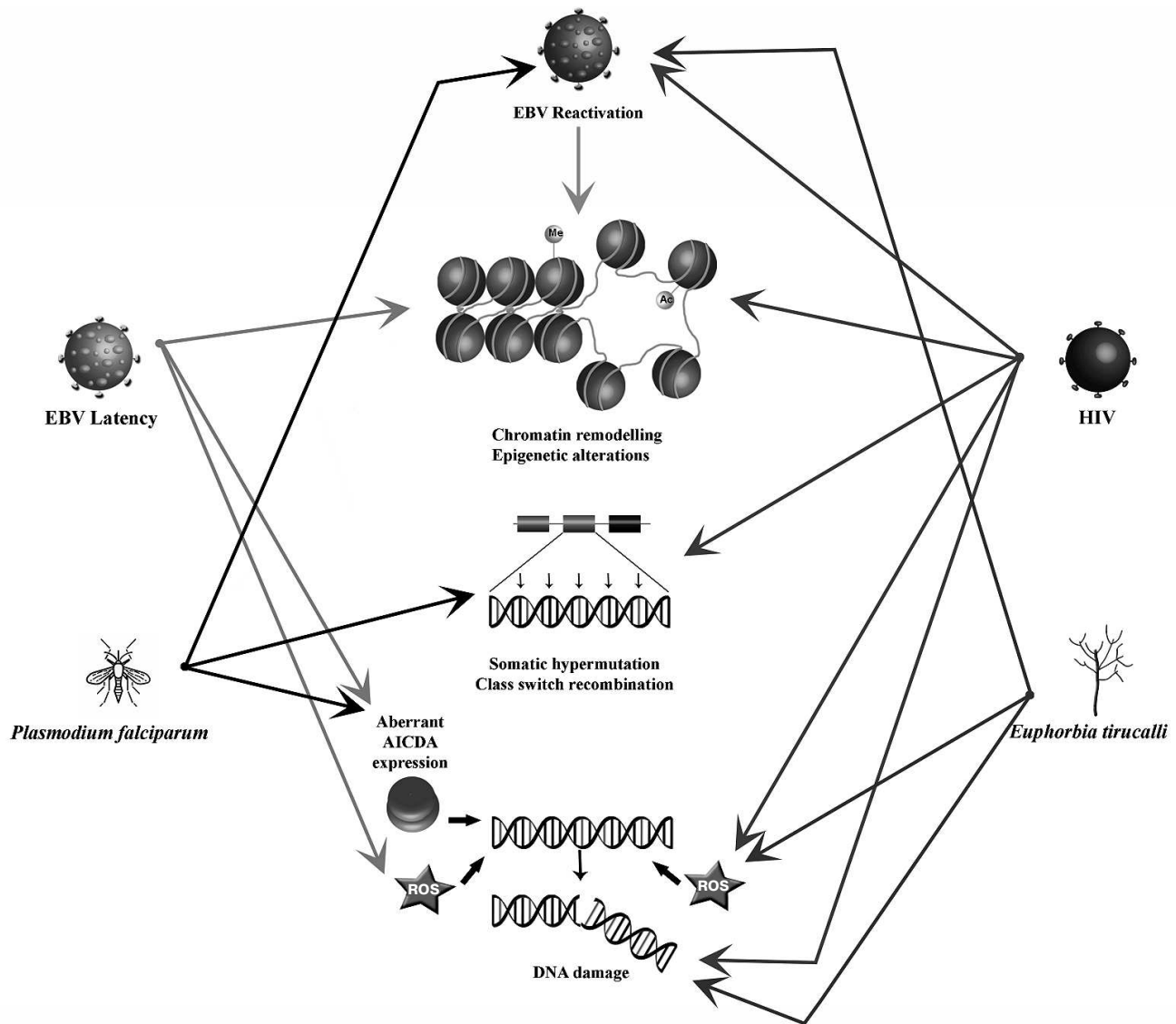
Alternatively, since the risk of BL remains elevated in patients under combined antiretroviral therapy (cART) and with normal CD4 counts [82, 83], a direct role of HIV in BL oncogenesis can be postulated. Our recent studies have demonstrated that the HIV-1 transactivator protein Tat, a small protein that is secreted into blood by infected cells and capable of penetrating B-cells, can modify their nuclear organization. It induces the displacement of one *MYC* allele from the periphery of the nucleus to the center, in close proximity with *IGH*, as a consequence of aberrant activation of *RAG1* and *MYC* [18]. This proximity between *MYC* and *IGH* could predis-

pose to BL development. Tat can also significantly increase oxidative stress-derived DNA damage in B-cells leading to a general chromosomal instability, which could potentially induce diffuse large B-cells lymphoma or Hodgkin lymphoma [84].

***Plasmodium falciparum*.** The association of malaria with endemic BL, the most common tumor in young children in tropical Africa, was observed for the first time almost 50 years ago [39, 85]. Malarial infection is caused by a protozoan parasite of the genus *Plasmodium*. It is transmitted by a bite of a female mosquito of the genus *Anopheles*, mostly present in hot areas. Even though several species of *Plasmodium* exist, only five can cause the disease in humans [86]. Among them, the *P. falciparum* species is associated with a high morbidity and mortality in Africa [87]. Such infections can profoundly affect B-cell metabolism, promoting polyclonal activation and an abnormal production of antibodies. *Plasmodium falciparum*-infected erythrocytes express erythrocyte membrane protein 1 (PfEMP1) [88], whose cystein-rich inter-domain region I α can activate B-cells [89]. The *MYC* and *IGH* loci move close to each other in activated B-cells [41, 45], thus the probability of the t(8;14) translocation is increased. Moreover, *P. falciparum* and *P. chabaudi* can induce an aberrant expression of AICDA in germinal center B-cells in both humans and mice [39, 49]. As a consequence, mice chronically infected with *P. chabaudi* exhibit a widespread genomic instability and develop mature B-cell lymphomas [49].

Effects induced on host cells by BL etiological factors

Factor	Effect	Effector	Reference
EBV latency	chromatin remodeling	EBNA-1, EBNA-2, LMP	[58, 59]
	DNA damage via ROS	EBNA-1	[55]
reactivation	epigenetic alteration	EBNA-1, LMP	[66]
	AICDA overexpression	EBNA-3C	[63]
	DNA damage via ROS	Zta	[66, 67]
	premature chromatin condensation	BGLF4 kinase	[68, 70]
HIV	epigenetic alteration	Zta	[66]
	B-cell activation		[34, 79]
	DNA damage via ROS	Tat	[18]
<i>P. falciparum</i>	<i>IGH-MYC</i> colocalization	Tat	[18]
	EBV reactivation	Tat	[34]
	B-cell activation	CIDR1 α	[41]
<i>E. tirucalli</i>	AICDA overexpression		[39, 49]
	EBV reactivation	CIDR1 α	[39, 89-91]
	DNA damage via ROS	latex	[98, 99]
	EBV reactivation		[96, 101]



Factors affecting processes implicated in oncogenesis and nuclear architecture remodeling

Also, the memory B-cells that are most susceptible to the CIDR1alpha domain-mediated activation often harbor a latent EBV. It has been demonstrated that CIDR1alpha can also induce EBV reactivation and its lytic cycle [89]. Indeed, chronic and repeated exposure to *P. falciparum* leads to virus reactivation from latency, an increased number of latently infected B cells in germinal centers, and elevated EBV viral load [36, 39, 90, 91]. In addition, *P. falciparum* alters the immune surveillance against EBV since exposure to holoendemic malaria induces suppression of EBV-specific T cell immunosurveillance [92, 93] and defects in EBV-specific CD8⁺ T-cell differentiation [94].

***Euphorbia tirucalli*.** *Euphorbia tirucalli*, a plant belonging to the Euphorbiaceae family, is commonly used as an ornamental or hedge plant. It is endemic in African

countries including Angola, Erythrea, Ethiopia, Kenya, Malawi, Mauritius, Rwanda, Senegal, Sudan, Tanzania, Uganda, and Zanzibar [95]. Interestingly, its geographical distribution is very similar to that of the endemic BL [96]. The plant has been frequently observed in houses of BL patients in the Eastern Africa [97], suggesting a possible link with BL pathogenesis. Little evidence exists on a direct role of *E. tirucalli* in modifying the nuclear organization. However, plant extracts have a high genotoxic potential and can increase DNA breakage and oxidative damage in cell cultures of human leukocytes in a dose-dependent manner [98, 99]. *Euphorbia tirucalli* can also alter the nuclear organization in B-cells by activating the EBV lytic cycle, as it contains EBV-activating substances such as 4-deoxyphorbol ester [95-97, 100]. When added to EBV-positive B-lymphocytes, *E. tirucalli* extracts

induced chromosomal abnormalities including ones on chromosome 8 [96, 101]. Finally, B-cells treated with the *E. tirucalli* extracts produced lymphomas when injected into nude mice [97].

Nuclear organization and chromosome positioning in the nuclear space are characteristic features of different cell types. Their modification by biological processes (e.g. epigenetic modifications, presence of DNA breakage) can result in increased risks of oncogenic translocations. In B-cells, recombination events that naturally occur during the processes of maturation and antibody formation can also alter the nuclear organization. These processes are affected by exogenous factors like EBV, HIV-1, the malaria parasites, or *Euphorbia tirucalli*. They can induce deregulation of chromatin-related genes, epigenetic changes, and excessive DNA damage provoking large-scale nuclear remodeling, which can potentially lead to the development of BL-specific translocations. The main changes introduced by each of these factors are summarized in the table and figure. However, knowledge of the exact role(s) played by these factors in the generation of BL-specific translocation and BL oncogenesis is still incomplete. Further studies could help in understanding the mechanisms leading to the Burkitt lymphoma etiopathogenesis.

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