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REVIEW

Chromosomal translocations among the healthy human population: implications in oncogenesis

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Abstract Chromosomal translocations are characteristic features of many cancers, especially lymphoma and leukemia. However, recent reports suggest that many chromosomal translocations can be found in healthy individuals, although the significance of this observation is still not clear. In this review, we summarize recent studies on chromosomal translocations in healthy individuals carried out in different geographical areas of the world and discuss the relevance of the observation with respect to oncogenesis.

Keywords Leukemia · Lymphoma · Neoplasia · Carcinoma · Sarcoma · Genomic instability · V(D)J recombination

Background

Chromosomal translocations are genomic alterations that result in the joining of heterologous chromosomes. Such a misjoining can lead to either the juxtaposition of certain oncogenes to the enhancer/promoter elements of other loci or novel fusions resulting in the formation of activated oncoproteins (Fig. 1) [1–3]. Many chromosomal translocations have been reported to date; however, an unusual and interesting observation has been their frequent incidence in cancers of the hematopoietic origin, namely leukemia and lymphoma [4–15]. Together, they constitute only around 8–10 % of the total cancer cases, yet more than 500 different translocations have been described thus far. Lack of in-depth studies and appropriate techniques hampered detection of such translocations in solid tumors. However, recently a tremendous advancement has been made in the identification of such chromosomal abnormalities in carcinomas and sarcomas. Studies have shown that common epithelial cancers like breast, prostate, thyroid cancer, and renal carcinoma also possess gene fusions as a result of translocations [16–20]. This has opened a new window in the use of such translocations as biomarkers in diagnosis and prognosis of cancers like carcinoma and sarcoma, which so far was the case only in leukemia and lymphoma.

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Translocations in cancer

The Philadelphia chromosome was the first translocation to be identified and described in the literature [4]. It results in the fusion of chromosome 22 and 9, which brings together the *BCR* and *ABL* genes, leading to the formation of an activated tyrosine kinase [21–23]. The t(14;18) translocation, between the *BCL2* gene on chromosome 18 and the immunoglobulin heavy chain (*IgH*) locus on chromosome 14, is the most common translocation in human cancer. It is characteristically present in follicular lymphoma (FL) and some cases of diffuse large B cell lymphoma (DLBL) [3]. It juxtaposes the *BCL2* gene along with its promoter to the *IgH* enhancer, thereby leading to its overexpression [24–28]. The majority of the breaks in chromosome 18 occur in the *BCL2* major breakpoint region or minor breakpoint cluster region and recently the mechanism of fragility of these regions was identified [28–30]. Some other well-known translocations are the c-*MYC-IgH* translocation in Burkitt's lymphoma, *NPM-ALK* translocation in anaplastic large cell lymphoma, and the diverse translocations involving the *BCL6* gene in DLBL [31–36]. As mentioned

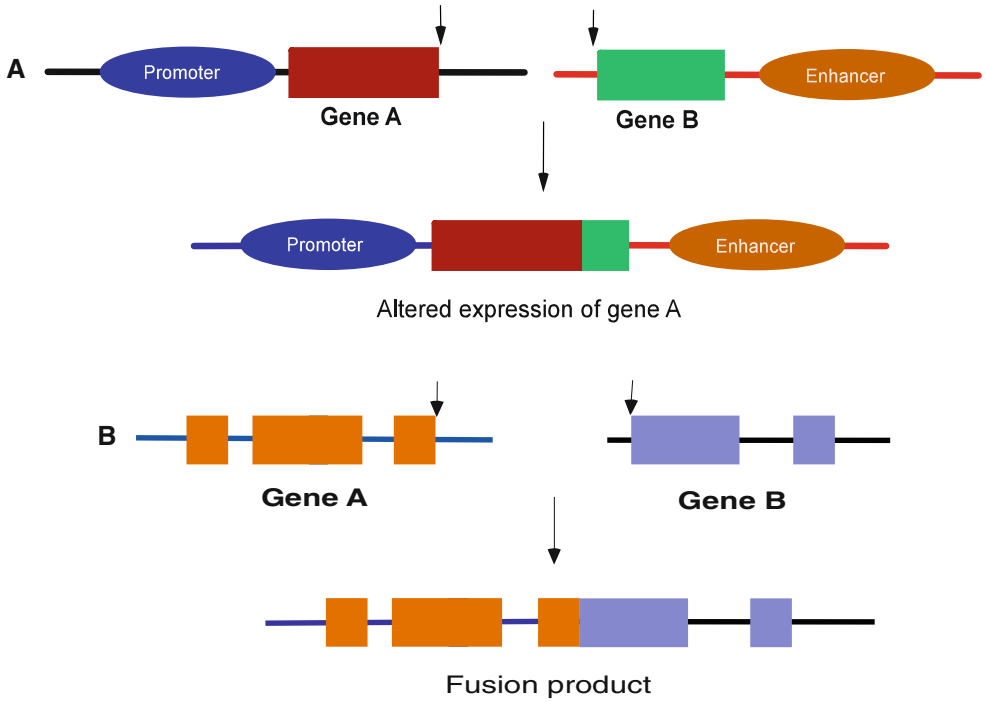

Fig. 1 Chromosomal translocations resulting in juxtaposition of promoter/enhancer elements to oncogenes or chimeric fusion proteins. In hematological cancers, like leukemia and lymphoma, translocations can result in the juxtaposition of the coding region of a gene (gene A) to enhancer/promoter elements of another gene (gene B) (**a**). This results in the enhanced expression of the gene A under the influence of either the enhancer or alternative promoters. Alternatively, translocations can also result in the formation of a fusion/chimeric protein, which may have a novel or enhanced function (**b**). For example, upon translocation, gene A can join with gene B, resulting in a fusion product. Altogether, these alterations can lead to changes in the cellular physiology and morphology, thereby resulting in malignant transformation

above, not many translocations had been described in carcinomas and sarcomas, until recently. Some of the translocations that have been identified are *TMPRSS2-ETS* translocations in prostate cancer, *EWS* translocations in Ewing's sarcoma, *ETV6-NTRK3* translocations in breast carcinoma, and others, as described previously [16–20, 37, 38]. Recently, the incidence and mechanism of these translocations in cancer have been extensively reviewed and summarized [11, 39–41].

Translocations in healthy individuals

In the recent past, an important yet puzzling observation has changed the outlook towards translocations being used as biomarkers in cancer. Multiple studies have shown the presence of some of these translocations in lymphocytes of peripheral blood of healthy individuals [42–46]. Though the number of such cells in circulation is low, it nevertheless leads to ambiguity during diagnosis of these cancers using chromosomal translocations as markers and while studying the progression of the disease. The translocations detected among the healthy individuals include those involving the *BCL2-IgH*, *BCR-ABL, NPM-ALK*, *BCL1-IgH*, and *BCL6* loci.

The *BCR-ABL* translocation or the Philadelphia chromosome is the genetic hallmark of chronic myelogenous leukemia (CML) [1]. During follow-up studies on CML patients, the presence of the *BCR-ABL* fusion mRNA was detected even in those patients who were cured following treatment [47]. Further studies found blood cells from 23 out of 117 healthy individuals, including both children and adults to have *BCR-ABL* translocation [47]. Moreover, the occurrence seemed to be age-dependent, being more in adults, which could be explained since CML occurs rarely in children [47]. Alternatively, increased probability of accumulating mutations or exposure to stimulating agents could augment the development of translocations in adults. Similar incidence of this translocation was also reported by another group (Table 1) [48]. However, there are no studies to identify the molecular mechanism responsible for the development of the *BCR-ABL* translocation in healthy individuals. Since the number of positive cases in healthy individuals for this translocation exceeds that of the disease, it remains to be seen how many of them will actually be at risk of developing CML.

The t(2;5) translocation involving the *NPM* and *ALK* genes is characteristically found in anaplastic large cell lymphoma (ALCL) [49, 50]. Similar to the Philadelphia

Table 1 Leukemia/lymphoma-associated gene fusions in healthy individuals

Translocation	Assay system	Cells	Frequency	Reference
t(9;22)	Nested RT-PCR	Peripheral blood leukocytes	p190 BCR/ABL 11/16 (69 %) p210 BCR/ABL 4/15 (27 %)	Bose et al. [48]
	Nested RT-PCR	Peripheral blood leukocytes	23/117 (19.7 %)	Biernaux et al. [47]
t(2;5)	RT-PCR, Southern hybridization	Peripheral blood leukocytes	14/29 (48.3 %)	Trumper et al. [49]
	Real-time PCR	Lymph nodes and spleen	20/31 (64.5 %)	Maes et al. [50]
t(11;14)	Real-time qPCR	Peripheral blood leukocytes	1/100 (1 %)	Hirt et al. [51]
t(14;18)	Nested PCR	Peripheral blood leukocytes	19/230 (8.3 %)	Paltiel et al. [102]
	Nested PCR	Peripheral blood mononuclear cells	40/254 (15.7 %)	Zignego et al. [71]
	Nested PCR	Peripheral blood leukocytes	31/55 (56.4 %)	Henriksson et al. [103]
	Nested qPCR	Peripheral blood mononuclear cells	10/23 (43.5 %)	Scheerer et al. [104]
	Semi nested PCR	Bone marrow aspirates Peripheral blood lymphocytes	89/224 (39.7 %)	Rauzy et al. [105]
	Nested qPCR	Peripheral blood mononuclear cells, umbilical cord cells	69/127 (54.3 %)	Liu et al. [106]
	Seminested qPCR	Peripheral blood mononuclear cells	26/57 (45.6 %)	Dolken et al. [56]
	Nested qPCR	Peripheral blood leukocytes	30/34 (88.2 %)	Fuscoe et al. [57]
	PCR Southern blot/ seminested PCR	Lymph node tissue	19/48 (39.6 %)	Molina et al. [107]
	Nested qPCR	Peripheral blood mononuclear cells	25/64 (39.1 %)	Cole et al. [108]
	Seminested PCR	Peripheral blood mononuclear cells, granulocytes, lymphocytes	6/9 (66.7 %)	Limpens et al. [58]
	Seminested qPCR, P^{32}-labelling	Peripheral blood mononuclear cells	70/146 (47.9 %)	Ji et al. [68]
	Nested qPCR	Peripheral blood leukocytes	57/122 (46.7 %)	Bell et al. [69]
	PCR	Lymph nodes	18/108 (16.6 %)	Corbally et al. [109]
	Nested qPCR	Peripheral blood lymphocytes	40/84 (47.6 %)	Liu et al. [55]
	Seminested PCR and Southern blot	Lymphoid tissue	10/25 (40 %)	Aster et al. [62]
	PCR and Southern blot	Lymph nodes and tonsils	13/73 (17.8 %)	Limpens et al. [110]
	Real-time qPCR	Peripheral blood mononuclear cells	287/644 (45 %)	Dolken et al. [67]
	Nested PCR, real-time PCR	Peripheral blood mononuclear cells	16/125 (12.8 %)	Ladetto et al. [111]

chromosome, this gene fusion also results in the formation of a constitutively activated tyrosine kinase, which has oncogenic potential. The t(2;5) translocation alone is insufficient to cause the lymphoma, which was reiterated by the fact that it was found to be circulating in the peripheral blood of healthy individuals [49, 50]. In one study, which used a combination of RT-PCR and Southern blotting techniques, 14 of 29 healthy volunteers (48 %) showed the presence of the t(2;5) translocations in lymphocytes [49]. Another study followed, showing similar results using both cytogenetic and sensitive molecular biology methods [50]. However, it is not yet clear whether the cells containing this translocation persist due to a survival advantage or arise due to multiple, independent translocations. More studies involving analysis of a larger number of healthy individuals as well as follow-up on positive cases is a pre-requisite to better understand the origin of translocation and its prognosis in ALCL.

Another translocation detected in healthy individuals is the t(11;14) translocation, involving the *BCL1* gene present in mantle cell lymphoma (MCL) [13, 14]. However, the frequency at which it was found was very low (1 in a group of 100 individuals) from a European population [51]. Studies from an Indian population also showed that the incidence of this translocation is rare [52]. Out of the 210 healthy Indian volunteers studied, none was positive for this translocation [52]. Both these studies have used sensitive detection assays of quantitative real-time PCR and nested PCR followed by Southern hybridization, respectively. It is hypothesized that this translocation may not be the initiating event in the pathogenesis of MCL and additional preceding mutations may be required. This would

explain its very low incidence in healthy individuals. A follow-up study on healthy individuals carrying this translocation showed that these t(11;14)-positive cells could persist for a long period of time and probably expand to acquire further aberrations before transformation [53]. Since only limited studies have analyzed this translocation, further studies from different populations with an increased sample size and more sensitive techniques are required.

In another study, inverse PCR was employed to detect the presence of mixed lineage leukemia (MLL) translocations in the peripheral blood of healthy individuals [46]. Of the healthy individuals, 49 % were shown to harbor the MLL translocations. Two main types of rearrangements, t(4;11) and t(9;11), were found upon sequencing, which constituted 66 and 20 % of the total translocations, respectively. It was suggested that the frequent breaks in the 11q23 locus could be due to extended exposure to various exogenous and endogenous chemical agents.

The t(14;18) translocation in healthy individuals

Among the different translocations studied, t(14;18) or the *BCL2-IgH* translocation is the most commonly reported, even among the healthy population. It is detected in nearly 90 % of the FL patients and around 20 % of the DLBL patients. Using various types of PCR assays, this translocation has been detected in the healthy individuals. The prevalence of t(14;18) translocation in the healthy population from Europe and America was determined to be around 40–60 %, depending on the sensitivity of the assay system, and the sample size of the donors (Table 1) [54–60]. In a recent study, it was shown that the incidence of t(14;18) translocation in Japanese population was lower (16 %) when compared to that in the German population (52 %) [61]. However, a previous study comparing the frequency of t(14;18) translocation between Japanese and American population did not find much difference between the two [62]. This could probably be due to the small number of samples analyzed during this study. More recently, we have determined the incidence of t(14;18) translocation among the healthy population in India [52]. We employed nested PCR followed by Southern hybridization using *BCL2* specific probes and the sensitivity of the assay was estimated to detect one translocation bearing cell among 10^7 cells [52]. Upon analysis of the blood samples from 253 healthy donors, we found that 87 individuals were positive for t(14;18) [52]. The observed incidence of around 34 % was lower than that seen in the American and European countries. It is worth pointing out that the incidence of FL itself varies across geographic regions. In the Western population, FL has a prevalence of around 30–40 % among all the non-Hodgkin's lymphoma [63], while in India its occurrence has been estimated to be only around 13 % [64, 65]. Hence, it could suggest a direct correlation between occurrence of FL and the presence of t(14;18) in healthy people, as the incidence of FL in Western countries is much higher than that in India as well as other Asian countries.

Previous studies on the transgenic mice expressing the *BCL2*-IgH translocation showed accumulation of the B cells, but development to the malignant lymphoma occurred only after a long latency period [24, 66]. This indicated that the t(14;18) translocation alone was not sufficient for initiating the development of FL and that further oncogenic mutations may be required for transformation into a cancerous cell.

Factors influencing t(14;18) in healthy individuals

The role of additional elements other than those responsible for causing the t(14;18) translocation like RAGs or DNA DSB repair proteins, in inducing translocations, has been a subject of debate. Some studies, including ours, have shown that with an increase in age, the frequency of t(14;18) translocation increases [52, 55, 67, 68]. However, a number of studies did not find any such correlation [57, 59–61]. This discrepancy could be due to the fact that in the majority of the studies that did not find the correlation, even though the number of individuals analyzed were more than 200, the frequency of incidence of t(14;18) positives was very low [59–61]. This could probably be due to the smaller amount of DNA analyzed for each individual in these studies. Moreover, in case of the study that analyzed 481 healthy subjects (one of the largest samples sizes studied), real-time PCR assay could increase the chances of false negatives, since this assay requires the presence of at least ten copies of the rearranged allele for minimum detection [59]. Therefore, an under-representation of the frequency of t(14;18) translocation in healthy individuals in these studies could be responsible for the inability to find its correlation with age.

With respect to gender, one study suggested a higher incidence of this translocation in males as compared to females [68], which could explain why males are more prone to non-Hodgkin's lymphoma than females. However, due to the insufficient sample size, this correlation could not be proved to be statistically significant. Besides, in a few other studies, no significant correlation between gender and the occurrence of t(14;18) translocation could be observed [52, 60]. In our study, we had analyzed for a possible correlation between the ethnicity and the prevalence of the translocation in the Indian population. For this, we classified all the 253 healthy volunteers, but were unable to find any significant correlation (Table 2). In a

Table 2 Geographic distribution of t(14;18) translocation in the healthy individuals in the Indian population

Healthy individuals	North		South		East		West	
	No. of individuals	% positive	No. of individuals	% positive	No. of individuals	% positive	No. of individuals	% positive
Male	17	7 (41.2 %)	115	42 (36.5 %)	22	8 (36.4 %)	9	2 (22.2 %)
Female	9	1 (11.1 %)	66	23 (34.8 %)	12	3 (25 %)	6	2 (33.3 %)
Total	26	8 (30.8 %)	181	65 (35.9 %)	34	11 (32.4 %)	15	4 (26.6 %)

All the healthy individuals studied have been broadly classified into four categories on the basis of their native places being in the northern, southern, eastern, or western parts of India. The percentage of people positive for the t(14;18) translocation has been calculated. The number of males and females in each region along with the percentage positive for t(14;18) have also been determined

different study, a positive correlation between smoking and the occurrence of t(14;18) translocation was observed [69]. However, more studies are required in this direction to draw any major conclusions. Another interesting observation has been that in patients having chronic hepatitis, liver cirrhosis, or hepatocellular carcinoma due to hepatitis C virus (HCV) infection, the incidence of t(14;18) was much higher (26 %) as compared to HCV-negative patients having similar liver abnormalities (3.6 %) [70, 71]. It is possible that HCV infection may provide the necessary antigenic stimuli for the maintenance of these cells in circulation.

Exposure to environmental pollutants or carcinogens is known to play a role in the generation of translocations in normal individuals. In an interesting study, it has been shown that the frequency of t(14;18) translocation in healthy individuals exposed to benzene was lower than normal age-matched controls [72]. By quantitative PCR analysis, this study found that 37 workers with benzene exposure had a decreased level of t(14;18) in their blood cells. 16.2 % of these workers had more than ten copies of the t(14;18) junctions as compared to 55 % of 20 controls that were not exposed to benzene [72]. This data suggests that the t(14;18)-bearing cells, a subset of B cells, could be more susceptible to the toxicity of benzene, resulting in their reduced numbers. However, studies have also shown that increased incidence of t(14;18) translocation occurs in farmers exposed to pesticides [73]. Previously, there has been evidence to suggest pesticide exposure as one of the major factors responsible for increased incidence of NHL [74–76]. In particular, exposure to a commonly used fumigant, phosphine, enhanced the development of chromosomal rearrangements involving chromosome 14 [77]. In an interesting study, it was found that a correlation could be drawn between chromosomal instability at specific fragile sites in human genome and certain specific chemicals, pesticides, and herbicides, suggesting a site-specific cytogenetic effect within cells [75]. This is in tandem with diverse chemicals having such site-specific consequences in vitro [78]. It was observed that increased breaks at all loci did not always lead to increased rearrangements as was seen for fragile sites 1q21, 3p14, and 9q12 [75]. However, in many cases, such an effect could be seen. In particular, it was noted that individuals exposed to herbicides like eradicane and 2,4-D had an elevated number of breaks at chromosomal loci 18q21, which harbors the *BCL2* oncogene and subsequently had its increased rearrangement with 14q32, unlike the control and unexposed individuals [75]. Hence, it is possible that increased exposure of such chemicals could lead to increased double-strand breaks in the genome, especially at fragile sites like the *BCL2* major breakpoint region and many others, thereby accounting for the higher frequency of translocations in such exposed

individuals. More recently, a long-term study was carried out to understand the relation between pesticide exposure and follicular lymphomagenesis [79]. This study showed that the t(14;18) clones persisted and expanded, particularly in farmers exposed to pesticides rather than the unexposed farmers. In addition, these cells represented bona fide FL precursors at different stages of tumor progression. Therefore, now it remains to be seen whether one can predict how many of these t(14;18) harboring healthy individuals, would actually go on to develop the follicular lymphoma.

Chromosomal translocations and the immune system

The majority of the chromosomal translocations in cancer are largely confined to cells of the immune system and have been shown to be caused by lymphoid-specific processes such as V(D)J recombination or class switch recombination (CSR). Interestingly, from our studies on a healthy Indian population, it was observed that individuals under the age of 20 years had a very high frequency of incidence of the t(14;18) translocation as compared to all other age groups. Even more interesting was the higher incidence of the translocation in females as compared to males. Although this phenomenon needs to be investigated further, one can speculate the role of the immune system in this regard. At a younger age, one can envisage a more actively developing immune system and perhaps more of the immunological processes like V(D)J recombination or CSR to occur. It is known that with an increase in age there is reduced V(D)J recombination activity and an overall decreased immune response [80–82]. A lower Rag2 expression in pro-B cells has been shown in aged mice, which could directly diminish the V(D)J recombinase activity [83]. Another study showed that newborns displayed an increased nucleolytic processing, especially with respect to Artemis protein (associated with V(D)J recombination), indicating that it could be important for modulating the immune system in children [84]. Hence, at a younger age, these processes could increase the susceptibility of the developing B and T cells to generate chromosomal translocations. Interestingly, an increasing number of translocations have been identified in leukemic cells from children, which seem to be caused by the RAG proteins during early development [85]. A remarkable increase in the RAG-mediated *HPRT* deletions at functional cryptic RSS at the later stages of fetal development also suggests that cryptic RSS sites at various genomic loci could be susceptible to RAG cleavage during specific periods of pediatric development [86].

It is also becoming increasingly clear that there are significant differences in the immune responses between male and females. There are reports suggesting that females mount a more vigorous immune response against identical antigens and also carry larger numbers of resident immune cells, thereby eliciting a stronger response [87]. Moreover, it was observed that females exhibit a higher activity of TdT, a key enzyme involved in V(D)J recombination, suggesting that modulation of the processing machinery could affect the immune repertoire [84]. This can probably explain the bias towards more females carrying the translocation in younger ages. However, further studies are required to get a clear picture for this observation.

Origin of chromosomal translocations

In the recent past, cancer stem cells have caught the attention of researchers in the field of cancer biology [88]. Although initially elusive, recent studies have been successful in isolating this population from leukemic cells and have been shown to be sufficient for the initiation, regeneration, and maintenance of leukemia in mice [89, 90]. More recently their presence has been detected in other forms of cancers like those in the central nervous system, breast, lungs, and colon [91–93]. However, the cellular origins of the cancer stem cells have remained elusive thus far. Since hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs) are thought to be closely related and are similar in many ways, the genesis of LSCs has always been an intriguing question. HSCs have the capacity for self-renewal and are maintained for longer periods of time in an organism. Hence, it can be envisaged that LSCs could be derived from HSCs upon induction of several mutations, especially chromosomal translocations (Fig. 2a). Alternatively, various committed progenitor cells could also be a source of LSCs, after accumulation of mutations that render these cells "stem-cell like" by reactivation of the stem cell program machinery (Fig. 2b) [94]. Different studies have now shown that some of these stem cells or early progenitor cells could indeed harbor pathogenic chromosomal translocations. It was reported that in childhood acute lymphoblastic leukemia, the leukemic-specific rearrangements t(9;22) and t(4;11) could be detected in a high percentage of progenitor/stem cells, which were $CD34^{+}CD19^{-}$ [95]. In another study, it was shown that *ETV6-RUNX1* (*TEL1-AML1*) fusions were confined to B cell progenitor cells $CD34^{+}CD38^{-}CD19^{+}$ and there was no effect on the size of the normal HSC population by the LSC expansion [96]. In contrast, the major breakpoint *BCR-ABL1* fusions, encoding the P210 BCR-ABL fusion protein, were found to have an HSC origin and were present in the $CD34^{+}CD33^{-}CD19^{+}$, $CD34^{+}CD33^{+}CD19^{-}$ and $CD34^{-}CD33^{+}CD19^{-}$ cells. Interestingly, the minor fusion protein was shown to have a B cell progenitor origin, which

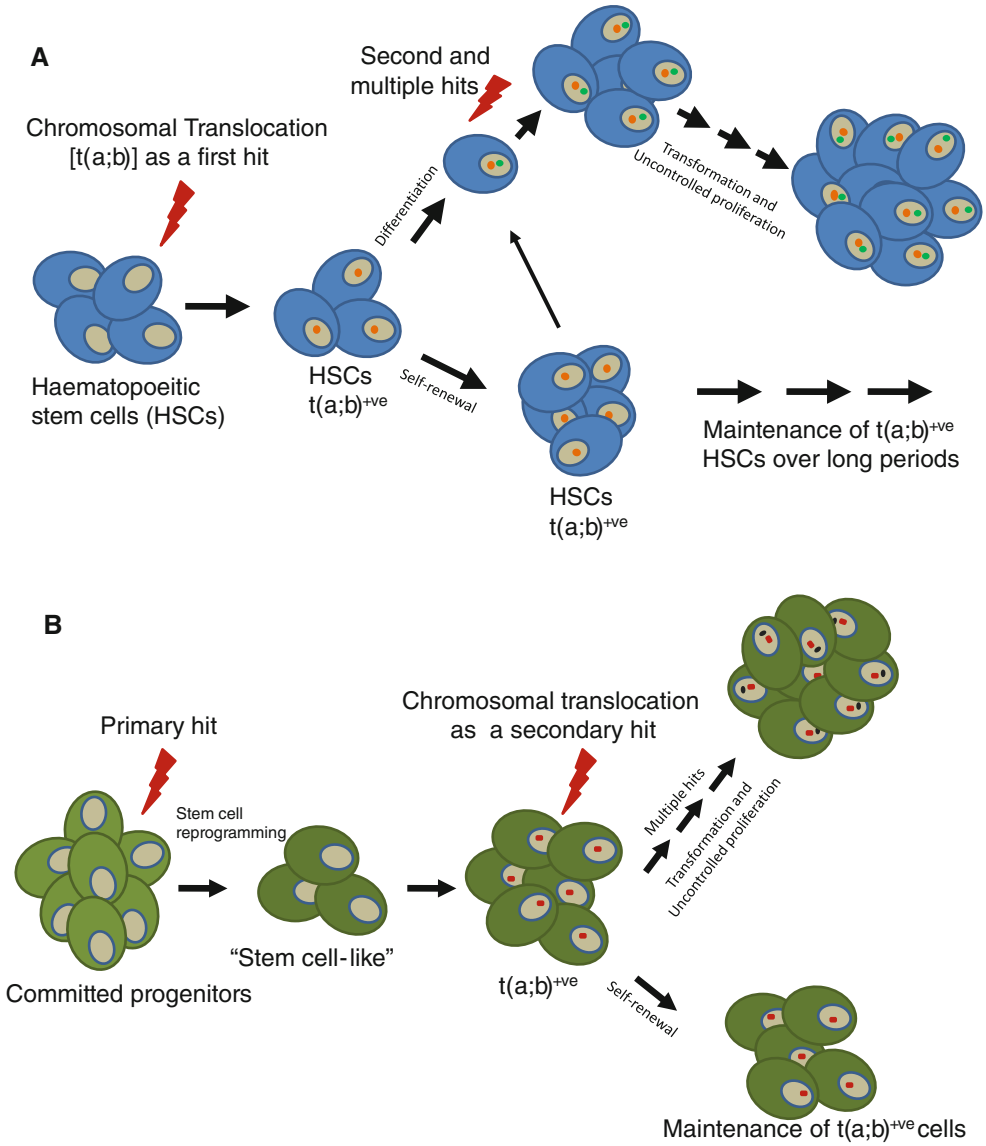

Fig. 2 Models for transformation of a normal cell into cancer cell. **a** Hematopoietic stem cells can acquire chromosomal translocation as a primary hit and these cells can either differentiate or be maintained in stem cell compartments over long periods of time. The replicating, differentiating cells (leukemic stem cells) can then acquire secondary mutations over a period of time and develop into cancerous cells. **b** Alternatively, committed progenitors cells might undergo cellular reprogramming in order to get converted into stem cell-like cells, which upon acquiring secondary hits could become like cancer stem cells, responsible for the generation of the tumor over a period of time

suggests that the two types of *BCR-ABL* fusion represented distinct tumor entities [96]. All these studies suggest that there are different compartments in which cancer-initiating cells responsible for causing different types of leukemia and lymphoma can exist. Therefore, it is important to identify the leukemia/lymphoma initiating cells in various cancers so that these cells can be targeted more effectively and specifically. Moreover, it is believed that HSCs are generally more resistant to radiation and other therapies, therefore targeting the translocation-bearing tumor initiating cells will be more appropriate during development of therapeutic strategies.

Role of translocations in oncogenesis

Chromosomal translocations generally lead to deregulation of genes and hence, differential expression of respective proteins. The t(14;18) translocation results in the overexpression of the anti-apoptotic BCL2 protein thereby providing the cells with a survival advantage. It is possible that this could help in the persistence of such translocation-bearing cells in circulation for a longer time, which upon further oncogenic hits may get transformed into a malignant cell. Recent studies suggest that the t(14;18)-bearing cells in the healthy individuals might act as FL-like B cells

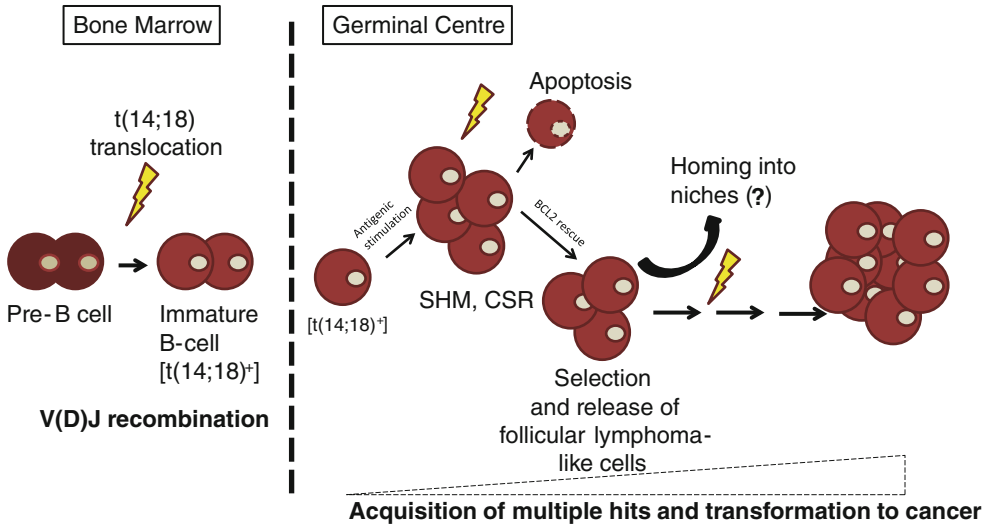

Fig. 3 Model of initiation and progression of t(14;18)-bearing cell into follicular lymphoma. The pre-B cells, in the bone marrow, undergoing V(D)J recombination could develop the t(14;18) translocation and generate $t(14;18)^+$ immature B cells. These cells upon antigen presentation in the germinal center undergo somatic hypermutation and class switch recombination, further acquiring possibly pathogenic mutations and could get selected upon antigenic stimulation. Such cells may evade apoptosis due to overexpression of the BCL2 protein and may be released in circulation or homed into undefined niches. These cells, which are more follicular lymphoma-like, now act as intermediates and may accumulate secondary aberrations in order to develop into the lymphoma

(Fig. 3) [97]. The translocation-bearing cells seemed to be enriched in IgM memory cells (IgD^+), further showing that such t(14;18) bearing B cells were not naive [97, 98]. These cells, being $CD27^+$, would have transited through the germinal center. They also have additional features that are more FL-like and therefore could act as novel intermediates during the early steps of lymphomagenesis; but how do such cells originate? The sequences of the breakpoint junctions from both healthy individuals and patients are mostly similar, suggesting that the translocations arising in healthy individuals are not mechanistically different from those in patients [7, 54]. The translocation-bearing healthy cells are also thought to overexpress BCL2; however, no studies have been performed to confirm this. Since the t(14;18)-bearing normal cells are memory cells, they would persist for a long time in circulation and upon appropriate stimulation, by antigens (like the HCV antigen described before), could proliferate more and attain further oncogenic hits. Few studies have tried to establish this long-term clonal persistence of such t(14;18)-bearing cells in healthy individuals, by performing follow-up studies on the positive cases over a period of few years [54, 97, 98]. Sequence analysis has also shown that while the majority of the positive cases possess only one breakpoint, some do show the presence of more than one breakpoint region [54]. It can therefore be suggested that though initially there is a clonal expansion and persistence of a single t(14;18)-bearing clone, with time, independent hits may lead to the formation of multiple cells bearing different t(14;18) translocation breakpoint junctions. Further long-term and follow-up studies are needed to understand the step-by-step progression of translocation-bearing cells into tumor cells.

In mouse models of the *MLL-ENL* translocation in MLL, it was observed that DNA damage response (DDR) induces a pro-senescence program to prevent *MLL-ENL* oncogene-induced leukemogenesis [99]. This suggests that the gene fusion alone, although causing myeloproliferation, cannot promote progression into acute leukemia and requires DDR inhibition. It was also noted that preventing the initiation of senescence or DDR leads to augmentation in the LSC population, suggesting that the fusion does not directly induce tumorigenesis and requires an interplay of several other partners. Recently, it was shown that in case of CML, the stem cell population could survive independent of the *BCR-ABL* fusion and was not oncogene addicted [100]. The *BCR-ABL*-depleted stem cell population had the ability to maintain their population in vivo and upon *BCR-ABL* expression could reinitiate transformation into leukemia. This shows that unlike the *MLL-ENL* fusion, in some cases the development of translocation could be a secondary event, and may be required to trigger the process of leukemia progression. In an interesting study, it was shown that *MLL* fusions, in particular *MLL-ENL,* could influence hematopoietic lineage commitment when occurring in the T cell progenitor cell and cause a switch from lymphoid to myeloid lineage during leukemogenesis by reprogramming [101]. Therefore, it suggests that depending on the type of cell, the translocation originates in, the gene fusion can exhibit alternative functions and promote tumorigenesis. However, this also provides a plethora of proteins that could be identified and act as novel therapeutic targets in the future.

Conclusions

It is evident that many chromosomal translocations can also be seen in healthy individuals, besides their occurrence in patients. In almost all of these cases, the frequency of translocation in healthy individuals is many fold higher to the incidence of the respective cancer. This implies that only a small fraction of chromosomal translocation-bearing cells present in healthy individuals can undergo malignant transformation. Therefore, in the coming years, the focus of research may shift to the identification of the environmental and physiological aspects responsible for development of cancer, after a single cell in the body acquires a particular translocation.

Perspective

The long-held view that chromosomal translocations are genetic hallmarks of leukemia, lymphoma, and other types of cancers, and can be used as biomarkers for identification of tumor cells, is fast disappearing. It is increasingly becoming clear that chromosomal translocations are not sufficient to cause transformation of normal to cancer cells, but requirement of either additional preceding or succeeding mutations is essential. Since many such genetic lesions do not lead to any specific changes on the cell surface, expulsion of such cells from the system by our immune response is not possible. Evidence for presence of translocation-bearing HSCs or progenitor cells can possibly explain the persistence of such cells over long periods of time. It will be important to study whether such stem/progenitor cells are more susceptible to development of genomic rearrangements and thus strategies can be developed to specifically target and eliminate them in patients. At the molecular level, it is seen that the translocation breakpoint junctions in healthy individuals are similar to that in patients. However, as in the case of *BCL2-IgH* translocation, it is not proven whether the differential expression of the affected protein like BCL2, indeed occurs. It is possible that there could be some mechanism by which the aberrant expression of those oncoproteins, despite the translocation, is suppressed in normal cells. However, with the gradual acquiring of certain mutations, the oncoproteins get expressed and activated. The microenvironment around the translocation-bearing normal cells can also play a critical role in transforming the cells more towards cancer-like. Identification of specific niches where such translocation-bearing cells reside could be a challenging yet critical aspect in the future.

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