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Translocations affecting human immunoglobulin heavy chain locus

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Translocations involving human immunoglobulin heavy chain (IGH) locus are implicated in different leukaemias and lymphomas, including multiple myeloma, mantle cell lymphoma, Burkitt's lymphoma and diffuse large B cell lymphoma. We have analysed published data and identified eleven breakpoint cluster regions (bcr) related to these cancers within the IgH locus. These ~1 kbp bcrs are specific for one or several types of blood cancer. Our findings could help devise PCR-based assays to detect cancer-related translocations, to identify the mechanisms of translocations and to help in the research of potential translocation partners of the immunoglobulin locus at different stages of B-cell differentiation.

Keywords: translocation, human immunoglobulin heavy chain, oncogenesis, lymphoma, leukaemia, B-cell differentiation.

Introduction. One hundred years ago German cytologist Theodor Boveri proposed that translocations may give rise to cancer [1]. Translocations are the transfer of a piece of one chromosome to a non-homologous chromosome or to a new site on the same chromosome. Indeed, translocations are associated with many cancers, including sarcomas, lymphomas, leukaemias *etc*. [2]. These translocations involve specific loci and genes. Translocations may place genes in new linkage relationships, produce chimeric genes and could generate chromosomes without normal pairs [3]. Human immunoglobulin heavy chain locus is one of the most frequent partners in translocations leading to leukaemias and lymphomas. Here we shall consider translocations involving this locus, its potential partners and mechanisms leading to translocations and lymphomagenesis.

Mechanisms of translocations. Translocations result from erroneous double-strand breaks (DSB) repair in DNA [4]. The DSBs appear in physiological and pathological processes and under the influence of external conditions such as oxidative stress and ionizing radiation (for review see [5]). DSBs also occur in immunoglobulin genes during lymphoid cell maturation [6].

The appearance of DSBs activates the cellular DNA repair machinery that catalyses the joining of broken chromosome ends [7] that can occur either by homologous recombination (HR) or by non-homologous end joining (NHEJ). NHEJ joins the ends of the broken chromosome; this repair mechanism is error-prone and can result in variety of rearrangements: deletions, duplications, and inversions. Furthermore, translocations may occur when the broken ends of two non-homologous chromosomes are joined together.

Chromosomal translocations may result in tree possible scenarios: (1) deregulation of important genes, and

particularly proto-oncogenes and tumour suppressor genes crucial for regulation of most cellular processes [8–10]. This happens either by juxtaposition of oncogenes to a transcription control element of another gene on a different chromosome, thereby leading to an abnormal expression of the translocated gene or by relocalization of the translocated region in the nuclear space [11, 12]; (2) the translocation may result in the formation of a unique fusion gene, which in turn codes for an activated form of the protein that affects the normal cellular physiology; (3) some translocations, particularly non-reciprocal ones, may lead to changes in gene dosage, *i. e*. loss of tumour suppressor genes or duplication of oncogenes.

Translocations in lymphomas and leukaemias. Vast majority of lymphomas and leukaemias are caused by translocations. The elevated frequency of translocations in this case is due to high amount of DSBs at immunoglobulin genes generated by RAG1/2 during V(D)J recombination, T-cell receptor (TCR) gene rearrangement and activation-induced (DNA-cytosine) deaminase (AID) during somatic hypermutation and class switch recombination essential for creation of antigen repertory [6].

V(D)J recombination is a physiological process during which variable (V), diversity (D) and joining (J) segments of immunoglobulin (Ig) or T-cell receptor (TCR) genes are rearranged and lead to great diversity of the Ig/TCR repertoire. This process is mediated by lymphocyte-specific endonucleases (RAG1, RAG2) which cut the regional V(D)J genes at flanking recombination signal sequences (RSS) consisting of specific highly conserved heptamer and nonamer sequences with a non-conserved spacer (12 or 23 nucleotides) in-between [13, 14]. Subsequently, the coding segments are joined using the classical non-homologous end-joining (NHEJ) pathway. Translocations during V(D)J-recombination may lead to different cancers, *e. g*. multiple myeloma, mantle cell lymphoma, or childhood acute lymphoblastic leukemia (see below).

Somatic hypermutation and class switch recombination in the Immunoglobulin heavy chain locus (IgH) also play a key role in generating antibody diversity. Activation-induced (DNA-cytosine) deaminase [13, 15, 16] participates in both processes. AID deaminates the cytosines present in single-stranded regions (during transcription or formation of R-loops) into uracil, which results in a mismatch. This can be further processed by uracil N-glycosylase/AP endonuclease, finally leading to either a mutation or a DSB [14, 17–20]. The DSB generated is an intermediate for class switching and, therefore, if unrepaired, can be a suitable candidate for illegitimate joining. This is supported by recent studies, where it was demonstrated that the breaks in the *c-myc* gene locus during t(8;14) translocation, characteristic of Burkitt's lymphoma, are induced by AID 10 [21–24]. The *c-myc* region has also been suggested to form G-loop structures on plasmid DNA, which can be bound by AID [25].

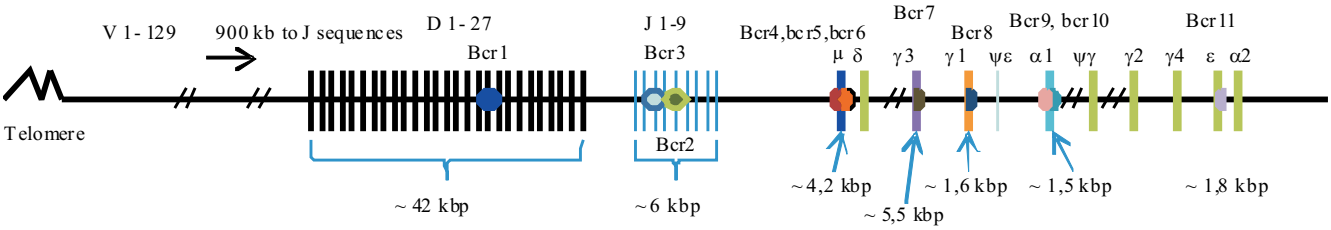
Translocations in the human immunoglobulin heavy chain locus. Active recombination occurring at the IgH and TCR loci makes them ideal partners for translocations; indeed, many cancers are linked to translocation in these loci (for review see [3]). In the present review we shall concentrate on translocations involving the IgH located in the subtelomeric region of the 14q chromosome at 14q32.33. The IgH spans 1250 kilobases (kb). It consists of 4 parts: V (variable), D (diversity), J (joining), and C (constant). Each part contains a significant amount of genes, 129 *IGHV* genes, 27 *IGHD* segments belonging to 7 subgroups, 9 *IGHJ* segments, and 11 *IGHC* genes [21]. These genes are the subjects to V(D)J-recombination in bone marrow, and class-switch recombination in germinal centers.

Translocations in the IgH locus during the B-cell differentiation could involve different parts of the locus and lead to a different type of cancers. Below we shall concentrate on the translocation hotspots also called breakpoint cluster regions (*bcrs*) within the IgH region. Translocations in the IgH locus have been extensively characterized [26–52]; reviewed in [36, 52, 53], but so far, no comprehensive analysis of the localization of *bcrs* in this locus has been done.

Breakpoint and translocation clusters were identified in several lymphomas; their average size is ~1 kbp [54]. We have identified bcrs involved in translocations with different partners leading to lymphoid malignancies. We have analysed published data to identify the breakpoint regions in cancers with translocations involving the IgH locus (Mantle cell lymphoma, Burkitt's lymphoma, diffuse large B-cell lymphoma, and multiple myeloma). We have found 195 individual transloca-

Breakpoint cluster regions in the human immunoglobulin heavy chain gene locus

Breakpoint cluster region	Type of cancer	Number of cases	IgH region	*bcr* size, bp	Coordinates on IgH map (ref)
*bcr*1	Mantle cell lymphoma	3	IGHD5-18	978	929160–930137
*bcr*2	Mantle cell lymphoma,	18	IGH J4-J5-J6	1060	959075–960135
	Burkitt's lymphoma	5			
*bcr*3	Mantle cell lymphoma	3	IGH J2-J3-J4	1184	957695–958878
*bcr*4	Mantle cell lymphoma,	6	IGHM	995	962031–963025
	Burkitt's lymphoma	7			
*bcr*5	Mantle cell lymphoma,	3	IGHM	1083	963016–964099
	Burkitt's lymphoma	10			
*bcr*6	Mantle cell lymphoma,	2	IGHM	1340	964148–965487
	Burkitt's lymphoma	5			
*bcr*7	Diffuse large B-cell lymphoma,	2	IGHG3	731	1049447–1050177
	Multiple myeloma,	2			
	Burkitt's lymphoma	4			
*bcr*8	Multiple myeloma,	5	IGHG1	1087	1077375–1078461
	Burkitt's lymphoma	10			
*bcr*9	Burkitt's lymphoma	17	IGHA1	1278	1111692–1112969
*bcr*10	Multiple myeloma,	8	IGHA1	463	
	Burkitt's lymphoma	4			1113339–1113809
*bcr*11	Burkitt`s lymphoma	4	IGHE	416	1232681–1233096



Breakpoint cluster regions in the human immunoglobulin heavy chain gene locus

tion breakpoint sequences in the IgH locus. These were grouped into bcrs, with the condition that one ~1 kbp *bcr* should include no less than 3 individual translocation events. We could identify eleven *bcrs*. These data are summarized in Table and Figure.

Mantle cell lymphoma (MCL) is caused by a t(11:14) involving IgH and CCND1 loci [54]). The translocation is thought to occur during V(D)J recombination [55]. Indeed, most MCL-related breakpoints are located in the JH region. They are concentrated in two bcrs (*bcr*2 and *bcr*3) in JH regions 2–4 and 4–6 [28, 36, 46, 49, 50, 54, 55]. An additional *bcr* (*bcr*1) is located in the D region, what is not very characteristic of MCL [49].

IgH/c-myc translocations (t(8:14)) lead to Burkitt's lymphoma (BL) [42, 43]. These translocations occur

during somatic hypermutation (SH) [56] or class switch recombination (CSR) [44]. *Bcrs* for BL thus occur mostly in JH regions [40] and the constant region of the IgH locus, precisely in μ, γ3, α1, γ1 and ε genes [40, 43].

The *WHSC1* (Wolf-Hirschhorn syndrome) gene located on chromosome 4 is the main IgH translocation partner in multiple myeloma. This translocation occurs during CSR [34, 57]. Logically, breakpoint regions for multiple myeloma (*bcrs*4–8, 10) are localized in the constant region [34, 57].

Diffuse large B-cell lymphoma (DLBCL) is linked to translocations with *CCND3* and *CCND4* genes on chromosome 3 [40]). In general, this translocation occurs during CSR [58] and somatic hypermutation [59]. The *bcr* for DLBCL (*bcr*7) is localized in the γ2 gene (constant region).

Interestingly, several *bcrs* (*bcr*2, 4, 5–7, 10) are not specific for one type of cancer. These bcrs are located in the regions that are the subjects to V(D)J recombination (*bcr*2), CSR (*bcr*4–8; 10) and SH (*bcr*2, 4–8, 10). This suggests that these *bcrs* in the IgH locus are in contact with several different potential translocation partners at the same time. Whether it happens in all B-cells, or there are subsets or individual B-cells where IgH bcrs contact specific partners is not yet known. This question might be answered by using a circular chromosome conformation capture (4C) technique [29] on individual cells and cell populations. The BCRs identified in the present review may serve as convenient baites for this technique. Further studies will be necessary to answer the posed questions.

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Транслокації, обумовлені локусом важкого ланцюга гена імуноглобуліну людини

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Резюме

Транслокації за участі локуса важкого ланцюга гена імуноглобулінів відіграють певну роль в онкогенезі багатьох лімфом і лейкемій, серед яких множинна мієлома, лімфома мантійної зони, лімфома Беркітта та дифузна В-клітинна лімфома. На основі аналізу опублікованих даних ми виділили 11 областей, у яких відбуваються транслокації, що призводять до вищезгаданих лімфом і лейкемій. Кожна з таких областей (розміром приблизно 1000 пар нуклеотидів) може брати участь у транслокаціях, які спричиняють один або декілька типів раку. Отримані результати можна використовувати при розробці діагностики транслокацій, які викликають рак крові, а також при ідентифікації потенційних транслокаційних партнерів локуса важкого ланцюга гена імуноглобулінів на різних стадіях диференціювання В-лімфоцитів.

Ключові слова: транслокації, важкий ланцюг імуноглобуліну людини, онкогенез, лімфома, лейкемія, диференціювання В-клітин.

Транслокации, обусловленные локусом тяжелой цепи гена иммуноглобулина человека

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Резюме

Транслокации с участием локуса тяжелой цепи гена иммуноглобулинов играют определенную роль в онкогенезе многих лимфом и лейкемий, включая множественную миелому, лимфому мантийной зоны, лимфому Беркитта и диффузную В-клеточную лимфому. На основе анализа опубликованных данных мы выделили 11 областей, в которых происходят транслокации, приводящие к вышеупомянутым лимфомам и лейкемиям. Каждая из таких областей (размером примерно 1000 пар нуклеотидов) может участвовать в транслокациях, являющихся причиной одного или нескольких типов рака. Полученные результаты можно использовать при разработке диагностики транслокаций, вызывающих рак крови, а также при идентификации потенциальных транслокационных партнеров локуса тяжелой цепи гена иммуноглобулинов на разных стадиях дифференцировки В-лимфоцитов.

Ключевые слова: транслокации, тяжелая цепь иммуноглобулина человека, онкогенез, лимфома, лейкемия, дифференцировка В-клеток.

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