Biochimica et Biophysica Acta 1786 (2008) 139–152

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Chromosomal translocations in cancer

Mridula Nambiar, Vijayalakshmi Kari, Sathees C. Raghavan *

Department of Biochemistry, Indian Institute of Science, Bangalore 560 012, India

ARTICLE INFO

Article history:
Received 12 January 2008
Received in revised form 15 July 2008
Accepted 19 July 2008
Available online 31 July 2008

Keywords:
Leukemia
Lymphoma
Neoplasia
DNA repair
Double-strand break
Carcinoma
Sarcoma
Genomic instability
V(D)J recombination

ABSTRACT

Genetic alterations in DNA can lead to cancer when it is present in proto-oncogenes, tumor suppressor genes, DNA repair genes etc. Examples of such alterations include deletions, inversions and chromosomal translocations. Among these rearrangements chromosomal translocations are considered as the primary cause for many cancers including lymphoma, leukemia and some solid tumors. Chromosomal translocations in certain cases can result either in the fusion of genes or in bringing genes close to enhancer or promoter elements, hence leading to their altered expression. Moreover, chromosomal translocations are used as diagnostic markers for cancer and its therapeutics. In the first part of this review, we summarize the well-studied chromosomal translocations in cancer. Although the mechanism of formation of most of these translocations is still unclear, in the second part we discuss the recent advances in this area of research.

Contents

* Corresponding author. Tel.: +80 2293 2674; fax: +80 2360 0814.
E-mail address: sathees@biochem.iisc.ernet.in (S.C. Raghavan).

0304-419X/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbcan.2008.07.005

1. Introduction

The role of genetics in cancer has been a matter of debate over time. Theodor Boveri first conceptualized that malignancy may result due to chromosomal disturbances, essential for normal cell function [1,2]. However, it was in 1960 that Nowell and Hungerford discovered the association of Philadelphia chromosome with chronic myeloid leukemia (CML). This was later shown to originate due to translocation between chromosomes 9 and 22 [3,4]. Around the same time another chromosomal translocation was identified involving reciprocal rearrangement of chromosomes 8 and 21 in acute myelogenous leukemia (AML) patients [5]. Since then the field of cancer cytogenetics witnessed a lot of new developments and many other malignancies, especially haematologic, were found to be associated with chromosomal aberrations [6].

Chromosomal translocation is a term used to describe the chromosomal rearrangements, involving interchange of parts between two non-homologous chromosomes. The translocations are generally classified as reciprocal and non-reciprocal translocations. Reciprocal translocation occurs when segments between two chromosomes are exchanged. This can occur between any two chromosomes and at various sites along the length of the chromosome. Non-reciprocal translocation (also known as *Robertsonian*) occurs when two acrocentric chromosomes fuse near the centromeric region leading to the loss of short arms and also reduction in the chromosomal number [7].

Translocations can broadly have two consequences. It can lead to the juxtaposition of the coding region of a gene near the transcriptionally active promoter/enhancer region of another gene, hence leading to over-expression of the former gene (Fig. 1). Examples of such events are the IgH-*BCL2* (Fig. 1a) and IgH-*MYC* (Fig. 1b) translocations where *BCL2* and *MYC* are the target genes whose expression levels increase due to their repositioning near the immunoglobulin heavy chain genes which are actively transcribed in B cells [8-10]. Other examples include rearrangements of the *BCL6* gene with the promoter elements of multiple genes, a characteristic feature of diffuse large B cell lymphoma (Fig. 1c) [11] and *TMPRSS2-ETS* translocations, which have been recently identified in prostate cancers (Fig. 1d) [12]. Translocations can also result in the formation of a

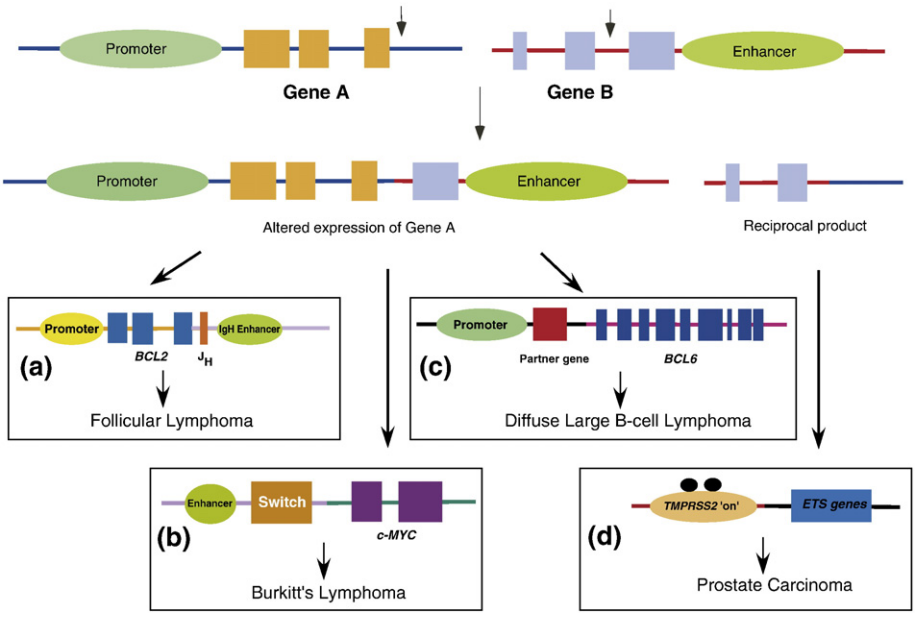

Fig. 1. Chromosomal translocations resulting in juxtaposition of promoter/enhancer elements to oncogenes. In some lymphoma and leukemia, translocations result in juxtaposition of the coding region of a gene (gene A) to enhancer elements of another gene (gene B). This leads to enhanced expression of the gene A under the influence of either the enhancer or alternative promoters. (a) Follicular lymphoma patients harbors the most well-studied translocation, the t(14;18), wherein the *BCL2* gene on chromosome 18, comes under the regulation of the IgH enhancer on chromosome 14. This leads to the over-expression of the BCL2 protein, which confers anti-apoptotic properties to the cell. The breaks on the *BCL2* gene are focused to a 150 bp region known as the MBR and on chromosome 14 breaks occur at any of the six J_H segments in the immunoglobulin heavy chain loci. (b) Burkitt's lymphoma is characterized by the presence of the t(8;14) translocation between the *c-MYC* gene on chromosome 8 and the IgH loci on chromosome 14. However, unlike the t(14;18) this translocation occurs at the switch regions of the IgH constant chain gene segments, thus bringing *c-MYC* near the IgH enhancer. This process is presumed to occur during the class switch recombination of Ig genes. (c) Diffuse large B cell lymphoma is the most common non-Hodgkin's lymphoma around the world and comprises of various translocations involving the *BCL6* gene on chromosome 3. The partner chromosomes in these translocations could be different and it results in the deregulation of the BCL6 protein, important for B cell development. In these translocations, usually *BCL6* comes under the influence of its partner genes' promoter elements resulting in its over-expression. (d) Prostate cancer is one of the most common epithelial carcinomas and recently it has been shown to harbor certain chromosomal translocations. One of the most common aberrations seen in this carcinoma is the translocation of *TMPRSS2* gene on chromosome 21 with the *ETS* family of genes. The *ETS* genes code for nuclear transcription factors which have been implicated in the regulation of cellular growth and differentiation and play a role in several malignancies. The *TMPRSS2* gene is prostate specific and androgen responsive. Therefore, upregulation of the *ETS* genes occurs due to the regulatory elements on this gene in response to androgens. The lines in bold represent the double-stranded DNA and the boxes represent the exons of the genes.