Available online at www.sciencedirect.com
ScienceDirect
Pathologie Biologie 55 (2007) 73–83
PATHOLOGIE BIOLOGIE
http://france.elsevier.com/direct/PATBIO/

# The *BCL6* proto-oncogene: a leading role during germinal center development and lymphomagenesis

# Le proto-ongène BCL6 : une protéine clé dans le développement des centres germinatifs et l'oncogénèse des lymphomes

Fabrice Jardin [a,b,*], Philippe Ruminy [b], Christian Bastard [b], Hervé Tilly [a,b]

[a] *Département d'hématologie clinique, centre Henri-Becquerel, Rouen, France*
[b] *Groupe d'étude des proliférations lymphoïdes et laboratoire de génétique oncologique, centre Henri-Becquerel, Rouen, France*

Received 21 March 2006; accepted 4 April 2006
Available online 03 July 2006

**Abstract**

The *BCL6* proto-oncogene encodes a nuclear transcriptional repressor, with pivotal roles in germinal center (GC) formation and regulation of lymphocyte function, differentiation, and survival. BCL6 suppresses p53 in GCB-cells and its constitutive expression can protect B-cell lines from apoptosis induced by DNA damage. BCL6-mediated expression may allow GCB-cells to sustain the low levels of physiological DNA breaks related to somatic mutation (SM) and immunoglobulin class switch recombination which physiologically occur in GCB-cells. Three types of genetic events occur in the *BCL6* locus and involve invariably the 5' non-coding region and include translocations, deletions and SM actively targeted to the 5' untranslated region. These acquired mutations occur independently of translocations but may be involved in the deregulation of the gene and/or translocation mechanisms. The favorable prognostic value of high levels of *BCL6* gene expression in NHL seems well-established. By contrast, the relevance of SM or translocation of the gene remains unclear. However, it is likely that non-Hodgkin's lymphomas (NHL) harboring the most frequent translocation involving *BCL6*, i.e. t(3;14), are characterized by a common cell of origin and similar oncogenic mechanisms. Several experiments and mouse models mimicking *BCL6* translocation occurring in human lymphoma have demonstrated the oncogenic role of BCL6 and constitute a rational to consider BCL6 as a new therapeutic target in NHL. BCL6 blockade can be achieved by different strategies which include siRNA, interference by specific peptides or regulation of BCL6 acetylation by pharmacological agents such as SAHA or niacinamide and would be applicable to most type of B-cell NHL.


**Résumé**

Le proto-oncogène *BCL6* code pour un répresseur transcriptionnel qui joue un rôle crucial dans le développement normal et pathologique des centres germinatifs en régulant la différenciation, la survie et les fonctions lymphocytaires B. BCL6 réprime notamment p53 et protège ainsi le lymphocyte B de l'apoptose p53-dépendante induite par les cassures double-brins nécessaires lors des processus de maturation d'affinité ou de commutation de classe. Trois types de modifications génétiques peuvent être observés dans les lymphomes et impliquent constamment la région 5′ non codante du gène. Elles comprennent les translocations, les délétions et les mutations somatiques (MS). Ces MS surviennent indépendamment des translocations mais pourraient être impliquées dans la dérégulation du gène ou dans les mécanismes moléculaires qui conduisent aux translocations. Si l'impact pronostique favorable de l'expression de *BCL6* dans les lymphomes paraît bien établi, l'impact clinique des MS ou des réarrangements du gène n'est, en revanche, pas établi. Toutefois la translocation t(3;14)(q27;q32), la translocation impliquant *BCL6* la plus fréquente, s'associe à un phénotype tumoral particulier et à des voies oncogéniques distinctes de celles associées à la t(14;18). Le rôle oncogé-

*Abbreviations:* ABR, alternative breakpoint cluster region; AID, activation-induced deaminase; BCR, B-cell receptor; CSR, class switch recombination; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; G, germinal center; HCR, hyper cluster region; HDAC, histone deacetylase; MMC, major mutation cluster; MTC, major translocation cluster; NHL, non-Hodgkin's lymphoma; SM, somatic mutations; SNP, single nucleotide polymorphism; STAT, signal transduction and activators of transcription.

* Corresponding author. Tel.: +33 2 32 08 22 23; fax: +33 2 32 08 22 83.
*E-mail address:* fabrice.jardin@rouen.fnclcc.fr (F. Jardin).

0369-8114/$ - see front matter © 2006 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.patbio.2006.04.001

nique de *BCL6* a pu être récemment démontré dans des modèles expérimentaux, et permet d'envisager une thérapie ciblée sur BCL6. Le blocage de BCL6 peut être ainsi obtenu par des ARN d'interférence, par des peptides empêchant spécifiquement le recrutement de co-répresseurs, ou en régulant le niveau d'acétylation de la protéine à l'aide d'agents pharmacologiques tel que SAHA ou la niacinamide.


*Keywords:* BCL6; Germinal center; Somatic mutation; Lymphoma

*Mots clés :* BCL6 ; Centre germinatif ; Mutations somatiques ; Lymphome

## 1. Introduction

The *BCL6* gene, located on chromosome 3q27 and coding for a transcriptional repressor, was cloned in 1993 [1–3]. Just over 10 years later, knowledge concerning this gene and its product has improved considerably. Identification of factors acting with the BCL6 protein as well as delineation of several target genes have allowed a determination of its biological function [4,5]. Notably, the impact of somatic mutations (SM) and other genomic events in deregulating *BCL6* gene function have emerged, which appear to shift B-cells towards the lymphomagenic pathway. Identification of factors repressing *BCL6* [6,7] or engineering of mouse models mimicking human non-Hodgkin lymphomas (NHL) with *BCL6* translocation [8] have open a therapeutic area, allowing to consider the proto-oncogene *BCL6* and its product as a novel pharmacological target [9,10].

## 2. *BCL6*: gene and protein

The *BCL6* gene is located at the telomeric extremity of chromosome 3 and spans 26 kb [2,11], with its organization shown in Fig. 1. The gene contains 10 exons and at least two types of mRNA are generated by alternative splicing, which include or exclude exon 1B [12]. The ATG signal for initiation of protein synthesis is localized within exon 3. The first *BCL6* intron is a highly conserved region and, together with the first non-coding exon, contains proposed regulatory elements at its 5′ extremity [13–15]. Notably, this intronic region also displays frequent genetic alterations in lymphomas (Fig. 1).

The BCL6 protein is a 706 amino acid transcription repressor composed of an amino-terminal BTB domain (bric-a-brac, tramtrack, broad complex), also called Pox virus zinc (POZ finger) domain, and six zinc finger (ZF) domains at the carboxy-terminus [16]. These domains regulate transcription of target genes via distinct interactions. The homodimeric and heterodimeric BTB/POZ domain, displays a conserved protein–protein interaction motif, and is required for the repressive activity of the protein (Fig. 2). This domain interacts directly with the silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) corepressor (or its relative N-CoR), which in turn associates with both mSIN3A (a mammalian ortholog of the yeast SIN3 corepressor) and histone deacetylases (HDACs) to constitute a large repressing complex [16–18]. The interactions between the BCL6 BTB domain via its lateral groove with SMRT, N-CoR and additional corepressors such as BcoR (BCL6 interacting corepressor) are mutually exclusive and most likely compete for binding at this site [19]. In addition, the BTB domain interacts with several other proteins which are members of the BTB/POZ-zinc finger family (BAZF, LRF, PLZF) [20–22]. A second region located in the middle of the molecule contains an additional autonomous *trans* repression domain, which is also responsible for the interaction with mSIN3A [18]. Several additional protein partners, detected by tandem mass spectrometry, remain to be characterized [23].

The BCL6 ZF bind DNA in a sequence specific manner, leading to the transcription repression of target genes. The

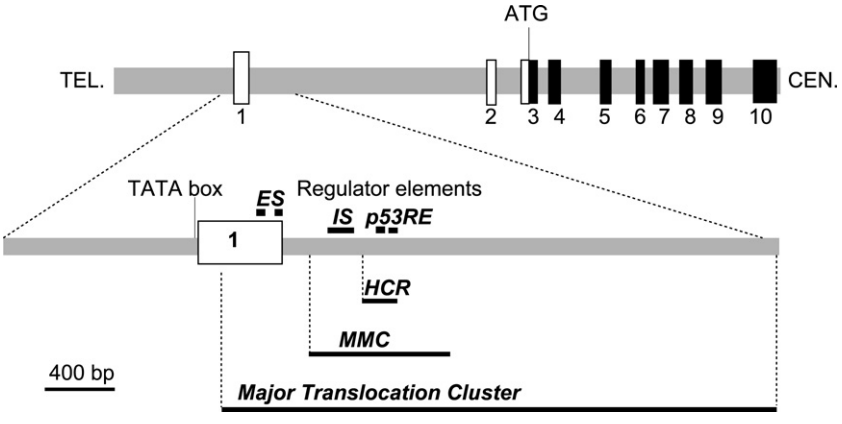


Fig. 1. Schematic representation of the human *BCL6* gene.
Locations of the main genetic alterations observed in lymphomas are shown. SM cluster downstream of the first non-coding exon in a ~ 800 bp region (MMC). Breakpoints cluster in a 3.3 kb region (MTC). A ~120 bp breakpoint hypercluster region (HCR), located within the MMC displays a high mutational rate. This region includes internal deletion overlap. Regulatory elements of the 5′ non-coding region with silencer activity (ES: exon sequence, IS: intron sequence) and p53-response element (p53RE) are indicated. These elements can be involved by mutations, deletions or translocations. Coding and non-coding exons are indicated by filled and empty boxes, respectively.