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Review

Follicular lymphoma (FL): Immunological tolerance theory in FL

Ricardo García-Muñoz [a,*], Carlos Panizo [b]

[a] Hematology Department, Hospital San Pedro, Logroño, La Rioja, Spain
[b] Hematology Department, Clínica Universidad de Navarra, Pamplona, Spain

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ABSTRACT

The ultimate cause of follicular lymphoma (FL) remains unknown. Remarkably, almost nothing is known about immunological tolerance mechanisms that might contribute to FL development. Immunological tolerance mechanisms, like other stimuli, also induce persistent changes of B cell receptors that induce genetic instability and molecular aberrations promoting the development of a neoplasm.

Using the same method as Burnet, we provide a new perspective taking advantage of the comparison of a normal linear B cell differentiation process and FL development within the framework of clonal selection theory. We propose that FL is a malignancy of cells that acquire both translocation t(14;18) and self-BCR, inducing them to proliferate and mature, resistant to negative selection. Additional genetic damage induced by non-apoptotic tolerance mechanisms, such as receptor editing, may transform a self-reactive B cell with t(14;18) into an FL. The result of tolerogenic mechanisms and genetic aberrations is the survival of FL B cell clones with similar markers and homogenous gene expression signatures despite the different stages of maturation at which the molecular damage occurs. To antagonize further growth advantage due to self-antigen recognition and chronic activation of tolerance mechanisms in the apoptosis-resistant background of FL B cells, inhibitors of BCR signaling may be promising therapeutic options.

Contents

* Corresponding author at: Hematology Service, Hospital San Pedro, c/Piqueras 98, Logroño, La Rioja 26006, Spain.
E-mail address: rgmunoz@riojasalud.es (R. García-Muñoz).

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1. Introduction

Burnet's clonal selection theory, immunological tolerance and the idea of self and non-self discrimination set the scene for modern cellular immunology. In 1960, Frank M. Burnet, during his Nobel lecture, presented the theoretical implications of immunological tolerance and the self-recognition hypothesis, and hoped that his thoughts would guide scientists towards novel discoveries in immunology. The theory formulated by Burnet provides a framework for interpreting the novel findings in follicular lymphoma (FL) biology and introduces the idea of immunological tolerance as a novel mechanism to promote lymphoid malignancies.

A landmark contribution is the "clonal" point of view. It recognizes that expendable lymphocytes can be regarded as belonging to clones stemming from somatic mutation, or conceivably, other inheritable changes. Each such clone will have some individual characteristic and in a special sense will be subject to an evolutionary process of selective survival within the internal environment of the body.

In 1960, Burnet and Medawar were co-recipients of the Nobel Prize for the discovery of acquired immunological tolerance.

Burnet's reflections about tolerance state that:

a) A stem cell, on differentiation, becomes a lymphocyte carrying a specific pattern of B cell receptor (BCR).
b) If an immune pattern (B cell receptor) is generated by a random process, a mechanism must exist by which any "self-reactive" cells that may emerge can be eliminated or functionally inhibited.
c) More than one mechanism may be needed to establish and maintain this intrinsic immunological tolerance toward self-components.

The ultimate cause of FL remains unknown. FL is a tumor of germinal center B cells in which centrocytes fail to undergo apoptosis because they have a chromosomal rearrangement t(14;18), that prevents the normal BCL2 gene from switching off [1,2]. It has been postulated that a second genetic "hit", or even simple exposure to antigen in a cell with a BCL2 translocation, could result in the development of lymphoma because once it begins proliferating in response to antigen, it does not respond to the usual stimuli for apoptosis [2]. Remarkably, self-antigen recognition by FL B cell receptors (BCRs) has been described in 26% of cases [3]. The molecular anatomy of the t(14;18) genetic alteration suggests that it occurs prior to antigen exposure, in an immature B cell that expresses nuclear TdT (nuclear enzyme terminal deoxynucleotidyl transferase) in the bone marrow (BM) and results from an error in primary V[variable], D[diversity] and J [joining] gene recombination induced by the RAG (recombinase activating genes) complex [4]. FL cells typically express surface IgM and IgD, and have somatic hypermutations in the variable region of their immunoglobulin genes [1,2,4]. Interestingly, if 26% of FL BCR recognize self-antigens [3] but retain the capacity to differentiate from B cell precursors to mutated FL cells, this implies that some tolerance mechanisms fail and FL evades immunological tolerance.

Immunological tolerance mechanisms, in a way similar to other stimuli, also induce the persistence of BCR changes that induce genetic instability and molecular aberrations that promote the development of a neoplasm [5–8].

In the present article, we first review tolerance mechanisms for avoiding self-reactivity in FL cells. We then propose a hypothesis in which tolerance mechanisms play a key role in FL development.

The objective of this review is to present a hypothesis about the generation of FL in the light of the clonal selection approach.

Hypothesis: During B cell development translocation t(14;18) protect self-reactive B cells increasing resistance to elimination. Self-BCR-auto-antigen interaction induce chronic activation of tolerance mechanisms specially receptor editing. Unfortunately sometimes this mechanism increases genomic instability and promotes additional genetic damage that induces FL progression or transformation to aggressive B cell neoplasm.

2. The Burnet's rules of tolerance and autoimmunity [9]

The basic hypothesis of the origin of autoimmune disease depends on the emergence of a clone or a small number of clones of lymphocytes capable of damaging interaction with normal cells of organ or tissue involved. Each clone is initiated from a cell which has developed an immune receptor adequately reactive with an accessible self-antigen as a result of V/D/J and K/L gene recombination in bone marrow or during somatic mutations in germinal centers. Crucially, this newly self-reactive cell ("forbidden clone") is anomalously resistant to inactivation by central and peripheral tolerance check points [9].

3. FL B lymphocytes qualify as a malignant forbidden clone

FL can be conceived as a logical and lineal development of the forbidden clone concept formed within the framework of clonal selection theory. In humans, B cells develop from progenitors within the BM. The stages of B cell ontogeny from pro-B to pre-B to early B to mature B cell are marked by the expression of the BCR for antigen on the cell surface at the early stage of B cell development. The fact that immature B cells are forced to engage with the environment as a test of self-reactivity (negative selection) may induce some lymphocytes to correct their self reactivity and edit their heavy or light chains (receptor editing). Any normal lymphocyte capable of reacting with them will be eliminated or self-reactivity corrected.

Immunoglobulin rearrangement is hierarchical. In pro-B cells, DH-JH joining precedes VH-DJH rearrangement; followed by VL-JL joining in the late-stage pre-B cells. Clones with an immune receptor sufficiently reactive with an available self-antigen can be the result from a V/D/J gene recombination in BM or during somatic mutations in germinal centers. If a newly self-reactive cell ("forbidden clone") is anomalously resistant to inactivation by central and peripheral tolerance checkpoints, it can produce an autoimmune disease or a lymphoid malignancy.

FL B cells qualify as a malignant forbidden clone because they carry the translocation t(14;18), which induces increased resistance to apoptosis, and also express self-reactive BCRs, which induce chronic activation of tolerance mechanisms Fig. 1.

If we assume that the acquisition of (self-reactive) BCR is simultaneous with the acquisition of genetic or molecular disturbances such as t(14;18) in FL B cells, several important questions need to be answered.

a) Why can these B cells not be eliminated or inhibited by tolerance mechanisms?
b) Why can these B cells not produce their BCR as an autoantibody and induce an autoimmune disease?
c) What is the driving force to induce genetic and molecular abnormalities in these self-reactive B cells?

4. The essence of the FL forbidden clone concept

On differentiation, a FL stem cell becomes a B cell carrying a specific BCR (sometimes self-reactive BCR) that acquire the translocation t(14;18)(q32;q21) involving the anti-apoptotic gene