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Special Review

B-cell neoplasia in a developmental framework

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Like every other cell that has maintained its ability to divide, cells of the B-lymphocyte lineage may turn into malignant tumors. B-cell neoplasia has a number of special features that set it apart from tumor development in other tissues, however. They can be briefly summarized as follows:

The life cycle

The life cycle of B-lymphocytes includes reversible shifts between proliferating and resting stages. Development from pro-B through pre-B to mature B-cells involves a series of cell divisions and sequential rearrangements of the immunoglobulin genes. The mature, virgin B-cell switches to a resting phenotype and expresses surface immunoglobulin. Binding of a cognate antigen and a variety of helper factors can activate it to transform into an immunoblast and to divide. Virgin B-cells that are not activated within a limited period of time die by apoptosis. Under the influence of a continuing antigenic stimulus, the activated cells expand clonally. After the disappearance of the antigen, they turn into resting, long-lived memory cells.

B-cells can also attain the resting G_0 stage by differentiation into plasma cells (PCs). PCs are often referred to as terminally differentiated end cells, but there is no evidence that they ever lose the ability to divide. The existence of highly differentiated but nevertheless rapidly growing plasmacytomas actually speaks against this notion.

Constitutive activation of the proliferation-stimulating c-myc gene

B-cells become prone to neoplasia when they are prevented from leaving the cycling compartment according to their program. Constitutive activation of c-myc, a proliferation-stimulating gene, at any of the three points where the B-cells are bound to stop in G_0 can play an essential, rate limiting role in the genesis of B-cell neoplasia. High grade, human lymphomas, largely Burkitt lymphomas (BLs), believed to originate from virgin or memory B-cells are triggered by the juxtaposition of c-myc to constitutively active immunoglobulin sequences by chromosomal translocation (for review see Klein, 1989b). In the mouse and the rat, the corresponding Ig/myc translocation-carrying tumors originate from plasma cells (for review see Klein and Klein, 1985). This looks like a species-related difference, but it is more likely to reflect differences in genetic susceptibility, stimulatory cofactors and the likelihood of progression promoting secondary changes.

Prevention of apoptotic death

Prevention of apoptotic death by the constitutive activation of bcl-2 can generate low grade lymphomas. Most follicular lymphomas carry a 14;18 translocation that juxtaposes bcl-2 and IgH (Gauwerky and Croce, 1993). Normally, B-cells that do not encounter their cognate antigen within a limited period of time eliminate themselves by programmed cell death. Constitutively activated bcl-2 protects them from apoptosis. The lymph node microenvironment that normally stimulates the proliferation of legitimately activated B-cells may trigger the neoplastic development of cells with an illegitimate bcl-2/IgH translocation. A similar situation may prevail in B-cell-derived chronic lymphocytic leukemia (CLL) where bcl-2 is highly expressed, although only about 10% of the CLLs carry Ig/bcl-2 translocation (Schena *et al.,* 1993). The mechanism of bcl-2 activation in the rest is unknown. If both follicular lymphoma and CLL are originally triggered by illegitimate bcl-2 activation, their different histopathology may reflect differences in the homing patterns of the cells from which they have originated.

IgH enhancer-bcl-2 transgenic mice show a picture consistent with this interpretation (McDonnell *et al.,* 1989; Korsmeyer *et al.,* 1993). They show a high level of lymphocytosis and their B-lymphocytes survive for several weeks *in vitro* in contrast to the lympocytes of ordinary mice that die after a few days.

Rearrangement of the immunoglobulin genes

Rearrangement of the immunoglobulin genes involves a special risk for the translocations mentioned in the two preceding sections and thereby for B-cell neoplasia. Rearrangement of the T-cell receptor (TCR) genes provides a similar risk factor for T-cell leukemia (for review see Rabbits, 1994). The precise mechanism for the illegitimate translocations is not known, but the location of the breakpoints within the Ig-locus carrying chromosomes suggests that the recombinases involved in the physiological rearrangement of the immunoglobulin genes may participate in the process. Therefore, the translocations may be regarded as accidents of the physiological rearrangement. Surprisingly, the 8;14 (IgH/myc) translocation breakpoints were found to differ between the high endemic BLs, where J or, more rarely, V sequences were involved, and the sporadic BLs where a switch region was frequently affected (Magrath, 1990). There is a corresponding difference in the c-myc breakpoints. In high endemic BLs, the breakpoint is usually 5' of the intact gene, whereas in sporadic BLs it is in the first exon or the first intron, leading to the "decapitation" of the long leader sequence in exon 1, while the coding second and third exons are preserved. These differences were taken to suggest that the sporadic and the high endemic forms of BL arise from B-cells at different stages of differentiation. This probably reflects the involvement of different cofactors in the two forms.

Indirect evidence indicates that the translocations do not interfere with the progress of physiological immunoglobulin rearrangement and other aspects of the B-cell differentiation program, not even in cases where they occur at a very early stage of B-cell development. Recently, we have found an exceptional

mouse plasmacytoma that carries an N-myc/kappa translocation and expresses only N- but not c-myc (Axelson *et al.,* 1994). N-myc is only open for transcription in early pro- and pre-B-cells. It is likely that the chromatin of the kappa gene becomes accessible for transcription and rearrangement around the same time. The *functional* rearrangement of the heavy and light chain genes takes place at a later stage. The occurrence of the kappa/N-myc translocation in a plasmacytoma suggests that this translocation has occurred at the pro- or pre-B-cell stage, but failed to affect the continued rearrangement of the immunoglobulin genes and the differentiation of the cells into mature PCs.

Another indication that points in the same direction came from our study of Epstein-Barr virus (EBV)-transformed human pro-B-cells in which no immunoglobulin rearrangement has taken place. Seven parallel sublines of a fetal liver derived pro-B line, FLEB14, were carried *in vitro* for periods between 19 and 36 months (Altiok *et al.,* 1989). In 6 of the lines, 14q+ markers appeared during culture. They had been generated by reciprocal translocations between chromosome 14, that broke at the switch-mu (Smu) region, just as in the BL- associated typical (IgH/myc) translocations, and another autosome that was different in each line. The translocation carrying subclone overgrew the original diploid cells. Similar translocations have not been observed in ordinary EBV-carrying lymphoblastoid cell lines (LCLs), generated by the proliferation of mature immunoblasts.

In pre-B cells, the chromatin region of the immunoglobulin loci opens up for transcription well in advance of the rearrangement of the Ig-genes, as reflected by the production of sterile mu-transcripts. This was also found in the FLEB14 sublines. We concluded that the early pro-B cells may be particularly vulnerable to illegitimate recombination. The different translocations in the FLEB14 sublines may have provided their host cell with a selective advantage, due to the juxtaposition of transcriptionally accessible Ig-sequences and unknown genes from the different partner chromosomes that may facilitate growth under culture conditions. No IgH/myc translocations were observed, but they were not expected either. There is no reason why the constitutive activation of myc should convey any selective advantage on the FLEB cells. All EBV-immortalized lines express c-myc, like other proliferating cells. Constitutive activation of myc by juxtaposition to an Ig-locus would make no difference *in vitro*. The situation is quite different *in vivo*. Following the rearrangement of the Ig-loci, mature B-cells are programmed to turn into resting cells. They downregulate myc, but continue to express their immunoglobulin genes, destined to serve as receptors for the cognate antigen. Another phenotypic shift from proliferating to resting B cells occurs after the antigen-driven expansion of the appropriate antibody producing clone, upon the waning of the antigenic stimulus. Accidental juxtaposition of myc to an Ig locus prior to this shift prevents the cell from leaving the cycling compartment. Instead, it acquires an absolute selective advantage that opens the way for further neoplastic development.

Other evidence to support the notion that Ig/myc translocations can occur in early pro- or pre-B-cells has been obtained by Bhatia *et al.* (1992). They have shown that the IgH-V genes of the non-translocated chromosome 14 are in the germ line configuration in a substantial fraction of the IgH/myc translocation-carrying BL-lines , indicating that the translocation has taken place at the pro-B-cell stage.

Additional genetic changes during lymphoma development

The Ig/myc and the Ig/bcl-2 translocations discussed in the earlier sections can be regarded as rate-limiting events of decisive importance for the development of the Ig/myc carrying BLs and rodent (mouse and rat) plasmacytomas, as well as for the Ig/bcl-2 carrying human follicular lymphomas, respectively, because they are found in virtually all tumors of the same type. There are several lines of evidence to indicate, however, that they are necessary but not sufficient requirements, and that additional changes are required. Facsimile experiments with Ig-enhancer (Emu)-myc transgenic mice were particularly informative (Adams *et al.,* 1985). Such mice have no resting B-cells, only blasts. More than 90% develop B- and pre-B cell lymphomas, proving that the constitutively activated myc gene is tumorigenic for lymphocytes of the B-lineage, as expected. The lymphomas are monoclonal, however, indicating the need for additional changes. An even more stringent argument can be made for the bcl-2 transgenics. These mice do not develop any lymphomas by themselves (McDonnell *et al.,* 1989) but bcl-2 x myc double transgenics show a greatly accelerated lymphoma development, compared to the myc-transgenics (Strasser *et al.,* 1990). This is understandable, in view of the fact that constitutively activated myc tends to drive the cells into apoptosis, whereas constitutive expression of bcl-2 protects against apoptosis.

In the myc transgenics, lymphoma development can be accelerated in other ways as well: by infection with the v-abl-carrying Abelson virus or by crossing the mice with Emu-bcl-1 (cyclin D1) or Emu-ras transgenic mice (Lovec *et al.,* 1994).

The need for secondary changes is also confirmed by the recent successful detection of Ig/myc translocations by PCR in the preneoplastic intraperitoneal granulomas of pristane oil-treated mice by PCR (Janz *et al.,* 1993). The frequency of the translocations greatly exceeds the plasmacytoma frequency and is also found in pristane-treated mice that do not develop PCs.

Several types of secondary changes have been identified in the BL system. Approximately 60% of established BL lines and 30% of examined biopsies were found to carry mutated p53 (Farrell *et al.,* 1991; Gaidano *et al.,* 1991; Wiman *et al.,* 1991). It is easy to explain why p53 mutations are selectively favoured. We have found that expression of wild type p53 in a mutant p53-carrying BL line leads to massive apoptotic death (Ramqvist *et al.,* 1993). This was attributed to contradictory signaling. The constitutively activated myc gene supplies a proliferation-stimulating signal, whereas wild type p53 induces growth arrest. The apoptotic response could be prevented by raising the bcl-2 level by direct transfection (Wang *et al.,* 1993), or, more indirectly, by expressing the bcl-2-inducing EBV-encoded membrane protein, LMP1 (Okan *et al.,* 1995).

Wild type p53 can be stabilized at a high steady state level by a variety of treatments. DNA damage is a powerful inducer (Lane, 1992). Chromosome breakage and other cytogenetic aberrations may occur continuously in a growing tumor. This, in combination with the proliferation-driving effect of the constitu-

tively activated myc gene may bring the Ig/myc translocation carrying BL cell continuously to the brink of apoptosis. Mutant p53 does not bind to DNA and fails to induce growth arrest or apoptosis. The selective value of p53 mutations may be sought in their protective effect against apoptosis in myc-driven cells (Evan *et al.*, 1992). BL lines that carry wild type p53 may have circumvented the apoptotic reaction by p53-independent mechanisms. Their study may provide a rich source for the identification of such mechanisms. It is also of interest to note that EBV-LCLs of non-neoplastic origin do not carry p53 mutations, as a rule, not even after many years of prolonged *in vitro* propagation. This is understandable because EBV has evolved its own mechanisms to protect its host cells from apoptosis.

Other secondary changes have been particularly studied in AIDS-associated non-Hodgkins lymphomas (NHLs) (Gaidano and Dalla Favera, 1995). They belong to two categories. EBV-associated immunoblastomas resemble the lymphoproliferative diseases in transplant recipients and in congenital T-cell immunodeficiencies. The other group consists of monoclonal lymphomas that carry Ig/myc translocations. In contrast to the EBV-carrying high endemic BLs that belong to a single, well defined morphological group, the AIDS-associated, myc-translocation-carrying lymphomas belong to a broad variety of morphological types (Delacluse *et al.*, 1993). Conceivably, immune surveillance may prevent the phenotypic diversification of the high endemic BLs that arise in immunocompetent persons. Most of the latter diversify on *in vitro* culture, as discussed in another section below, but the drift to a more lymphoblastoid cell type is accompanied by the upregulation of the immunogenic EBNAs (EBV-encoded nuclear antigen family) and LMP proteins. Such cells can only grow in immunodefective hosts.

Additional changes in AIDS-associated NHL included p53 mutations (60%), ras mutations (15%), deletion of the terminal part of the long arm of chromosome 6 (15%) and mutation of bcl-6 (20%) (Gaidano and Dalla Favera, 1995). The occurrence of ras mutations in the AIDS-related lymphomas is puzzling, since lymphomas of similar histology that arise in immunocompetent hosts do not carry ras mutations.

p53 mutations are not found in the AIDS-related immunoblastomas, only in the BL-like, myc-translocation carrying tumors. This is consistent with the argument advanced above. p53 mutations are equally frequent in the EBV-negative and EBV-carrying BLs. This is also in line with what has been said above, with the added consideration that EBV-carrying BLs do not express LMP1 and other EBV-encoded growth transformation-associated proteins that are known to protect cells from apoptosis.

Bcl-6 is a novel protooncogene candidate. It belongs to the family of zinc domain containing transcription factors and maps to 3q27, a site of frequent chromosomal breaks in B-cell lymphomas. In certain subgroups of AIDS-associated lymphomas, particularly in diffuse, large cell lymphoma (DLCL), bcl-6 is frequently truncated at the 5' end. Rearrangements of bcl-6 are consistently absent in AIDS-associated small non-cleaved cell lymphomas (SNCCL). In spite of the fact that bcl-6 rearrangements and myc translocations are present in a similar fraction of AIDS-NHL (20%), they are never found in the same tumor, suggesting that these two genetic lesions may represent mutually exclusive molecular pathways in the development of AIDS-associated NHL.

Is there a relationship between the known cellular function of the activated oncogene and the grade of malignancy in B-cell lymphomas?

A relationship is most clearly evident by comparing Ig/myc and Ig/bcl-2-carrying lymphomas (Klein, 1991). Myc activation is associated with high grade lymphomas, bcl-2 with low grade lymphomas, as already detailed above. Occasionally, an Ig/bcl-2 translocation carrying tumor may acquire a second, Ig/myc translocation and progress to high grade malignancy. The development of 90-95% pre-B and B-cell lymphomas in myc transgenic but not in bcl-2 transgenic mice is in line with the corresponding clinical picture (Adams *et al.*, 1985). The highly synergistic tumorigenic effect of the two oncogenes in double transgenic mice (Strasser *et al.*, 1990) is, moreover, consistent with the apoptotic risk of myc-activated cells and the protective effect of bcl-2.

It is less easy to rationalize the fact that the 11;14 (bcl-1/IgH) translocation-carrying lymphomas are low grade malignancies (Gauwerky and Croce, 1993). The bcl-1 gene encodes cyclin D1, a protein that promotes cell division. Emu-bcl-1 transgenic mice have no phenotype, however, although lymphoma development is greatly accelerated when they are crossed with c-myc transgenics (Lovec *et al.*, 1994). This emphasizes the important and possibly multiple role of activated myc and throws doubt on the postulated role of cyclin D1 as merely a downstream effector of myc.

The role of EBV

EBV is regularly associated with two B-cell-derived tumors as already mentioned: immunoblastomas that arise in congenitally or iatrogenically T-cell- suppressed persons and BLs that arise in the tropical rain forest regions of Africa. The former are regularly associated with EBV. African BLs carry EBV in 96% of the cases, sporadic BLs in 20% and AIDS-associated lymphomas in 30% (Magrath, 1990).

What is the role of the virus in lymphoma development?

This question can be most easily discussed for the immunoblastomas. Similarly to EBV-LCLs *in vitro*, they express 9 proteins, the 6 nuclear antigens (EBNA1-6) and the 3 membrane antigens (LMP1, 2A and 2B). Eight of them (all except EBNA1) can serve as targets for the cytotoxic T-lymphocyte (CTL)-mediated rejection response. Persons with an intact T-cell system eliminate them readily. Current evidence suggests that the latently persisting virus of the normal seropositives is carried by small, resting B-lymphocytes that express EBNA1 only (Fu Chen *et al.*, 1995). EBNA1 was not found to elicit CTL-responses, in spite of numerous attempts (Levitskaya *et al.*, 1995). Recent evidence indicates that this is due to a processing block, specifically induced by the long glycine-alanine repeat sequence of the EBNA1 molecule (Masucci and Ernberg, 1994).

When EBV-carrying resting lymphocytes transform into immunoblasts, they switch on the full program to produce all 9 proteins (for review see Klein, 1994). This elicits a vigorous CTL response, directed against peptides derived from one or several of the 8 immunogenic proteins. The choice depends on the HLA class I phenotype of the host. Individuals with a deficient T-cell

system may fail to mount an efficient response. Immunoblasts may then proliferate and the resulting lymphoproliferative disease (LPD) may progress from poly- to oligoclonal and finally monoclonal lesions. If allowed to proceed without interference, they kill the patient. They can be made to regress by releasing immunosuppression (in solid organ transplant recipients), or by the adoptive transfer of donor type T-lymphocytes (in bone marrow transplant recipients).

Immunoblastic proliferation is thus due, at least initially, to the breakdown of host surveillance, rather than to any cellular change.

It is not known if and to what extent EBV contributes to the pathogenesis of the EBV-carrying form of BL. The following considerations (Klein *et al.,* 1989a) are potentially relevant:

i. In African patients with a high EBV-load, the frequency of EBV-carrying B-cells is below the level of detectability by EBNA staining (approximately 0.1%). Most B-cells are EBV negative. The fact that 96% of the high endemic BLs nevertheless carry EBV implies that the chance of developing BL is much higher in an EBV-carrying, than in an EBV-negative B-cell. This is the same as to say that EBV contributes to the pathogenesis of the virus-carrying form of the lymphoma.

ii. BL cells express only EBNA1. This virally encoded protein is known to bind to the origin of latent viral replication and is required for the maintenance of the viral episomes, but has no known effect on the B-cell phenotype. EBNA1 transgenic mice develop B-cell lymphomas in a high frequency (Wilson and Levine, 1992), however, indicating that the protein may nevertheless play some important role in the tumorigenic process.

A similar argument can be formulated, *mutatis mutandis*, for the association of EBV with approximately half of all Hodgkins lymphomas (HL) (for review see Pallesen *et al.,* 1993). Similarly to EBV-carrying nasopharyngeal carcinomas (NPCs) and T-cell lymphomas, EBV-carrying HL cells express EBNA1 and the membrane antigens, but not EBNA2-6. The regularity of the association suggests that the virus may play some etiological role in these cases as well, but the existence of EBV-negative HLs with similar histological features and the unknown nature of the HL precursor cell make the association more doubtful. A more compelling argument can be made for NPC and certain forms of T-cell lymphoma, the lethal midline granuloma in particular, that show a virtually 100% association with EBV.

Summary

The development and differentiation of B-lymphocytes has a number of unusual features. One of them stems from the rearrangement of the immunoglobulin genes and the generation of antibody diversity. The ability of the cognate antigen to activate and to trigger the clonal expansion of B-cells that carry a complementary surface immunoglobulin receptor, is another. Rapid apoptotic death of the non-activated lymphocyte is a third. The reversible shift between resting and activated states and the maintained ability of the fully differentiated plasma cell to divide are some of the relevant consequences.

Tumor development can be directly related to the disruption of this life cycle at one point or another. EBV-induced activation of resting B-cells into immunoblasts endows the target cells with unlimited growth potential, as shown by their immortalization *in vitro*. This is normally counteracted by the immune surveillance of the host, shaped by the selective power of our coexistence with the virus over millions of years. Congenital, iatrogenic or virus (HIV)-induced immunodeficiency may permit the development of progressive lymphoproliferative disease. Interference with the normal apoptotic death program by the accidental juxtaposition of the bcl-2 gene to an immunoglobulin locus may cause low grade lymphoma. The corresponding juxtaposition of c-myc, a proliferation stimulating oncogene, can trigger the development of a high grade lymphoma, but probably only after additional mutations. Similar Ig/myc juxtaposition may occur in specific mesenteric or intraintestinal plasma cell populations or their precursors in mice and rats and lead to plasmacytoma development. All Ig/myc translocations act by preventing the carrier cell from leaving the cycling compartment.

Neoplasia can thus be seen as a disturbance of normal developmental programs. Depending on environmental and/or genetic predisposition, accidents of gene displacement and specific vulnerabilities of the preneoplastic cell, the phenotypic properties of the tumor and the degree of its malignancy can be placed in a comprehensible biological framework.

KEY WORDS: *B-lymphocytes, myc, EBV, Burkitt lymphoma, apoptosis*

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