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B-cell receptor signaling in the genesis and maintenance of B-cell lymphoma

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Lymphomas constitute a number of different diseases that have been subdivided into two broad categories, Hodgkin's and non-Hodgkin's lymphoma (NHL). Hodgkin's disease comprises a uniform set of malignancies primarily defined by the presence of Reed–Sternberg giant cells, whereas NHL is a heterogeneous set of clinical entities. The number of cases of NHL is almost tenfold that of Hodgkin's disease [1]. In addition, the number of newly diagnosed cases of NHL has increased by almost 80% in the last 25 years. This dramatic increase does not correlate with age, gender or infectious agents, and cannot be accounted for by the onset of HIV-associated B-cell lymphomas [2]. As a result, NHL are currently the fifth most common form of cancer in the USA, after breast, prostate, lung and colon cancer [101]. NHL is one of the few cancers whose incidence and mortality rates have risen in the past 35 years. Despite the increase in the incidence of NHL, the etiology of these lymphomas remains elusive, and current therapeutic approaches rely on traditional, nonspecific chemotherapeutic approaches.

The diagnosis of NHL encompasses different clinical entities. Approximately 85–90% of all NHL in the USA consist of B-cell lymphomas [3]. Among the B-cell NHLs, aggressive lymphomas account for 45–50% of new diagnoses. The two most common forms of aggressive NHL are diffuse large B-cell lymphoma and Burkitt's lymphoma. These two types of malignancies involve neoplastic B cells that have a surface phenotype that is consistent with that of mature, activated B cells. Specifically, they express B-cell antigen receptors (BCR) on their surface, which contain mutations consistent with the process of affinity maturation during a germinal center reaction [4]. These cells also express other molecules that are normally expressed by postgerminal B cells [5]. There are other B-cell NHLs that have a similar cellular composition. These include follicular lymphomas, mucosal-associated lymphoid tissue

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lymphomas and mantle-cell lymphomas [3]. All of these B-cell NHL share a B-cell surface phenotype, including BCR expression. The nature of additional mutations, possibly involving oncogenes and tumor suppressor genes, has been postulated to explain their biological differences [6]. The one characteristic they have in common, namely BCR expression and evidence of antigen-dependent activation, may suggest that the BCR and an antigen may have an important role in the genesis of these tumors.

Dameshek and Schwartz originally proposed that antigenic stimulus could contribute to the development of lymphomas nearly 50 years ago [7]. Throughout the years, a large amount of circumstantial evidence has implicated chronic inflammation in lymphomagenesis. There are prior hints that antigenic stimulus can play a role in lymphomagenesis. First, retroviral infection of mice elicits T-cell lymphomas only in those strains of mice that can mount an immune response to the virus [7,8]. Second, infection with *Helicobacter pylori* is an apparent cause of human lymphomas in mucosal-associated lymphoid tissue and gut-associated lymphoid tissue [9]. Treatment with antibiotics to eradicate infection elicits remission of these tumors, as if they might have been sustained by antigenic stimulus from the microbe [10,11]. Third, mice with graft versus host disease consequent to bone marrow transplantation frequently develop T-cell lymphomas; immunosuppression of the mice prevents the tumors [12]. Fourth, chronic antigenic stimulation by infection may contribute to the genesis of Burkitt's lymphoma [13, 14]. Fifth, the gene-expression profiles of diffuse large B-cell lymphomas resemble those of B cells that have mounted a response to antigen [15], and the tumor cells display high-affinity antigen receptors on their surface, as if they had been subjected to the selective pressure of an antigen [4,16–18]. Sixth, our own studies demonstrate a causal relationship between BCR-derived signals and elevated levels of *MYC* in the genesis of B-cell lymphomas in mice [19]. These findings prompt the hypothesis that an antigenic stimulus may cooperate with other tumorigenic influences in the genesis of lymphoma.

MYC oncogene

A number of genetic lesions have been implicated in the genesis of lymphoid tumors. One such genetic alteration involves the dysregulation of the proto-oncogene *MYC*. The *MYC* gene encodes a short-lived, transcriptionally active protein that is expressed in many tissues. *MYC* is highly regulated in lymphoid tissues [20]. This gene was originally identified as the cellular version of the viral oncogene, *v-myc*. The proto-oncogene *MYC* plays an important role in the control of cellular proliferation [21,22], size [23,24], differentiation [25] and apoptosis [20, 26]. The molecular mechanism by which *MYC* regulates those cellular processes remains unclear; however, it probably involves some form of transcriptional activity [21–26]. Overexpression of *MYC* has been implicated in diverse forms of human tumors. First, the gene can drive proliferation of diverse cells and engender cellular immortalization [27]. Extended proliferation is a hallmark of neoplastic cells; in addition, it exposes cells to an increased risk of mutation. Second, there is evidence that *MYC* may be directly mutagenic because of its ability to destabilize the genome [28,29]. This in turn could help propel tumor progression. Third, in some settings, *MYC* can protect cells from programmed cell death that might otherwise ensue genetic damage or other checkpoint triggers [30–32]. Our work adds a fourth to this list, albeit one that is specialized to lymphoid cells. By breaking tolerance, *MYC* may expose B and T cells to sustained stimulation by autoantigens, providing yet another force that can foster cellular proliferation and the genomic hazards that ensue. Lymphomas figure prominently among the tumors in which *MYC* has been incriminated [20]. This may reflect important roles played by *MYC* in the regulation of lymphoid-cell development, proliferation and survival [21,22,32–34].

Signaling by the B-cell antigen receptor

The BCR is a multicomponent complex consisting of antigen-recognition elements non-covalently associated with separate signaling components, similar to the T-cell receptor or the high-affinity receptor for IgE. The antigen-recognition element of the BCR is a membrane-bound antibody, composed of heavy- and light-chain immunoglobulins (Igs), which specifically bind antigen but cannot transduce signals themselves. Instead, antigen-dependent aggregation of the BCR induces tyrosine phosphorylation of the associated Igα and Igβ chains within immunoreceptor tyrosine-based activation motifs by Src family kinases. This tyrosine phosphorylation, in turn, activates numerous signaling pathways resulting in acute B-cell activation, followed by B-cell proliferation and survival, differentiation and antibody production [35]. In addition, BCR expression is required throughout the lifespan of a normal B cell. The correct assembly and expression of a pre-BCR, and then BCR, is required for progression through the many checkpoints of B-cell development [36]. Failure to express a surface B-cell receptor results in deletion, while expression of an autoreactive BCR can result in cell death, anergy or receptor editing [37]. Naive and resting mature B cells rely on constitutive, or tonic, BCR signals for their continued survival [38]. The nature of this signal has proven to be quite enigmatic, including its origin. It is still debated if the signal is genuinely constitutive, or is originated by a low level of receptor cross-linking by either an auto-antigen or weak interactions of the BCR heavy chains. As with normal B cells, the fate of malignant B cells appears to be tied to survival signals originating from the BCR.

Genetically modified mouse models of cancer as a tool to study the molecular basis of pathogenesis & as a preclinical model for experimental therapeutics

Spontaneous mouse models of disease offer several advantages over *in vivo* models that are based on the xenotransplantation of human tumor cells into immunocompromised animals. A valid mouse model of cancer should mimic the human disease, including the underlying genetics and important aspects of the pathogenesis. In this instance, spontaneous mouse models of cancer can be used to genetically dissect the contributions of genetic modifiers to disease progression and establish cause-and-effect relationships. Genetically modified, spontaneous mouse models of disease can be used as important platforms for testing drug candidates in preclinical models. All of these issues are significant in allowing for the early screening of many drug candidates and decreasing the amount of time to determine the nature of the experimental therapeutic compound that will likely fail in humans.

Lessons learned from studies in mouse models of B-cell lymphomas

The mouse models we have developed have proven valuable for the study of the mechanisms by which *MYC* regulates B-cell tolerance and homeostasis. Our results, obtained from these models, have enriched our view of how *MYC* may contribute to tumorigenesis in several ways. First, the ability of *MYC* to replace cytokine function in T and B cells may be a critical step in the development of cytokine-independent clones. This is a necessary prerogative for the genesis of lymphoid tumors [32]. Second, the ability of *MYC* to confer resistance to passive cell death may help overcome the cell-cycle checkpoints that are activated in response to genetic damage. Third, the ability of *MYC* to break tolerance could expose lymphoid cells to sustained proliferative stimulation by autoantigen, a circumstance that might well favor tumorigenesis. In support of this notion, we have shown that experimental autoimmunity facilitated by *MYC* can lead to a murine lymphoma closely resembling Burkitt lymphoma [19]. We suggest that the suppression of anergy by *MYC* may figure in the genesis of several forms of human lymphoma, including AIDS-associated NHLs. Furthermore, the actions of the constitutive and cognate-antigen-triggered signals derived from the BCR lead to the development of

phenotypically distinct B-cell malignancies, providing a novel system for the study of the biochemical basis of both types of signals.

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Bibliography

1. Staudt LM. Molecular diagnosis of the hematologic cancers. N Engl J Med 2003;348:1777–1785. [PubMed: 12724484]
2. Staudt LM, Wilson WH. Focus on lymphomas. Cancer Cell 2002;2:363–366. [PubMed: 12450791]
3. Harris NL, Jaffe ES, Stein H, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood 1994;84:1361–1392. [PubMed: 8068936]
4. Kuppers R, Rajewski K, Hansmann ML. Diffuse large cell lymphomas are derived from mature B cells carrying V region genes with a high load of somatic mutation and evidence of selection for antibody expression. Eur J Immunol 1997;27:1398–1405. [PubMed: 9209491]
5. Morse HC 3rd, Anver MR, Fredrickson TN, et al. Bethesda proposals for classification of lymphoid neoplasms in mice. Blood 2002;100:246–258. [PubMed: 12070034]
6. Pasqualucci L, Naumeister P, Goosens T, et al. Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. Nature 2001;412:341–346. [PubMed: 11460166]
7. Dameshek W, Schwartz RS. Leukemia and auto-immunization- some possible relationships. Blood 1959;14:1151–1158. [PubMed: 13813891]
8. Lee JC, Ihle JN. Chronic immune stimulation is required for Moloney leukaemia virus-induced lymphomas. Nature 1981;289:407–409. [PubMed: 6970336]
9. Jones RG, Trowbridge DB, Go MF. *Helicobacter pylori* infection in peptic ulcer disease and gastric malignancy. Front Biosci 2001;6:E213–E226. [PubMed: 11724680]
10. Casella G, Buda CA, Maisano R, Schiavo M, Perego D, Baldini V. Complete regression of primary gastric MALT-lymphoma after double eradication *Helicobacter pylori* therapy: role and importance of endoscopic ultrasonography. Anticancer Res 2001;21:1499–1502. [PubMed: 11396239]
11. Montalban C, Santon A, Boidexa D, Bellas C. Regression of gastric high grade mucosa associated lymphoid tissue (GALT) lymphoma after *Helicobacter pylori* eradication. Gut 2001;49:584–587. [PubMed: 11559658]
12. Gleichmann H, Gleichmann E, Schwartz RS. Immunogenetic requirements for the demonstration of a new form of immunocomplex-glomerulonephritis and malignant lymphoma in a chronic allogenic disease model. Verh Dtsch Ges Inn Med 1971;77:1153–1154. [PubMed: 5317324]
13. Burkitt DP. Epidemiology of Burkitt lymphoma. Proc R Soc Med 1971;64:909–910. [PubMed: 4329792]
14. Chapman CJ, Mockridge CI, Rowe M, Rickinson AB, Stevenson FK. Analysis of VH genes used by neoplastic B cells in endemic Burkitt lymphoma shows somatic hypermutation and intraclonal heterogeneity. Blood 1995;85:2176–2181. [PubMed: 7718888]
15. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–511. [PubMed: 10676951]
16. Ottesmeier CH, Thompsett AR, Zhu D, Wilkins BS, Sweetenham JW, Stevenson FK. Analysis of Vh genes in follicular and diffuse lymphoma shows ongoing somatic mutation and multiple isotype transcripts in early disease with changes during disease progression. Blood 1998;91:4292–4299. [PubMed: 9596678]

17. Lossos IS, Alizabeth AA, Eisen MB, et al. Ongoing immunoglobulin somatic mutation in germinal center B cell-like but not in activated B cell-like diffuse large cell lymphomas. Proc Natl Acad Sci USA 2000;97:10209–10213. [PubMed: 10954754]
18. Lossos IS, Okada CY, Warnke JM, Greiner TC, Levy R. Molecular analysis of immunoglobulin genes in diffuse large B-cell lymphomas. Blood 2000;95:1797–1803. [PubMed: 10688840]
19. Refaeli Y, Young RM, Turner BC, Duda J, Field KA, Bishop JM. The B-cell antigen receptor and overexpression of MYC can cooperate in the genesis of B-cell lymphomas. PLoSBiol 2008;6 (6):E152.
20. Boxer LM, Dang CV. Translocations involving c-myc and c-myc function. Oncogene 1999;20:5595–5610. [PubMed: 11607812]
21. Eilers M. Control of cell proliferation by Myc family genes. Mol Cell 1999;28:1–6.
22. Obaya AJ, Mateyak MK, Sedivy JM. Mysterious liaisons: the relationship between c-Myc and the cell cycle. Oncogene 1999;13:2934–2941. [PubMed: 10378690]
23. Johnston LA, Prober DA, Edgar BA, Eisenman RN, Gallant P. *Drosophila* myc regulates cellular growth during development. Cell 1999;98:779–790. [PubMed: 10499795]
24. Iritani BM, Eisenman RN. c-Myc enhances protein synthesis and cell size during B lymphocyte development. Proc Natl Acad Sci USA 1999;96:13180–13185. [PubMed: 10557294]
25. Hoffman B, Amanullah A, Shafarenko M, Liebermann DS. The proto-oncogene c-myc in hematopoietic development and leukemogenesis. Oncogene 2002;21:3414–3421. [PubMed: 12032779]
26. Prendergrast GC. Mechanisms of apoptosis by c-Myc. Oncogene 1999;18:2967–2987. [PubMed: 10378693]
27. Hurlin PJ, Dezfouli S. Functions of myc:max in the control of cell proliferation and tumorigenesis. Int Rev Cytol 2004;238:183–336. [PubMed: 15364199]
28. Mai S, Fluri M, Siwarski D, Huppi K. Genomic instability in MycER-activated Rat1A-MycER cells. Chromosome Res 1996;4:365–371. [PubMed: 8871825]
29. Felsher DW, Bishop JM. Transient excess of MYC activity can elicit genomic instability and tumorigenesis. Proc Natl Acad Sci USA 1999;96:3940–3944. [PubMed: 10097142]
30. Shi Y, Glynn JM, Guilbert LJ, Cotter TG, Bissonnette RP, Green DR. Role for c-myc in activation-induced apoptotic cell death in T cell hybridomas. Science 1992;257:212–214. [PubMed: 1378649]
31. Lord JD, McIntosh BC, Greenberg PD, Nelson BH. The IL-2 receptor promotes lymphocyte proliferation and induction of the *c-myc*, *bcl-2* and *bcl-x* genes through the transactivation domain of Stat5. J Immunol 2000;164:2533–2541. [PubMed: 10679091]
32. Refaeli Y, Field KA, Turner BC, Trumpp A, Bishop JM. The proto-oncogene MYC can break B-cell tolerance. Proc Natl Acad Sci USA 2005;102(11):4097–4102. [PubMed: 15753301]
33. Douglas NC, Jacobs H, Bothwell AL, Hayday AC. Defining the specific physiological requirements for c-Myc in T cell development. Nat Immunol 2001;2:304–315.
34. Trumpp A, Refaeli Y, Oskarsson T, et al. c-Myc regulates mammalian body size by controlling cell number but not cell size. Nature 2001;414:768–773. [PubMed: 11742404]
35. Okada T, Maeda A, Iwamatsu A, Gotoh K, Kurosaki T. BCAP: the tyrosine kinase substrate that connects B cell receptor to phosphoinositide 3-kinase activation. Immunity 2000;13:817–827. [PubMed: 11163197]
36. Melchers F. B cell development and its deregulation to transformed states at the pre-B cell receptor-expressing pre-BII cell stage. Curr Top Microbiol Immunol 2005;294:1–17. [PubMed: 16323425]
37. Kraus M, Alimzhanov MB, Rajewsky N, Rajewsky K. Survival of resting mature B lymphocytes depends on BCR signaling via the Igab heterodimer. Cell 2004;117:787–800. [PubMed: 15186779]
38. Monroe JG. ITAM-mediated tonic signaling through the pre-BCR and BCR complexes. Nat Rev Immunol 2006;6:283–294. [PubMed: 16557260]

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