



The link between T helper balance and lymphoproliferative disease

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Summary Lymphoproliferative disorders comprise a heterogeneous group of neoplasms whose behaviors range from indolent to very aggressive. The increased incidence seen in the context of immunodeficiency provides evidence that the host immune system plays a vital role in their pathogenesis. We believe that T-helper (Th)-2 dominant states favor development of lymphoproliferative disorders, including lymphoma, and conversely T-helper (Th)-1 immunity protects against lymphoproliferative disease. The age distribution of lymphomas favors childhood and post-reproductive senescence, suggesting that exposure to these periods of Th-2 bias constitutes a key risk factor for developing the disease. The tendency of lymphomas to arise in Th-2 biased locations such as mucosal interfaces, immunoprivileged sites, and regions of B-cell differentiation may likewise reflect a corresponding spatial predilection. Various clinical conditions or treatments that shift Th1/Th2 balance, including HIV infection, transplant-related immune suppression, and autoimmune disorders, can also influence the status of lymphoproliferative diseases.

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Introduction

A recent report of 26 cases of lymphomas and other lymphoproliferative disorders (LPD) seen in patients receiving tumor necrosis factor (TNF)- α inhibitors, etanercept and infliximab, has further fueled the debate regarding the potential link between LPD and immune disturbances [1]. A growing body of direct and circumstantial evidence supports an association between immunosuppression and risk of LPD. However, the precise nature of this relationship remains unclear, and the relative paucity of cases involving both disease categories has

limited epidemiologic inquiry [2]. We propose that T helper (Th) balance is the key determinant linking immune status and LPD. Specifically, we advance the concept that Th-2 dominance favors development of LPD, and that Th-1 immunity protects against the development and progression of LPD.

Epidemiologic evidence

The Th-1 and Th-2 classes of immunity and their respective function have been well described. Their relationship to LPD may be better understood by examining the spatial and temporal distributions of Th-1 and Th-2 immunity in the body and over time.

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Temporal distribution

The Th-1/Th-2 balance profile passes through three distinct phases [3] during the aging process. Robust from birth, Th-2 immunity maintains a high level of functionality throughout adult life. Conversely, Th-1 immunity-lacks maturity at birth, does not become fully developed until reproductive age, and ultimately declines after age 40. A net Th-2 dominance marks the period from birth to young adulthood. Peak Th-1 activity occurs during the reproductive years, accompanied by a relatively stable Th-1/Th-2 equilibrium, the period of pregnancy notably excepted. Th-2 dominance once again emerges during the post-reproductive years, with a discrepancy between Th-2 and Th-1 that widens with age [4,5].

Hodgkin's and non-Hodgkin's lymphomas (NHL) are the two most aggressive forms of LPD. The incidence of Hodgkin's disease (HD) exhibits a bimodal age distribution with an initial peak in the 15–34 age group and a subsequent peak in a second group after age 55 [6]. The number of cases of NHL generally increases with age and peaks during senescence. Although NHL typically occurs in elderly patients, high-grade NHLs frequently do emerge in patients under the age of 30 [7]. The age-incidence distributions of HD and NHL conveniently combine to approximately superimpose on the Th-1/Th-2 balance curve. The trends suggest a possible excess risk of developing lymphoma during long periods of Th-2 bias. The risk appears related to cumulative exposure to Th-2 bias rather than a specific imbalance at any point in time. Indeed the first peak of incidence counterintuitively occurs during the twenties when Th-1 immunity has begun to prevail. This phenomenon may reflect a lag effect of the long preceding period of Th-2 bias. That the second peak occurs well into the period of Th-2 dominance during senility does not surprise. Thus, Th-2 bias appears to amplify the cumulative risk to developing lymphoma while Th-1 bias seems to mitigate it.

Spatial distribution

While lymphomas typically arise in lymphoid tissue, they may be present in nearly any organ system. If our hypothesis is correct, we would predict that lymphomas would occur in regions of the body that exhibit either high Th-2 activity, low Th-1 activity, or both. We propose classifying the regions of Th-2 bias into three categories: (1) native sites of Th-2 emergence and proliferation; (2) interfaces between the body and the extra-corporeal environment; and (3) immunoprivileged areas.

Native dwelling and proliferation sites for Th-2 immunity include the marrow, spleen, liver, and the lymphatic system. That these sites serve as host to a large proportion of LPDs including lymphomas likely reflects the sheer preponderance of Th-2 related cells trafficking in them.

Th-2 immunity predominates in parts of the body that provide interfaces with the external environment. Mucosa-associated lymphoid tissue (MALT) is ubiquitous in such locales. Lymphomas have been described in almost all plausible locations where the MALT system functions, including lung, orbital soft tissue, salivary gland, breast, thyroid, larynx, and trachea, among others [8]. Extra-nodal NHLs, which account for up to 40% of all NHLs, most commonly emerge in the gastrointestinal system [9].

The third notable regional classification comprises immunoprivileged areas such as the central nervous system (CNS), testicles, and eyes. Little has been published regarding Th-1/Th-2 immunity in these areas, although Th-2 dominance has been observed in the CNS [10]. We propose that these areas harbor a Th-2 bias which in turn predisposes to the development of lymphomas. Indirect evidence of Th-1 suppression in these regions includes the observation that HIV and other viruses, including Epstein–Barr virus, which normally serve as targets of Th-1 immunity use the CNS as a reservoir [11–13]. Indeed lymphomas have been observed in all of these regions [14–17].

The mechanism by which Th-1 cells protect against LPD presumably occurs via their contribution to cell-mediated immunity. Epstein–Barr virus (EBV) serves as a contributing factor in many cases of LPD. The interplay between virus with humoral and cellular immunity has become a topic of active debate in the literature and beyond the scope of this article. Since the relative shift away from Th-1 bias impairs surveillance of both oncogenic viruses and oncogene-potentiated host cells, our hypothesis supports the involvement of EBV or other oncogenic viruses in LPD formation and emergence.

Ultimately, it is hard to imagine that Th-2 bias itself intrinsically causes LPD. Th-2 bias is a common state in nature and LPD is still a rare condition. Furthermore, while patients who have a congenital absence of T-cell immunity do have an increased risk of LPD, the incidence rate remains low, and EBV has often become implicated in those cases where it does occur [18,19]. Indeed, the Th-2 bias may be better viewed as providing a favorable environment for or serving as a potentiator of another mechanism by which LPD becomes induced, involving EBV or some other as-yet-unidentified agent. Various other theories of causality have also

been proposed, but none have been unequivocally substantiated.

Clinical evidence

In the previous section, we elaborated on phases of aging and regions of the body that specifically predispose to LPD based on their immunologic circumstances of Th-2 bias. Clinical evidence also supports the role of Th-1/Th-2 balance in determining emergence and enabling control of LPD.

HIV

HIV is well known to preferentially impair Th-1 immunity and shift the immune system towards a Th-2 bias. Lymphomas demonstrate an excess prevalence in this population and are the most common tumors seen in the HIV population [20]. Immune reconstitution, which may rebalance Th-1/Th-2, appears to benefit patients with AIDS-related NHLs [21].

Transplantation

Solid organ transplant recipients suffer from higher rates of LPD, most commonly in EBV-mediated post-transplant LPD. Typical drugs used for immunosuppressive therapy, including cyclosporine, azathioprine, and mycophenolate mofetil, downregulate Th-1 function in favor of Th-2 based-immunity. As with HIV, transplant-related LPD appears to improve upon removal of immunosuppression or therapeutic augmentation of the Th-1 system [22,23].

Immunomodulators for autoimmune disorders

The advent of biologic solutions for various autoimmune ailments has dramatically changed the therapeutic landscape and the management of these diseases. In 1998, the regulatory approval of the TNF- α inhibitors etanercept and infliximab for the treatment of rheumatoid arthritis and Crohn's disease constituted one of the heralded successes of biologic therapy.

The ability of TNF- α blockers to promote apoptosis of T cells and deplete cell-mediated immunity [24] suggests that these agents may shift the immune bias towards Th-2. Our hypothesis predicts an excess risk for LPD in patients receiving TNF- α blockade. Previous reviews had failed to demon-

strate a statistically significant association between treatment on inflammatory bowel disease and increased incidence of lymphomas [2]. However, on March 4th of 2003, just months after the FDA approved a third TNF- α antagonist, adalimumab, another FDA panel convened to review 26 reported cases of lymphoproliferative disease, most of which were NHLs, in patients on TNF-blockade therapy.

Similar findings with respect to the increased incidence of lymphoma have arisen in the use of cyclophosphamide and cyclosporine for a whole range of autoimmune disorders from psoriasis to Wegener's granulomatosis. While the use of such immunosuppressive agents has positively impacted the course of disease, the resulting shift to Th-2 bias may unmask lymphomas [25,26].

Testing the hypothesis

Our hypothesis may be directly tested by correlating Th1/Th2 cytokines associated with varying clinical conditions, anatomic locations, and demographic situations with LPD. Many components of our proposal may be indirectly validated through empiric observations in clinical realms beyond what we considered in this paper. For instance, the impending broad use of novel biologic agents for patients with psoriasis creates a prospective opportunity to test our hypothesis. These drugs include TNF- α inhibitors and a humanized fusion protein that targets CD2 and inhibits LFA-3/CD-2 interaction [27]. An observed consequence of therapy during the trials for these compounds included T-cell depletion.

That the T-cell suppressive effects could shift the patients towards a Th-2 bias does not seem implausible. Compared to clinical trials, the duration of exposure to Th-2 bias in real patients may prove far more substantial given the chronic nature of psoriasis. Thus, occasional cases of lymphoproliferative disease may emerge as a consequence of long-term treatment with all novel biologic strategies for the treatment of psoriasis. Overall, however, the benefits accrued from the use of such biologics for debilitating chronic conditions may far outweigh the risks.

Conclusions

In this paper, we propose that Th-1/Th-2 balance is a key determinant of the development of lymphoproliferative disease including lymphomas. We

specifically propose that Th-2 bias favors the development of lymphomas while Th-1 immunity discourages it. We implicate the temporal profile of Th-1/Th-2 balance during the human lifespan as a major factor in explaining the bimodal age distribution of lymphomas. We also connote that the local Th-1/Th-2 balance requirements in various parts of the body comprises the basis for the spatial distribution of lymphomas. We also suggest that shifts in Th-1/Th-2 balance during various clinical scenarios influence the occurrence of lymphomas.

While many questions remain, the realization of our hypothesis could define an important first step in broadening the application of drugs that can alter Th-1/Th-2 balance to better affect disease course. In addition, questions continue to emerge regarding the role of Th-1/Th-2 balance in relation to fundamental biology and human diseases. By considering the temporal and spatial distribution of Th-1/Th-2 balance, as well as the changes in this balance during particular clinical scenarios, the framework of our hypothesis on lymphoma could provide the template for elucidating the mechanisms of new therapeutic approaches for a wide range of human diseases that relate directly or indirectly to the immune system.

References

- [1] Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002;46(12):3151–8.
- [2] Bebb JR, Logan RP. Review article: Does the use of immunosuppressive therapy in inflammatory bowel disease increase the risk of developing lymphoma? *Aliment Pharmacol Ther* 2001;15(12):1843–9.
- [3] Shearer GM. Th1/Th2 changes in aging. *Mech Ageing Dev* 1997;94(1–3):1–5.
- [4] Sandmand M, Bruunsgaard H, Kemp K. Is ageing associated with a shift in the balance between type 1 and type 2 cytokines in humans. *Clin Exp Immunol* 2002;127(1):107–14.
- [5] Ginaldi L, De Martinis M, D'Ostilio A. The immune system in the elderly: III. Innate immunity. *Immunol Res* 1999;20(2):117–26.
- [6] Medeiros LJ, Greiner TC. Hodgkin's disease. *Cancer* 1995;75(Suppl. 1):357–69.
- [7] Di Leonardo G, Torchio P, Pasqualoni E, Corrao G, Quagliano D. Incidence of malignant lymphoproliferative diseases by stage and histological variants in central Italy: a population based study 1982–1994. *Eur Rev Med Pharmacol Sci* 1998;2(2):65–74.
- [8] Zinzani PL, Magagnoli M, Galieni P et al. Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. *J Clin Oncol* 1999;17(4):1254.
- [9] Isaacson PG. Extranodal lymphomas: the MALT concept. *Verh Dtsch Ges Pathol* 1992;76:14–23.
- [10] Harling-Berg CJ, Park TJ, Knopf PM. Role of the cervical lymphatics in the Th2-type hierarchy of CNS immune regulation. *J Neuroimmunol* 1999;101(2):111–27.
- [11] Moraes Jr HV. Ocular manifestations of HIV/AIDS. *Curr Opin Ophthalmol* 2002;13(6):397–403.
- [12] Fujimoto H, Asaoka K, Imaizumi T, Ayabe M, Shoji H, Kaji M. Epstein–Barr virus infections of the central nervous system. *Intern Med* 2003;42(1):33–40.
- [13] Lambotte O, Deiva K, Tardieu M. HIV-1 persistence, viral reservoir, and the central nervous system in the HAART era. *Brain Pathol* 2003;13(1):95–103.
- [14] Wang ML, Younes A. Testicular lymphoma: a mysterious link between the testis and the brain. *Clin Lymphoma* 2002;3(3):173–4.
- [15] Shahab N, Doll DC. Testicular lymphoma. *Semin Oncol* 1999;26(3):259–69.
- [16] Chan CC, Buggage RR, Nussenblatt RB. Intraocular lymphoma. *Curr Opin Ophthalmol* 2002;13(6):411–8.
- [17] DeAngelis LM. Primary central nervous system lymphomas. *Curr Treat Options Oncol* 2001;2(4):309–18.
- [18] Mueller BU, Pizzo PA. Cancer in children with primary or secondary immunodeficiencies. *J Pediatr* 1995;126(1):1–10.
- [19] Ramos JT, Lopez-Laso E, Ruiz-Contreras J, Giancaspro E, Madero S. B cell non-Hodgkin's lymphoma in a girl with the DiGeorge anomaly. *Arch Dis Child* 1999;81(5):444–5.
- [20] Hooper WC, Holman RC, Clarke MJ, Chorba TL. Trends in non-Hodgkin lymphoma (NHL) and HIV-associated NHL deaths in the United States. *Am J Hematol* 2001;66(3):159–66.
- [21] Porcu P, Caligiuri MA. Acquired immunodeficiency syndrome-related lymphomas: future directions. *Semin Oncol* 2000;27(4):454–62.
- [22] Swinnen LJ. Organ transplant-related lymphoma. *Curr Treat Options Oncol* 2001;2(4):301–8.
- [23] Kiss TL, Spaner D, Daly AS et al. Complete remission of tumour with interleukin 2 therapy in a patient with non-Hodgkin's lymphoma post allogeneic bone marrow transplant associated with polyclonal T-cell bone marrow lymphocytosis. *Br J Haematol* 2003;120(3):523–5.
- [24] D'Haens G. Anti-TNF therapy for Crohn's disease. *Curr Pharm Des* 2003;9(4):289–94.
- [25] Knight A, Askling J, Ekbohm A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 2002;100(1):82–5.
- [26] Koo JY, Kadonaga JN, Wintroub BV, Lozada-Nur FI. The development of B-cell lymphoma in a patient with psoriasis treated with cyclosporine. *J Am Acad Dermatol* 1992;26(5 Pt 2):836–40.
- [27] Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN. A randomized, double-blind, placebo controlled phase III study evaluating the efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002;47(6):821–33.