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Extrafollicular Activities: Perspectives on HIV infection, germinal center-independent maturation pathways, and KSHV-mediated lymphoproliferation.

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Abstract
Early events in the pathogenesis of KSHV-associated lymphoproliferations in the context of HIV disease remain poorly understood. Recent research indicates that latent HIV infection causes persistent immune dysfunction in B cell follicles. Simultaneously, lack of T cell immune surveillance in the lymph nodes disregulates the biology of EBV. In sum, these defects bias B lymphocyte maturation away from traditional T cell-dependent germinal center-mediated pathways and towards extrafollicular pathways. Recent advances in B lymphocyte immunology suggest that extrafollicular maturation pathways for antibody secreting cells are more flexible and robust than previously believed. These responses are now understood to be both durable and antigen-specific, and even canonically germinal center-restricted events such as class switch recombination and somatic hypermutation have now been demonstrated in an extrafollicular context. As a lymphotrophic pathogen which causes disease primarily in the context of HIV and EBV co-infection, future studies examining the interactions of KSHV biology with extrafollicular B cell maturation pathways will be critical to uncovering key aspects of KSHV-mediated immune pathology.

Introduction
The association between Kaposi Sarcoma Herpesvirus (KSHV/HHV-8) infection and pathological lymphoproliferative diseases has been known for 20 years. Despite this, we know very little about how KSHV establishes infection in the lymphocyte compartment and how these events influence the disease process. Concurrently, the field of immunology has seen a number of new advances which fundamentally alter our understanding of the variety and flexibility of B lymphocyte-mediated immune responses to infection. New research elucidating T cell independent extrafollicular pathways for the development of functional antibody secreting B lymphocytes is particularly relevant to KSHV-associated pathogenesis, which commonly occurs in the context of massive T lymphocyte dysfunction caused by HIV disease. This brief review will place our current knowledge of KSHV infection and pathogenesis in B lymphocytes in the context of the most recent advances in B cell immunology.

Features of KSHV-associated lymphoproliferations
KSHV infection of B lymphocytes is associated with a variety of lymphoproliferative disorders, including: (1) Primary Effusion Lymphoma, a true monoclonal neoplastic lymphoproliferation [1] and (2) Multicentric Castleman Disease (MCD), a polyclonal reactive lymphadenopathy [2]. In both cases, some underlying defect in immune surveillance, such as HIV disease, precedes the onset of KSHV-associated lymphoproliferation. MCD is characterized by the concurrent presence of plasmablast-like KSHV-infected B lymphocytes concentrated in extrafollicular areas with hyalinized and involuted germinal centers [3,4]. Immunohistochemical and molecular studies of primary MCD specimens characterize infected cells in symptomatic MCD as polyclonal but monotypic IgM-lambda B lymphocytes [5]. These variably express maturation markers including CD27 [6] but lack evidence of class switch recombination and somatic hypermutation [5]. Although PEL resemble KSHV-infected B lymphocytes in MCD in that they are highly biased towards IgL expression, they are distinctly monoclonal and frequently display

hallmarks of germinal center maturation including somatic hypermutation and Ig class switching [7].

A shift in the immunological role of IgM plasmablasts and implications for MCD

The features of pathological lymphocytes in MCD are consistent with an extrafollicular maturation pathway. Until recently, the extrafollicular process by which IgM plasmablasts are produced was thought to be purely a product of innate immune activation, and the antibody secreting cells generated by this pathway were thought to be short-lived and of low value from the standpoint of immunological memory [8-10]. However, a recent study by Bohannon et. al. demonstrated long-term protective immunity against influenza virus arising from a GC-independent IgM response [11]. Interestingly, this response was maintained in the absence of T cell help, and the authors postulate that the extrafollicular IgM response could serve as an auxiliary pathway for humoral immunity to persist in the presence of serious defects in the T cell compartment, such as those that exist during HIV infection. Moreover, a new study of T cell subsets in primary MCD specimens demonstrated significantly decreased frequencies and increased markers of anergy/exhaustion in invariant natural killer T (iNKT) cells and associated memory B cell defects [12]. iNKT cells have received significant attention as an alternative source of T cell help in B lymphocyte maturation during the humoral immune response [13], and recent studies suggest that iNKT cell help is important for the early extrafollicular antibody response and the subsequent generation of an IL-10 secreting B regulatory response [14]. iNKT cells can also functionally substitute for Tfh producing a short-lived IgG response via a modified GC reaction [15]. Thus, we could imagine that in HIV disease, where Tfh subsets are significantly disregulated [16], iNKT cells could be co-opted to provide B cell help in the GC. The iNKT population subsequently becomes exhausted, thereby diminishing the extrafollicular regulatory response over time and contributing to the flares of KSHV-mediated extrafollicular lymphoproliferation and cytokine dysregulation that characterize MCD. Thus, KSHV-MCD may be linked to HIV disease because HIV-mediated deficiencies in traditional T cell-dependent, GC-mediated maturation alters extrafollicular B lymphocyte biology in a way that favors KSHV-associated lymphoproliferation.

Extrafollicular maturation: Unifying the viral pathogenic model

Unraveling the cellular origins of PEL is a difficult task for a number of reasons, the greatest of which is that there is no *in vitro* model for KSHV-mediated transformation of B lymphocytes. PEL-derived cell lines and primary specimens contain little information as to the natural history of the diseased cells because they generally lack lineage markers, with the exception of CD138, and only sporadically express activation markers [17]. Based on the distinct immunological features of MCD and PEL, the prevailing hypothesis is that PEL arises from KSHV infection of a post-GC memory subset, while MCD arises from infection of naïve B lymphocytes which undergo extrafollicular maturation during active disease. However, this hypothesis is dissatisfying for several reasons. First, PEL, like MCD, is highly linked to HIV disease, which, even when well controlled by antiretroviral therapy (ART), is associated with defects in the GC reaction and the depletion of memory B cells [18]; events which would reduce the number and viability of memory B cells as infection targets in the early stages of PEL pathogenesis. Moreover, this hypothesis requires the supposition that KSHV has distinct biological effects

leading to different disease states based on the target B cell subtype. A simpler model, from a molecular virology perspective, would be that both MCD and PEL arise from a common infection event with additional factors (genetic, environmental, co-pathogen, etc.) influencing the different disease manifestations. There is some evidence in the literature that monoclonal lymphomas [19], including PEL [20,21], frequently arise in patients with MCD, suggesting that a common pathogenic model is possible. However, because MCD and PEL are both rare and infrequently diagnosed, even among people living with HIV, it is difficult to determine epidemiologically whether convincing pathogenic links exist between the two disease states.

In the context of canonical B lymphocyte maturation, the post-GC features of PEL would generally preclude the idea of a common progenitor. However, recent studies in B lymphocyte immunology have begun to refute the GC-centered model as the only path for generating mature, class switched antibody-secreting cells. Notably, an elegant study by Di Niro et. al. recently demonstrated that an immune response to Salmonella infection (a pathogen noted for inhibiting GC formation) can produce antibody-secreting cells via antigen-specific activation, somatic hypermutation and class switch recombination in an entirely extrafollicular, GC-independent maturation pathway [22]. The idea that canonically GC-restricted events like class switch recombination and antigen-directed somatic hypermutation can occur in an extrafollicular context is a huge paradigm shift in the field of B lymphocyte immunology and necessitates the re-interpretation of a large body of literature. In the context of KSHV infection, these studies provide a framework in which PEL and MCD could arise from a common infection event and varying degrees of extrafollicular maturation (possibly dependent upon the original specificity of the infected lymphocyte and the inflammatory state provided by co-pathogens) could account for the apparent differences in maturation of the pathological lymphocytes in each disease entity. These advances in immunology allow us to propose a unified extrafollicular disease model for early KSHV pathogenesis in B lymphocytes.

Alterations in GC biology during KSHV pathogenesis

Both transgenic murine models and recent advances in KSHV molecular genetics have allowed more studies of KSHV pathogenesis to be performed in B lymphocyte systems. Is there new evidence in these studies supporting the idea that KSHV infection preferentially promotes extrafollicular maturation? Indeed, a variety of new studies into KSHV biology in lymphocytes, supports the hypothesis that KSHV proteins simultaneously promote extrafollicular maturation pathways and inhibit the germinal center reaction. Ballon et. al. recently reported two transgenic mouse models in which KSHV vFLIP is expressed at different stages of B lymphocyte differentiation (CD19 for immature B lymphocytes and Cγ1 for expression during and following GC maturation). Based on the model of MCD arising from naïve lymphocytes and PEL arising from a post-GC population, the authors expected the two models to differentially recapitulate the two disease states. However, both transgenic strains showed inhibited GC formation and reduced markers for GC-mediated maturation. However, phenotypes resembling both MCD (proliferation of polyclonal IgM-lambda plasmablasts) and PEL (monoclonal IgH, CD138+, B lineage negative proliferations) were observed [23]. Thus, expression of KSHV vFLIP in the lymphocyte compartment inhibits GC biology, but this does not preclude the emergence of a PEL-like disease state *in vivo*. The KSHV early lytic protein K4.2 has been shown to decrease cell

surface expression of immunoglobulin molecules by inhibiting the action of pERP1, a cellular chaperone protein. In the same study, pERP1 expression was demonstrated in KSHV infected cells in both MCD and PEL [24]. Importantly, pERP1 expression is highly enriched in marginal zone B lymphocytes [25], suggesting that the KSHV K4.2 protein is specifically evolved to manipulate immunoglobulin maturation in an extrafollicular context. Thus, although we have little direct evidence for an extrafollicular maturation pathway preceding transformation in PEL, it seems unlikely, given the combined inhibitory effects of HIV and KSHV infection on GC biology, that PEL arises from KSHV-infected cells transiting the germinal center or from infection events within the depleted memory compartment in HIV disease.

Influence of EBV as a co-pathogen in PEL

EBV co-infection is another important factor to consider in the development of PEL. The close association of EBV biology with the germinal center is well-characterized. Most notably, the EBV proteins LMP1 and LMP2A provide a signaling background which mimics the GC reaction in infected cells. In normal EBV biology, these mechanisms serve to establish a pool of latently-infected memory B cells. However, these mechanisms also promote tumorigenesis by increasing the survival of EBV-infected cells containing transforming mutations [26]. Many, but not all primary cases of PEL are positive for both KSHV and EBV. Interestingly, PEL which are EBV negative do not share the post-GC features of EBV+ PEL [7]. Moreover, although EBV is considered the more highly tumorigenic virus, microarray studies of cellular gene expression suggest that even in the background of EBV co-infection, KSHV appears to be the driving force behind much of the neoplastic signaling in co-infected lymphomatous effusions [27]. Although the low numbers of EBV negative PEL cell lines make robust conclusions difficult, it is possible that EBV co-infection mimicking GC biology rather than *de novo* KSHV infection of post-GC B cells is primarily responsible for the maturation features of PEL. Interestingly, recent transgenic mouse studies provide evidence that EBV proteins can also inhibit GC biology, particularly in the context of T cell defects. Expression of LMP1 and LMP2A in GC B lymphocytes under control of the AID promoter produced fatal lymphoproliferations only when both T and NK cells were depleted in the same animals [28]. In this model, which mimics EBV-HIV co-infection, there was a significant increase in the IgM plasmablast response, indicating that completion of the normal GC reaction was inhibited. Similarly, EBV LMP1 [29] and EBNA2A [30] can inhibit GC formation, diverting lymphocytes to an extrafollicular IgM antibody secretion program. Taken together with the fact that normal patterns of EBV protein expression are disordered in the context of HIV infection irrespective of immune status [31], we could conclude that EBV also participates in GC dysregulation in this context.

Conclusions

KSHV-associated lymphoproliferative diseases occur in the complex background of immune dysfunction associated with HIV infection, making unraveling early events in this disease process extremely difficult. Despite years of research, we are only beginning to understand the depth of immune dysregulation associated with latent HIV infection, which persists in the lymph nodes even in the context of effective antiretroviral therapy, diminishing the canonical humoral immune response and redirecting B lymphocyte biology towards poorly understood

alternative pathways. Interactions of this skewed environment, seem to influence the biology of the lymphotrophic herpesviruses in a way that contributes substantially to a pro-lymphomagenic environment in people living with HIV infection [32]. Moreover, new research in B cell immunology, a fraction of which is highlighted in this review, suggests that the generation of humoral immunity is more resilient and flexible than previously imagined. Ideally, this new understanding of T cell-independent antibody responses and the B lymphocyte biology associated with these responses should inform new avenues of investigation into the pathogenesis of gamma-herpesvirus associated disease during HIV infection.

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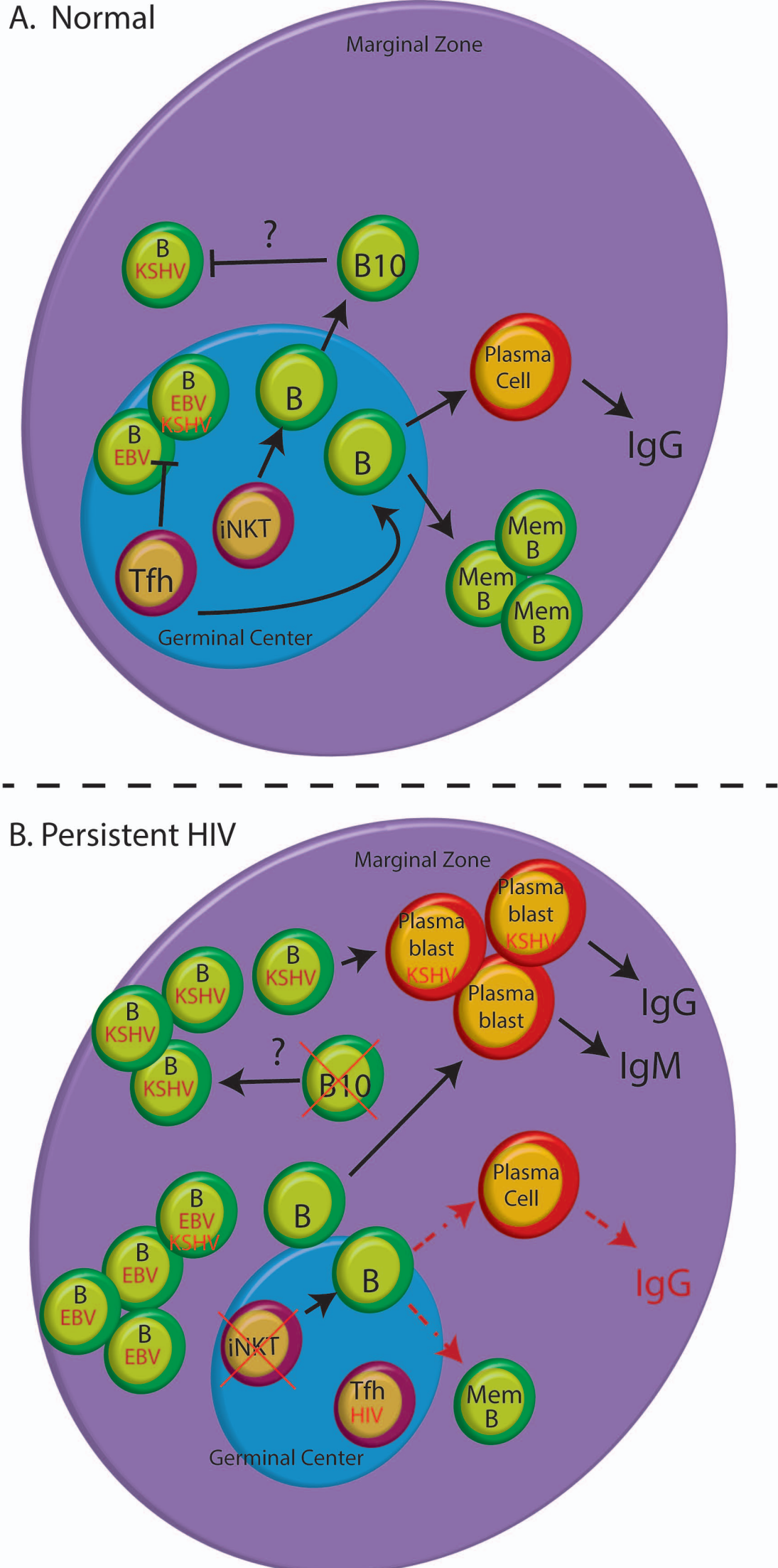
Figure Legend

Figure 1: Model of amplified extrafollicular B lymphocyte maturation during chronic HIV infection. (A) Normal lymph node functions including Tfh supplying adequate T cell help to support germinal center-mediated development of memory B lymphocytes and class-switched plasma cells in response to infections. EBV and KSHV infection are controlled and primarily latent. Follicular iNKT provide help and promote the extrafollicular regulatory environment which may affect proliferation of KSHV-infected cells in the marginal zone. (B) during persistent HIV infection Tfh function is decreased, decreasing (red lines) normal germinal center humoral immune responses and promoting auxiliary extrafollicular maturation pathways. Gamma-herpesvirus latency and pathophysiology is perturbed by alterations in the follicular/extrafollicular balance and regulatory responses mediated by iNKT are diminished.

- HIV disease damages germinal centers and biases immunity towards alternate pathways.
- Canonical B cell maturation can occur in the absence of germinal centers.
- Extrafollicular humoral immunity is more robust than previously thought.
- KSHV lymphoproliferations are associated with extrafollicular B cell maturation.


A. Normal
Marginal Zone
B KSHV
?
B10
B EBV KSHV
B EBV
B
B
Plasma Cell
IgG
iNKT
Tfh
Germinal Center
Mem B
Mem B
Mem B
B. Persistent HIV
Marginal Zone
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Plasma Cell
IgG
iNKT
Tfh HIV
Mem B
Germinal Center