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To cite this version:

Philippe Gaulard, Laurence de Leval. Follicular helper T cells: implications in neoplastic hematopathology.. Seminars in Diagnostic Pathology, 2011, 28 (3), pp.202-13. inserm-00616864

HAL Id: inserm-00616864

https://inserm.hal.science/inserm-00616864v1

Submitted on 24 Aug 2011

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FOLLICULAR HELPER T-CELLS : IMPLICATIONS IN NEOPLASTIC HAEMATOPATHOLOGY

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Supported in part by grants from the Fondation pour la Recherche Médicale (FRM)

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I. ABSTRACT

A distinct subset of T helper cells, named follicular T helper cells (T_{FH}), has been recently described. T_{FH} cells are characterized by their homing capacities in the germinal centres of B-cell follicles where they interact with B cells, supporting B-cell survival and antibody responses. T_{FH} cells can be identified by the expression of several markers including the chemokine CXCL13, the co-stimulatory molecules PD1 and ICOS, and the transcription factor BCL6. They appear to be relevant markers for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) and have helped to recognize subsets of peripheral T-cell lymphoma, NOS with nodal or cutaneous presentation expressing T_{FH} antigens that might be related to AITL. In B-cell neoplasms, T_{FH} cells are present within the microenvironment of nodular lymphocyte-predominant Hodgkin lymphoma and follicular lymphoma where they likely support the growth of neoplastic germinal centre-derived B cells. Interestingly, the amount of PD1+ cells in the neoplastic follicles might have a favourable impact on the outcome of FL patients.

Altogether, the availability of antibodies directed to T_{FH} -associated molecules has important diagnostic and prognostic implications in haematopathology. In addition, T_{FH} cells could represent interesting targets in T_{FH}-derived lymphomas such as AITL, or in some B-cell neoplasms where they act as part of the tumour microenvironment.

Key words: follicular T helper cells (T_{FH}), angioimmunoblastic T-cell lymphoma (AITL), T_{FH}-derived lymphomas, nodular lymphocyte predominant Hodgkin lymphoma, follicular lymphoma

II. INTRODUCTION

During the last years, a separate subset of T helper cells, named follicular T helper cells (T_{FH}) has been extensively described (for review, see [1-3]). T_{FH} cells are characterized by their homing capacities in the GC of B-cell follicles where they interact with B cells, supporting B-cell survival and antibody responses. T_{FH} cells are characterized by a gene expression signature distinct from that of other T-cell subsets [4], and they can be identified by an array of markers including the chemokine CXCL13, the co-stimulatory molecules ICOS, PD1, and the transcription factor BCL6 used by flow cytometry and/or immunohistochemistry on routinely fixed biopsies. These markers appear to be relevant for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) and have helped to recognize subsets of peripheral T-cell lymphoma, NOS with nodal or cutaneous presentation expressing T_{FH} antigens that might be related to AITL.[5, 6] In B-cell neoplasms, T_{FH} cells are present within the microenvironment of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and follicular lymphoma (FL) where they likely support the growth or survival of neoplastic germinal centre-derived B cells. Interestingly, presence of significant amounts of PD1+ cells in the neoplastic follicles might have a favourable impact on the outcome of FL patients.
In this review, we will summarize the main characteristics of T_{FH} cells with special attention to the markers useful for their identification, and describe the implications of T_{FH} cells in neoplastic haematopathology, both in T-cell lymphomagenesis or as part of the tumour microenvironment in some B-cell neoplasms.

III. FOLLICULAR HELPER T-CELLS

During the last years, T follicular helper (T_{FH}) cells have emerged as a separate minor functional subset of effector T helper (Th) cells, with a distinct gene signature and functions separable from the other known Th1, Th2, Th17 effector subsets.[1, 2] T_{FH} cells reside in reactive germinal centres and are specialized in providing help to B cells during the germinal cell (GC) reaction, thus allowing formation of long-lived antibody responses. The interactions between T_{FH} cells and B cells in the GC are critical to promote B-cell differentiation and survival and to allow the maturation process (Ig class-switch recombination and somatic hypermutation) which will result in the development of high-affinity long-lived plasma cells and memory B cells (for review, [7]). T_{FH} cell functions are mediated through the production of cytokines - including IL-10 or IL-21 and at a lesser extend IL-4 - that promote B-cell survival and antibody production, and through the engagement of co-stimulatory molecules (such as ICOS, CD28, CD40L, PD1, etc.) and other receptors (SAP, CXCR5, etc.) which favour strong interactions with B cells and consequently B-cell responses.

IL-21, likely the most characteristic cytokine produced by T_{FH} cells, also promotes T_{FH} survival in an autocrine manner. Both the CXCL13 chemokine and its receptor CXCR5 are expressed by T_{FH} cells. CXCR5, also present in germinal centre B cells, appears essential to T_{FH} localization and function, as it enables the migration of T_{FH} cells into CXCL13-rich areas in B-cell follicles. CXCL13 probably plays a major role as this chemokine, also produced by follicular dendritic cells, is critical for B-cell recruitment into germinal centres and for B-cell activation. Programmed death-1 (PD1) - a member of the CD28 costimulatory receptor family - is a negative regulator of T-cell activity that presumably regulates selection and survival of GC B cells - and inducible costimulator (ICOS) molecule - a CD28 homolog implicated in T-cell activation and differentiation - interact with countereceptors on B cells. The adaptator molecule SLAM-associated protein (SAP) is an important component of the T_{FH} signalling

pathway.[8] It is now established that the transcriptional repressor BCL6 drives T_{FH} formation.[9] BCL6 expression in T_{FH} cells is able to upregulate CXCR5, ICOS, PD1, IL-21R, IL-6R (and to downregulate CCR7). These effects can be antagonized by BLIMP1 which represses BCL6 and is downregulated in T_{FH} cells. To note, the effect of BCL6 on multiple T_{FH} genes appears at least partly mediated by the downregulation of many miRNAs, many of which are predicted to target T_{FH} genes (reviewed in: [10])

How to recognize T_{FH} cells in routine practice? – Several markers characteristically expressed by T_{FH} cells can be used in diagnostic practice either by flow cytometry and/or by immunohistochemistry on routinely fixed tissue samples to identify reactive or neoplastic T_{FH} cells. These include the cell surface molecules CXCR5, CD154, PD1, ICOS, CD200, and cytoplasmic SAP (SLAM-associated protein). [11-17] as well as the transcription factors BCL6 and MAF.[18-20] CD57 is less specific and is expressed in only a small proportion of T_{FH} cells.[21] In fact, beyond their specific function to provide help to B cell, the precise phenotypic definition of T_{FH} cells remains elusive since most of these T_{FH} markers can individually be expressed by other T cell subsets. Indeed, levels of ICOS or PD1 are found in activated T cells, and T_{FH} cells are best defined by high expression of CXCR5, ICOS, PD1, IL-21 and BCL6 (with low level of TBX21 (T-bet), GATA3, Rorγt and FOXP3 that characterized Th1, Th2, Th17 and T reg, respectively). Consequently, a combination, and more importantly the amount, of "T_{FH}" markers such as CXCR5, ICOS, PD1, is recommended to identify T_{FH} cells by flow cytometry analysis.[10] On tissue sections, where the possibity of multicolour analysis is limited, the use of several T_{FH} markers has been recommended [22] and attention should be paid to the distribution and intensity of the immunostainings. Among T_{FH} mediators, the chemokine CXCL13 appears quite specific. For

diagnostic purposes, CXCL13, PD1, ICOS and BCL6 most likely represent the most useful and robust immunohistochemical T_{FH} markers.

Interestingly, CD10, reported to be a sensitive marker for AITL by immunohistochemistry and/or flow cytometry [11, 19, 23-26], has not been identified in the gene signature of normal T_{FH} cells.[4] However, minor populations of CD3+/CD10+ have been detected in normal lymph nodes, or B-cell lymphomas.[27-29] raising the question whether CD10 could be assigned to a subset of normal T_{FH} cells.

As the development of T_{FH} cells has begun to be better understood, several questions have arisen. There is evidence that T_{FH} cells are heterogeneous comprising at least the GC- T_{FH} cells subset described above and non-GC T_{FH} including CD4+ T cells with a TFH phenotype that interact with B cells outside the germinal centres[10], and even circulating memory T_{FH} cells[30] that might explain some heterogeneity in the phenotypic profile of T_{FH} cells. It appears also more likely that T_{FH} cells result from a conversion of effector Th cells that acquired T_{FH} cell functions while interacting with B cells rather than they constitute a distinct lineage.[2, 10] Moreover, it is to note that not all follicular T cells are B-cell helper cells as some follicular T cells appear to have a suppressive function.[10, 31] In pathologic situations, T_{FH} cells seem to play an important role in autoimmunity. Their interest is also increased since T_{FH} have been shown to give rise to a significant proportion of peripheral T-cell lymphomas and finally may play important roles in some B-cell lymphomas.

IV. PERIPHERAL T-CELL LYMPHOMAS WITH A T_{FH} IMMUNOPHENOTYPE

Angioimmunoblastic T-cell lymphoma (AITL)

AITL represents the prototype of T_{FH} -derived lymphoma. Described in the seventies as a dysimmune non neoplastic condition, it has later been recognized as a subtype of peripheral T-cell lymphoma (PTCL), given the demonstration of cytogenetic alterations and clonal T-cell receptor (TCR) gene rearrangements in most instances and the identification of clearly malignant morphologic features in some cases (reviewed in de Leval et al.[32]). Recently, gene expression studies have demonstrated a T_{FH} signature in AITL [33-35] and the expression of T_{FH} markers in the neoplastic cells has been confirmed by immunostaining methods. AITL is reported as the second most common PTCL worldwide, but appears more prevalent in Europe (representing 29% of the cases) than in North America or Asia where its estimated prevalence is below 20% in a recent survey.[36, 37] The disease which affects elderly adults[38] is usually characterized by generalized peripheral lymphadenopathy, often with concomitant extranodal disease. It is typically manifested by systemic symptoms (fever, weight loss, skin rash, and arthralgias), and by laboratory testing polyclonal hypergammaglobulinemia and Coombs-positive hemolytic anemia are frequent. Occasional spontaneous remissions are reported. The median survival is <3 years in most studies, but a subset of patients experience long-term survival.[38]

In lymph nodes, AITL displays distinctive pathological features that may be categorized according to three overlapping architectural patterns, as decribed by Attygalle et al..[23] In pattern I, seen least frequently, the lymph node has a partially preserved architecture with hyperplastic follicles with poorly developed mantle zones, and a polymorphous infiltrate into the paracortex comprising more or less inconspicuous neoplastic cells, which tend to distribute around the follicles .[39]. This pattern is the most difficult to diagnose. In pattern II (AITL with depleted follicles), depleted follicles which may have Castleman's-like features are present. In pattern III (AITL without follicles), by far the most frequent, there is a complete effacement of architecture by a diffuse proliferation accompanied with prominent

irregular perivascular proliferation of FDCs.[23, 39] These patterns are thought to reflect morphologic evolution of the disease rather than clinical progression [14, 23 , 24, 39] In a substantial proportion of the cases, mixed patterns are observed (**Figure 2A**). The hallmark features of AITL found in all patterns are: (1) a diffuse (or predominantly paracortical in patterns I and II) polymorphous infiltrate including variable proportions of atypical neoplastic T cells, admixed with small lymphocytes, histiocytes or epithelioid cells, immunoblasts, eosinophils and plasma cells, usually spreading out in the capsule and perinodal tissue sparing the peripheral cortical sinus, (2) a marked proliferation of arborizing high endothelial veinules and (3) a more or less marked proliferation of follicular dendritic cells (FDCs) (**Figure 2B-C**). The lymphoma cells are medium-sized with round or slightly irregular nuclei, clear cytoplasm and distinct cell membranes. Large B-cell blasts, sometimes resembling Hodgkin or Reed Sternberg cells - are almost constantly present, usually but not always infected by EBV, usually scattered throughout the tissues, sometimes numerous (B-cell-rich AITL) (**Figure 2D**). AITL cases with a high content of B-blasts (B-cell-rich) raise differential diagnosis problems with T-cell/histiocyte-rich diffuse large B-cell lymphoma, a diagnosis which can be excluded due to the background containing eosinophils and plasma cells, the FDC expansion and the presence of EBV. Classical Hodgkin lymphoma (cHL) of mixed cellularity type can also be misdiagnoses when the B blasts have Reed Sternberg-like cell features and show CD30 and sometimes CD15 expression. In the latter cases, special attention should be paid to the presence of FDC expansion, cellular atypia and expression of CD10 and T_{FH} markers by the T-cell population and clonality analysis might be useful.[40] In practice, the distinction from THRLBCL and cHL is essential, as the latter represent separate entities requiring distinct clinical management and therapies.

The abundance of B cells, which does not seem to impact the clinical outcome [38, 41], correlates with the detection of B-cell clonality or oligoclonality.[42, 43] A subset of patients go on to develop an EBV-associated B-cell lymphoproliferation, in most instances an EBV-positive

diffuse large B-cell lymphoma, less commonly an EBV-negative B-cell or plasma cell neoplasms.[24 , 44 , 45] AITL cases with a high content of epithelioid cells (epithelioid variant of AITL), raise differential diagnosis issues as they can suggest a granulomatous disease or be mistaken for other histiocyte-rich B- and T-cell lymphomas or Hodgkin lymphoma.[40]

The neoplastic cells of AITL consist of mature αβ CD4+CD8- T-cells.[26, 28, 46, 47] Reduced or absent expression of pan-T-cell antigen(s) (most commonly sCD3, CD4, CD7) is frequently observed. Partial expression of CD30 by the neoplastic cells is not unusual.[26] In the majority of cases, coexpression of CD10 is observed in a variable proportion of the neoplastic cells [23, 26, 38, 48]

As indicated above, AITL has been recently characterized as the prototype of neoplasm derived from T_{FH} cells; accordingly, AITL neoplastic cells can be recognized by the expression of several markers characteristic although not entirely specific of the T_{FH} cells, including the cytoplasmic chemokine CXCL13, the cell membrane antigens PD1, ICOS, CD200, the adaptator molecule SLAM-associated protein (SAP) or BCL6 (**Figure 2E-H**).[11, 12, 13 , 14-19, 29, 49]. In addition, CXCR5 is also an excellent T_{FH} marker expressed by AITL cells.[12] This cell surface marker is easily detected by flow cytometry, but may be difficult to demonstrate on fixed paraffin tissue sections. It is particularly useful for the detection of the frequent minimal peripheral blood involvement characterized by an aberrant cell surface immunophenotype (most commonly CD10+ and/or sCD3- or dim) and/or expression of T_{FH} antigens.[50]

The identification of AITL in extranodal localizations, such as in bone marrow and skin biopsies, may be difficult because of the scarcity of neoplastic cells, especially in the absence of established diagnosis. Immunohistochemistry for CD10 and T_{FH} markers is helpful to identify the neoplastic elements, and molecular genetic studies may demonstrate clonal TCR rearrangement.[25, 51] In the bone marrow and skin infiltrates, CXCL13 may be more useful than CD10 which also stains the stroma and may be difficult to interpret. However, T_{FH}

markers are not entirely specific for AITL as a T_{FH} immunophenotype has also been reported in primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (see below).[6].

Moreover, the cellular derivation of AITL from T_{FH} cells likely provides a rational model to explain several of the peculiar pathological and biological features inherent to this disease, i.e. the expansion of B cells, the intimate association with germinal centres in early disease stages and the striking proliferation of FDCs as well as some of the clinical features including hypergammaglobulinemia and auto-immune manifestations. CXCL13 is probably a key mediator. This chemokine critical in B-cell recruitment into germinal centres and for B-cell activation, likely promotes B-cell expansion, plasmacytic differentiation and hypergammaglobulinemia. In addition, normal T_{FH} cells can suppress T-cell responses by inhibiting the proliferation and function of conventional CD4 T cells, specially through TGF-β and IL-10 production[31], and may therefore contribute to defective T-cell responses in AITL. Moreover, non-neoplastic cells typically represent a quantitatively major component of AITL and clinically, the manifestations of the disease mostly reflect a deregulated immune and/or inflammatory response rather than direct complications of tumour growth [38] supporting the concept of a paraneoplastic immunological dysfunction. Although the precise pathways and the mediators involved are only partly deciphered, a complex network of interactions is likely to take place between the tumour cells and the various cellular components of the reactive microenvironment. Different factors released by T_{FH} cells may be involved in B-cell recruitment, activation and differentiation (CXCL13), in the modulation of other T-cell subsets (IL21, IL10, TFGβ), or in promoting the vascular proliferation observed in the disease (VEGF, angiopoietin) [34, 52, 53], and may also act as autocrine factors (for review see [32]). CXCL13 may also attract mast cells which are a source of IL6 promoting Th17 differentiation.[54]

Perturbations of T-cell subsets may also favor EBV reactivation with expansion of EBV-infected B-immunoblasts, and occasional occurrence of an EBV-associated B-cell lymphoproliferative disorder. M2 macrophages expansion and T reg depletion could contribute to the immunosuppressive microenvironment in AITL and to the neoplastic T_{FH} expansion.[55, 56] Interestingly, it has been recently suggested that the microenvironment has prognostic relevance in AITL and a molecular prognosticator related to the microenvironment signature has been constructed.[35]

The molecular alterations underlying the neoplastic transformation of T_{FH} cells remain unknown (reviewed in [57]). By cytogenetic analysis clonal aberrations – most commonly trisomies of chromosomes 3, 5 and 21, gain of X, and loss of 6q - are detected in up to 90% of the cases (reviewed in [58]). Chromosomal breakpoints affecting the T-cell receptor (TCR) gene loci appear to be extremely rare. [59]

Follicular Peripheral T-cell lymphoma

The follicular variant of PTCL/NOS named after a pattern of growth intimately related to follicular structures, has been recently described. It comprises cases with a truly follicular pattern, mimicking follicular lymphoma,[60] T-cell lymphomas with a perifollicular growth pattern,[61] or involving expanded mantle zones, therefore mimicking progressive transformation of germinal centres or nodular lymphocyte predominant Hodgkin lymphoma with cellular aggregates of small/medium sized T cells in a background of small IgD+ lymphocytes (**Figure 3A-B**). Neoplastic cells are CD4+ BCL6+ CD10 +/- CD57-, with expression of T_{FH} molecules CXCL13, PD1 and ICOS (**Figure 3C-F)**.[5, 62] In view of the T_{FH} phenotype, the interaction with B-cells and FDC, and overlapping clinicopathologic

features with AITL in some cases [5, 63], the possible relationship to AITL is questionable. A recurrent chromosomal translocation t(5;9)(q33;q22) involving ITK and SYK tyrosine kinase, has been described in association with at least some follicular PTCLs,[64] but is otherwise rarely found in non-follicular PTCLs, which may support the concept of a distinct subtype. Interestingly, the fusion tyrosine kinase ITK-SYK has transforming properties *in vitro*, and induces a T-cell lymphoproliferative disease in mice resembling human PTCL through a signal that mimicks activation of the T cell receptor.[65-67] In addition, overexpression and activation of SYK appear to be a feature common to most PTCLs, and potentially represents a novel therapeutic target.[68, 69]

Other Peripheral T-cell lymphoma, not otherwise specified (PTCL,NOS) expressing T_{FH} markers

By definition, PTCL/NOS represents a heterogeneous category of T-cell neoplasms. However, besides the follicular variant of PTCL/NOS, up to one third of cases classified as PTCL/NOS based on their pathological features, have been found to harbour imprints of traces of the T_{FH} signature and/or to express T_{FH}-associated markers (CXCL13, ICOS, PD1, CD200,..) .[14, 22, 29, 49]. Importantly, careful review of the pathological and/or clinical features of these cases have emphasize that at least some of them exhibited other AITL-like features and likely represent AITL evolving into PTCL/NOS-like tumours with a high tumour cell content and partial lost of the characteristic microenvironmental background of full-blown AITL. Thus, a subset of PTCL/NOS cases appears related to or derived from AITL, and the spectrum of AITL may be broader than is currently thought.[33, 48, 57] It remains to be defined which criteria should be used to define the borders of AITL entity. In that respect, whether clinical and/or laboratory symptoms should be taken into account in borderline cases requires further investigation.

Cutaneous PTCL expressing T_{FH} markers

Recent studies show that primary cutaneous CD4+ small/medium sized T-cell lymphoma, a provisional entity in the updated WHO classification[70], may constitute another PTCL subtype with a T_{FH} phenotype, therefore suggesting its derivation from T_{FH} cells [6, 71]. The disease affects elderly adults and presents with cutaneous lesions without systemic manifestation. Histopathologic features include a dermic infiltrate by small/medium sized cells, with slight atypia and a CD4+ phenotype with expression of T_{FH} -associated molecules CXCL13, PD1, BCL6 (**Figure 4**). The neoplastic cells have the tendency to be admixed with reactive B cells, some of which are large and/or EBV-infected suggesting B-cell stimulation by T_{FH} cells.[71] Interestingly, the disease has an indolent clinical course and no systemic manifestation suggestive of AITL yet has been reported in the course of the disease. Besides, the significance of the observation of cases of mycosis fungoides, which express follicular helper T-cell marker, PD1 is unknown [13].

V. REACTIVE T_{FH} CELLS IN B-CELL AND HODGKIN LYMPHOMAS

In the past years, there has been increasing interest into the characterization of the presence and distribution of follicular T cells in a variety of B-cell and Hodgkin lymphomas, and several studies have highlighted the usefulness of T_{FH} identification as an adjunct to lymphoma diagnosis. Moreover, there is increasing evidence that the functional implications of T_{FH} cells interacting with neoplastic B cells are biologically relevant, and that T_{FH}-related markers may constitute valid biomarkers of prognosis or response to therapy in certain lymphoma entities. Incidentally, it has been reposted that PD1 is also expressed in the neoplastc B cells of small lymphocytic lymphoma/chronic lymphocytic leukemia, where the

expression can be increased by CD40 ligation, while it is not detected in the neoplastic cells of other small B-cell lymphomas.[17, 72] While the biological significance of this findings remains to be clarified, the diagnostic implications are obviously limited.

Diagnosis and differential diagnosis of Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

In nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), a disease entity dictinct from classical Hodgkin lymphoma (cHL), the neoplastic cells (referred to as LP cells) are B cells of germinal centre origin and are typically distributed in large nodular structures comprising numerous small IgD-positive B cells, scattered histiocytes, in association with a meshwork of follicular dendritic cells (FDCs).[70] The nodularity and the presence of rosettes of T cells surrounding the CD20+ (usually CD30- EMA+/-) LP cells have been proposed as a defining feature of NLPHL and considered a useful finding for its recognition.[73] The rosetting T cells in NLPHL have an immunophenotype of T_{FH} cells in that they are positive for CD57, BCL6 and PD1 (**Figure 5A**).[74, 75] Nam-Cha et al. examined the usefulness of several T_{FH} markers for the identification of T-cell rosettes in a large series of NLPHL and concluded to the superior diagnostic value of PD1 in comparison to CD57, BCL6 and CXCL13. PD1-positive and CD57-positive rosettes were demonstrated in 98% and 76% of the cases, respectively. Notably in their hands, no rosettes were observed with BCL6, and CXCL13 had a very low sensitivity (CXCL13-positive rosettes were seenin 7/58 cases).[75] Similar findings were reported by Churchill et al. who compared the sensitivity of PD1 and CD57 stainings for highlighting circles of T cells around neoplastic LP cells in NLPHL with classic nodular and/or serpiginous nodular architecture.[76]

Besides the most frequently encountered purely nodular pattern, NLPHL also encompasses less frequent architectural patterns including cases with a mixed nodular and diffuse pattern, cases with a purely diffuse pattern, and cases of NLPHL with T-cell/histiocyte-rich B-cell-like areas.[70] The correct identification of these morphologic variants and their distinction from T-cell/histiocyte-rich large B-cell lymphoma can pose diagnostic problems. The distinction is, however, of prime clinical importance, since NLPHL and THRLBCL represent distinct clinico-pathologic entities that require different management. In that respect, it has been suggested that the expression of PD1 might be useful in delineating the presence of PD1-positive rosetting around the LP blasts in cases of NLPHL with a diffuse pattern (**Figure 5B**) and in those depleted in small B-cells, while conversely a lack of PD1 rosettes was reported in THRLBCL.[75, 77] The results published by Churchill et al, however, while confirming the utility of PD1 for the identification of T-cell circles around LP cells in nodular and extrafollicular areas, question the utility of T_{FH} markers as adjuncts to the diagnosis of diffuse NLPHL and to the differential diagnosis with THRLBCL, as they observed a gradual loss of T_{FH} cell rosetting around LP cells upon progression to diffuse patterns, and conversely a subset of *de novo* THRLBCL appear to contain T_{FH} rosettes.[76]

Although the presence of PD1-positive rosettes around neoplastic cells is typical for NLPHL, it is not exclusive to NLPHL, as it may also be encountered, although less frequently, in cases of cHL, especially the lymphocyte-rich subtype, where a follicular T-cell lymphoma background is present in roughly half of the cases.[72, 75, 78]

Biologic relevance of PD1-positive T cells in B-cell and Hodgkin lymphomas

The cellular composition of the tumour microenvironment can significantly influence the outcome of different lymphoma entities. In follicular lymphoma (FL), the neoplastic cells

reside in follicular structures in association with follicular dendritic cells and follicular helper T cells. A gene expression profiling study published in 2004 identified two distinct immune response signatures relevant to the prognosis.[79] The immune response type one signature including genes overexpressed in T cells and monocytes, was associated with a favourable prognosis, while the immune response type two including genes expressed in dendritic cells and macrophages, was associated with a less favourable outcome. Subsequently, functional T-cell subsets have been examined for their distribution, abundance and association with prognosis. PD1-positive cells are present mainly in the follicular areas of FL, and are scarse or absent in the interfollicular/diffuse areas ; moreover, their abundance correlates with the histologic grade, as grade III lesions tend to contain less PD1-positive cells than usual grade I-II lymphomas [80, 81]. In particular, it has been found in at least two independent cohorts that higher numbers of PD1-positive lymphocytes are associated with improved overall survival in FL patients.[80, 82] Since the prognostic value of high numbers of PD1-positive cells appears to be independent of the classical prognostic index used to stratify FL patients, the abundance of PD1 might be incorporated in the future as a prognostic biomarker of FL. In addition to these observations, functional studies have confirmed the enrichment in T_{FH} cells in the FL microenvironment that display a specific activation profile characterized by the expression of IL-4, that could sustain FL pathogenesis.[83]

In classical HL, increased numbers of PD1 positive lymphocytes were found of negative prognostic significance for overall survival, as opposed to the number of FOXP3-positive regulatory T cells [72].

VI. - CONCLUSION

The recent recognition of the functional subset of T_{FH} cells specialized in providing B-cell help has provided new diagnostic tools that can be used in routine practice to diagnose AITL and some newly recognized subsets of T_{FH} -associated PTCL. In view of their critical functional properties, T_{FH} – specific biomarkers could be explored as new potential therapeutic targets not only in T_{FH}-derived lymphomas, but also in some germinal-centre derived B-cell lymphomas where reactive TFH cells may play an important role in modulating the growth and survival of the neoplastic cells.

VII. FIGURE LEGENDS

Figure 1 : Follicular helper T cells

Follicular helper T cells and derived lymphomas. Follicular helper T cells normally present in the light zone of reactive germinal center (upper left panel, immunostaining with anti-CD57) have been demonstrated as the cell of origin of several lymphoma entities (upper right panel, for details see text). The main distinctive immunophenotypic features of TFH cells are summarized in the lower panel table.

Abbreviations: CXCR5: Chemochine (C-X-C motif) receptor 5

CXCL13: Chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)

ICOS: Inducible T-cell Co-Stimulator (ICOS) protein

SAP: SLAM-associated protein (SH2D1A)

Figure 2: Angioimmunoblastic T-cell lymphoma

(A) Low power magnification of a case characterized by a mixed pattern, comprising large reactive follicles with an attenuated mantle zone, and a diffuse proliferation in association with increased vascularisation ; (B) High power view showing prominent vascularisation, and a mixed infiltrate comprising large blastic cells, eosinophils, and an infiltrate of small to medium atypical lymphoid cells ; (C) CD21 highlights a follicular dendritic cell meshwork, in association with follicles, (F) and outside the follicles ; (D) CD20 stains large blastic cells outside the follicles (F) ; (E-H) the neoplastic cells are positive for several T_{FH} markers including PD1 (E), CXCL13 (F), BCL6 (G) and c-MAF (H).

Figure 3 : Follicular peripheral T-cell lymphoma

(A) At low magnification there is a vaguely nodular pattern reminiscent of progressively transformed germinal centres, and scattered paler aggregates ; (B) the aggregates of pale cells representing the neoplastic population consist of atypical medium-sized lymphocytes with moderately abundant clear cytoplasm; mitotic figures are seen ; (C) the neoplastic cells which are CD3+ CD4+ (not shown) have strong membrane expression of PD1 ; (D) cytoplasmic granular positivity for CXCL13 ; (E) express CD10 ; and (F) show nuclear positivity for BCL6.

Figure 4 : Primary cutaneous small/medium-sized CD4+ T-cell lymphoma

(A)This lymphoma which presented as an isolated lesion of the eyelid in a 55 y-old man, consisted of a dense and diffuse lymphoid infiltrate occupying the the upper and mid-dermis ; (B) it was composed of small to medium sized slightly atypical lymphoid cells, with scattered histiocytes and larger cells ; (C and inset) the lymphoid cells had a CD2+ CD3+ CD4+ immunophenotype (not shown) with strong coexpression of PD1 in the majority of the cells.

Figure 5 : PD1 expression in nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

The classic nodular pattern (A-C) and the diffuse pattern (D-F) of NLPHL are illustrated. PD1 immunostaining is helpful to decorate rosettes of T cells around neoplastic LP cells in both nodular (E) and diffuse (F) areas.

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