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EDITORIAL

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Tumour infiltrating T-cells in gastric lymphoma

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Tumour infiltrating T cells (TIL's) are present in low grade lymphomas of all types [12]. They tend to be predominantly CD4+, and frequently express antigens associated with chronic activation such as class II MHC [5, 11, 15]. The idea that TIL's may interact with the tumour cells [10] and may have anti-tumour activity [13] has been explored over the years. In contrast, recent evidence which will be reviewed below, suggests that rather than having anti-tumour activity, TIL's may have a critical role in supporting the progression of B cell lymphomas arising in mucosa associated lymphoid tissue (MALT-type lymphomas). In a normal humoral immune response, T cells provide contact dependent and/or lymphokine-mediated help for B cell proliferation and differentiation. It is possible that by a parallel mechanism, activated TIL's provide help for the progression of low grade B cell lymphomas.

Yumoto et al. [21] analysed T cell receptor (TCR) Vβ usage in gastric lymphoma. They studied 10 primary gastric B cell lymphomas, 7 of which were said to be of MALT type (4 low grade, 3 high grade). They observed a preferential usage of Vβ2 in 4 cases, 3 of which were of MALT-type (1 low grade, 2 high grade) and 1 classified as a diffuse large B cell lymphoma. When dominant Vβ2 gene products were analysed in a single case of high grade MALT-type lymphoma, a predominant rearrangement of Vβ2 with Dβ2.1 and Jβ2.3 was observed in 6/9 clones tested. More importantly, the sequence between the VD and DJ regions, which are thought to encode for residues that recognise antigenic peptides, were shown to be identical in this case.

Restriction in the use of the different variable regions of the TCR β chain could reflect expansion of a group of cells by superantigen [8]. Superantigens, such as certain bacterial and viral products, activate T cells by binding directly to the TCR β chain. This process is dependent on MHC class II, though superantigen does not require processing. Rather than binding in the peptide groove, the superantigen binds to the 'outside' of the specific Vβ gene product and the class II molecule. The resultant T cell population which is expanded by superantigen has a bias in the use of particular TCR Vβ genes. However, with a relatively large precursor population of cells which superantigen would stimulate (up to approximately 10% of the total T cell population), it is unlikely that there would be evidence of clonality within TCR genes of the expanded population expressing an individual Vβ. Alternatively, T cells with specificity for conventionally processed peptides would have a much lower precursor frequency since considerably diversity in the TCR is generated by the combination of different V(D)J gene segments, the random insertion or deletion of N-nucleotides in the junctional regions and the pairing of different chains during T cell ontogeny [4, 18].

As a consequence, expansion of T cells by this route could conceivably result in an oligoclonal T cell population which would also be reflected in TCR V region dominance. However, since most T cell responses to complex antigens involve multiple peptides, it is hard to explain the data of Yumoto et al. [21] in this context. Interestingly, a study of TCR Vβ usage in Sjögren's disease, a condition known to be a precursor of MALT-type lymphomas in the salivary gland showed dominance of Vβ2 and Vβ13 gene expression [14, 20]. In a study of TCR Vα and Vβ gene usage by T cells infiltrating the thyroids of patients with autoimmune thyroid disease, including 4 patients with Hashimoto's thyroiditis from which thyroid lymphomas of MALT-type arise, unrestricted TCR Vβ but a restricted Vα gene usage was observed [3]. It has recently been observed that T cells in the intestinal mucosa are oligoclonal, and that different TCR Vβ's dominate in different individuals [2, 16]. The origin of these oligoclonal populations of T cells and their significance are not yet understood. It is possible however that V region dominance observed in mucosal lymphomas and autoimmune diseases in mucosal sites may be associated with this phenomenon.

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TCR gene usage by TIL's has been analysed in a number of other lymphomas. Studies have shown unrestricted TCR α and β gene usage in the TIL's associated with Hodgkin's disease and large cell B cell non-Hodgkin's lymphoma [19]. Gilks et al. [7] investigated TCR α gene usage in T cells infiltrating follicular lymphoma but did not reveal any bias in gene expression compared to peripheral blood lymphocytes from the same patients. In contrast, Wen et al. [17] showed clonal T cell populations in peripheral blood lymphocytes from 3/13 cases of chronic lymphocytic leukaemia (CLL) and 1/8 cases of multiple myeloma. These clonal T cell populations were thought to be involved in the recognition of tumour associated antigens, possibly tumour Ig itself. Indeed in one case of multiple myeloma, incubation of peripheral blood T cells with purified tumour Ig resulted in an increase in DNA synthesis.

The idea that T cells are involved in the pathogenesis of MALT-type lymphomas is supported by recent studies of Hussell et al. [9]. It was reported that malignant B cells from 3 low grade MALT lymphomas respond to certain strains of *Helicobacter pylori* in vitro. The increase in proliferation, expression of IL-2R and the increase in Ig secretion by malignant B cells, in the presence of *H. pylori*, was critically dependent on the presence of tumour infiltrating T cells. Furthermore, the strain of *H. pylori* responsible for stimulation of tumour cell populations was different in each case. This study implied that infiltrating reactive populations of T cells, instead of inhibiting tumour growth, as is often assumed, may be aiding the proliferation of malignant B cells. *H. pylori* antigens are highly variable and strains appear to have unique antigenic profiles [1, 6]. It is possible that the oligoclonal populations of T cells detected by Yumoto et al. [21] in gastric lymphoma are expanded by *H. pylori* peptides though the mechanism remains unclear.

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