British Sjögren's Syndrome Association

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Role of Lymphoid Chemokines in the Pathogenesis of Sialoadenitis and MALT Lymphomas in Sjögren's Syndrome

Research Grant 2005

Professor Pitzalis won the BSSA Research Grant in 2005. During his career he has built from scratch, a new independent laboratory based research group (the Experimental Rheumatology Group based in the ARC laboratory at the Guy's Campus) that currently consists of 18 Staff including 6 Postdoctoral Fellows, 5 Research Fellows, 5 PhD Students and 2 Research Assistants. His group has produced research of international standing. His work has also been presented at National and International meetings positively contributing to the reputation of the trust and school.

Role of Lymphoid Chemokines in the Pathogenesis of Sialoadenitis and MALT Lymphomas in Sjögren's Syndrome.

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Sjögren's Syndrome is a common autoimmune disease (0.2-2.1%), second only to rheumatoid arthritis (RA) among autoimmune rheumatic conditions. Much has been learnt in recent years on the pathogenesis of the disease. It is generally accepted that in Sjögren's Syndrome the immune system become aberrantly activated lymphocytes developing an autoimmune response against an unknown antigen(s) (or autoantigen-s) in the salivary and lacrimal glands (the most common exocrine glands affected). This process, mediated by humoral (antibody secreting B-lymphocytes) and cell mediated (cytotoxic T-lymphocytes) response leads to chronic inflammation with glandular damage and secondary dysfunction and the development of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia)[1;2]. One third of Sjögren's Syndrome patients also develops a systemic involvement with articular (wrists and hands) and internal organ (lung, kidney, bladder, oesophagus etc.) involvement. The etiology of Sjögren's Syndrome is unknown, despite a large number of studies have been focused on the detection of viruses, bacteria or other agents possibly involved as primum movens in the formation of the typical periductal lymphocytic infiltrates observed within Sjögren's Syndrome salivary glands. Moreover, the molecular mechanisms regulating the development and maturation of these lymphocytic aggregates within the glands are still unclear. The most severe consequence of Sjögren's Syndrome is the development of a non-Hodgkin lymphoma, more often of the MALT (mucosal associate lymphoid tissue) type occurring in approximately 5% of patients and a 44 fold increased risk in comparison to the normal population. The majority of these tumors developed within the salivary glands and are indolent, rarely degenerating in high grade B cell lymphomas[3]. Lymphomatous clones are believed to derive from the polyclonal B cell clones infiltrating the glands during the inflammatory phase of the disease. This theory has been supported by several findings, linking the B cell clones found in the Sjögren's Syndrome minor glands and the malignant clones found in the lymphomatous parotids and in other sites of lymphomatous dissemination[4;5]. Within Sjögren's Syndrome minor salivary glands these clones are believed to be selected and expanded within ectopic germinal centres (GC), which are structures similar to GC normally present in lymphoid organs and found in a sizable percentage of Sjögren's Syndrome patients[6].

Since these structures are believed to be the site of the antigen-driven immune response ongoing in the glands of Sjögren's Syndrome patients we become interest in the molecular mechanisms involved in their formation as these could then represent potential therapeutic targets. Our hypothesis based on work that ourselves generated in rheumatoid arthritis[7], but reported also in other chronic autoimmune conditions such as inflammatory bowel diseases[8], was that the aberrant expression of molecules belonging to the chemokine (CK) family correlates with the development of ectopic lymphoid structures, involved in the maintenance of the autoimmune process within the inflammatory sites.

CKs are small molecular weight proteins capable, upon ligation with specific CK receptors (CK-Rs) expressed on immune cells, to recruit such cells to lymphoid organs (spleen and lymph nodes) and inflamed tissues. CKs have been also recognized to be involved in lymphoid organ development, maturation and organization[9]. More recently few of these molecules called CXCL13, CCL21 and CXCL12 have been also shown to play a key role in survival and spreading of several lymphoid malignancies. In particular, CXCL13 production has been described in the stomach of patient with Helicobacter Pylori induced MALT lymphomas[10], while CCL21 and CXCL12 have been involved in lymphoid malignancy survival and spreading to metastatic sites[11-14].

In the first phase of our work (partially supported by BSSA) we devised and histological score that allowed us to correlate the degree of cellular organization of the inflammatory infiltrates formed within the salivary glands of Sjögren's Syndrome patients with the ectopic expression of lymphoid CKs. We demonstrated that within the Sjögren's Syndrome minor salivary glands the formation of ectopic lymphoid structures, characterized by the presence of T/B cell segregation (required for lymphocytes interaction), formation of high endothelial venules (functional for naïve lymphocytes recirculation) and fully formed germinal centres (necessary for B cell clones expansion ad selection) are associated with the ectopic production of CXCL13 and CCL21[15]. These data underline the importance of CXCL13 and CCL21 in the formation and development of glandular

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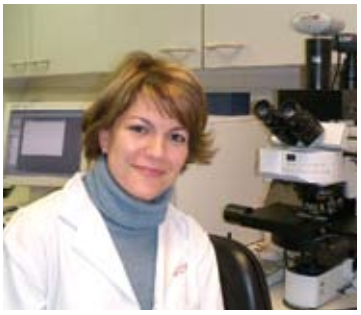
aggregates and consequently in the pathogenesis of Sjögren's Syndrome.

The next question was whether these CK were also involved in the pathogenesis of MALT lymphomas arisen in salivary glands of patients with Sjögren's Syndrome. In this part of our project we demonstrate that, within parotid glands with MALT lymphoma in patients with Sjögren's Syndrome, there are two diverse areas of lymphoid proliferation and these areas are associated with diverse CKs expression. We described a reactive areas characterized by reactive foci similar to those described in Sjögren's Syndrome minor salivary glands and malignant B cell areas. We demonstrated that CXCL13 and CCL21and CXCL21 are aberrantly expressed both at mRNA and protein level and associate with the reactive (non-malignant) component of the lymphoid proliferation. In contrast, CXCL12 was expressed both in the reactive and malignant areas by the cancerous B cells as well as by the infiltrated ducts. We next investigated the nature of CXCL13, CCL21 and CXCL12 producing cells and determined that monocytes/ macrophages are the main producer of the three molecules within the reactive areas both at protein and mRNA level, while MALT- extracted B cells as mentioned above aberrantly produce CXCL12. We finally demonstrated specific CK receptor (CK-R) expression on isolated lymphocytes from MALT samples, suggesting the involvement of these CK/CK-R systems in the migration, organization and survival of MALT-L lymphoid proliferation. All together these findings underline the role of CXCL13 and CCL21 not only in the organization of the ectopic lymphoid formation of aberrant lymphoid structures in SS15 but also in the maintenance of the ongoing local Ag-driven immune response leading to the lymphoma development. On the other hand, the evidence of the extensive CXCL12 production by malignant B cells and ductal epithelial cells suggest that within the glands this CK operated for the survival and spreading of the malignant B cell clones.

In conclusion our work has provided new insight in the pathogenesis of both Sjögren's Syndrome and its most severe consequence (MALT-lymphomas), providing evidence in support of CXCL13, CCL21 and CXCL12 as potential therapeutic targets in these conditions.



Francesca Barone who was funded from the BSSA grant.