ABSTRACT NUMBER: 1903

BTK Overexpression Is Associated with the Risk of Lymphoma in Primary Sjögren's Syndrome: Data from Whole Blood Transcriptome of 346 Patients Followed-up Prospectively for 10 Years

Pierre-Marie Duret[1], Tao Ye [2], Wan-Fai Ng [3], Alain Saraux [4], Valérie Devauchelle Pensec [5], Raphaele Seror [6], Veronique Le-Guern [7], Claire Larroche [8], Aleth Perdriger [9], Jean Sibilia [10], Jessica Tarn [11], Gaetane Nocturne [12], Xavier Mariette [13] and Jacques-Eric Gottenberg [14], [1]Hôpitaux civils de Colmar, COLMAR CEDEX, France, [2]GenomEAST platform / Institut National de la Santé et de la Recherche Médicale (INSERM), U1258, Institut de Génétique et de Biologie Moléculaire, IGBMC, Strasbourg, France, [3]Musculoskeletal Research Group Institute of Cellular Medicine Faculty of Medical Sciences Newcastle University, Newcastle, United Kingdom, [4]CHU de la Cavale-Blanche Brest, Brest, France, [5]University Hospital of Brest, Brest, France, [6]Hopitaux universitaires Paris Sud, Kremlin-Bicetre, France, [7]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France,, Paris, France, [8]Internal Medicine, Paris, France, Paris, France, [9]Rheumatology department, Rennes University Hospital, France, Rennes, France, [10]CHU Strasbourg, Strasbourg, France, [11]Institute of Cellular Medicine Newcastle University, Newcastle, United Kingdom, [12]Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France., Paris, France, [13]Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France, [14]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France

Background/Purpose: To identify a molecular signature associated with lymphomagenesis in primary Sjögren's Syndrome (pSS).

Methods: Whole peripheral blood samples were collected from 346 well-phenotyped pSS patients enrolled in the ASSESS prospective cohort. A transcriptomic analysis was performed using Clariom S Human Arrays (Affymetrix). Patients with a pSS-related Non-Hodgkin lymphoma (NHL) (historic or incident NHL) were compared with 3 control populations: i) Patients without lymphoma and without any risk factor, among 9 validated predictive factors of developing lymphoma (systemic complications, parotid swelling, purpura, lymphocytopenia, CD4/CD8≤0.8, rheumatoid factors, cryoglobulinemia, monoclonal component and low C4 levels) (this comparator limits the risk of including patients who might develop lymphoma later during follow-up); ii)

Patients without lymphoma but with moderate or high systemic disease activity at enrolment (ESSDAI≥5) (this comparator allows to identify relevant predictors in an at-risk population); iii) All patients without lymphoma. We focused on genes that were significantly differentially expressed in patients with lymphomas compared to each of these control populations.

Results: At enrolment, 13 patients had a history of lymphoma. During the 10-year follow-up, 9 patients developed an incident lymphoma. A total of 324 pSS patients had no lymphoma, including 110 patients with an ESSDAI≥5 and 61 patients without any risk factor of lymphoma. Gene Set Enrichment Analysis (GSEA) identified an over-expression of B-cell activation related genes in NHL-pSS, such as BAFF (p=0.007), APRIL (p=0.0009), BCMA (p=0.02) or BTK (p=0.0003) compared to patients without any risk factor of NHL. APRIL and BCMA were significantly up regulated when NHL-pSS patients were compared to all patients without NHL (p=0.002, p=0.04, respectively) but not BAFF (p=0.1). However, the gene expression profile of NHL-pSS patients compared to patients with an ESSDAI ≥ 5 did not show significant over expression of BAFF (p=0.3), APRIL (p=0.2) and BCMA (p=0.2). Conversely, the Bruton Tyrosine Kinase (BTK) gene was over expressed at enrolment, before the occurrence of lymphoma in patients with an incident NHL, in patients with a history of NHL, and in all NHL-pSS patients (either history of or incident) when compared to patients without any risk factor of developing lymphoma (p=0.006, p=0.005 and p=0.0003, respectively), to patients without lymphoma but with an ESSDAI ≥ 5 (p=0.03, p=0.02, p=0.003, respectively) and to all patients without lymphoma (p=0.02, p=0.01, p=0.0008 respectively).

Conclusion: BTK, a pivotal transducer of B-cell receptor, is over expressed in the peripheral blood of pSS patients before the occurrence of lymphoma. Conversely to BAFF, APRIL, and BCMA, BTK over expression is not related to a higher disease activity since BTK is up regulated in patients with lymphoma even when compared to patients with a moderate or high systemic disease activity and no lymphoma. BTK might therefore represent a pivotal pathogenic player in the transition from B-cell polyclonal activation to a monoclonal malignant proliferation. The present results suggest that BTK might represent a therapeutic target of interest in pSS.

Disclosure: P. Duret, None; **T. Ye**, None; **W. Ng**, None; **A. Saraux**, None; **V. Devauchelle Pensec**, Bristol_myers Squibb, 2, CHUGAI, 2, Chugai Pharma France, 8, Roche, 2; **R. Seror**, Bristol-Myers Squibb, 5, GlaxoSmithKline, 5, UCB, 5, Lilly, 5, Pfizer, 5; **V. Le-Guern**, None; **C. Larroche**, None; **A. Perdriger**, None; **J. Sibilia**, None; **J. Tarn**, None; **G. Nocturne**, None; **X. Mariette**, Biogen, 2, Bristol-Myers Squibb, 5, GlaxoSmithKline, 5, Janssen, 5, LFB Pharmaceuticals, 5, OSE Immunotherapeutics, 2, Pfizer, 2, 5, UCB Pharma, 5, 8; **J. Gottenberg**, Abbvie, 8, BMS, 2, 5, Lilly, 5, 8, Pfizer, 2, 5, Roche, 8, Sanofi-Genzyme, 5, 8, UCB, 5, 8.