SIOG 2017 - Abstract Submission

Track 2: Haem malignancies in the elderly and basic science

CLL

O08

TRANSCRIPTION FACTORS (BACH2 AND PRDM1) AND CHECKPOINT INHIBITORS EXPRESSION IN T-LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS AND AGE-MATCHED HEALTHY DONORS.

D. Luan [1], K. Willard-Gallo [2], J.-N. Lodewyckx [2], C. Solinas [2], C. Gu-Trantien [2], S. Garaud [2], H. Duvillier [1], B. Stamatopoulos [1], C. Sibille [3], D. Bron [1,*]

[1]Clinical Hematology Dpt, [2]Molecular Immunology Unit, [3]Anatomo-pathology Unit, Institut Jules Bordet, ULB, Brussels, Belgium

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I submit my abstract to be considered for the following award: None

Introduction: Aging is characterized by a progressive decline in immune surveillance that favors tumor development in older patients. We previously reported *BACH2* gene as a candidate tumor suppressive gene (TSG).

Objectives: We thus examined the expression of specific transcription factors (*BACH2 and PRDM1)* and checkpoint inhibitors (*PD-1* and *PD-L1*) in the major lymphocytes subsets for their potential role in immunosenescence.

Methods: Peripheral blood mononuclear cells were isolated from whole blood using Lymphoprep density gradient centrifugation. Lymphocyte subsets (CD19+, CD3+CD4+; CD3+CD8+) were isolated for subsequent molecular analyses using the MACS Technology (Miltenyi), with the purity of each lymphocyte subpopulation between 95%>99%. PD-1 (*PDCD1*), PD-L1 (*CD274*), *IL4*, *IFNG*, *BACH2* and *PRDM1* mRNA transcripts were quantified using qRT-PCR. *BACH2* and *BLIMP1 (PRDM1)* protein expression were examined by Western blotting.

Results: Blood samples were obtained from 60 healthy volunteers and 41 untreated B-cell chronic lymphocytic leukemia (B-CLL) patients (median: 67yo). Healthy donors (HD) between the ages of 20 to 90 years subdivided into <50 yrs (median: 36yo) and ³50 yrs (median: 65yo).

BACH2 mRNA expression in the HD groups is significantly down-regulated in CD4+, CD8+ T cells and CD19+ B cells from the older HD group (p=0.0012; 0.0045 and 0.0367, respectively). *BACH2* expression was further reduced in CD4+, CD8+ T cells and CD19+ B cells from CLL patients compared to HD well balanced for age (p=0.001; <0.0001 and 0.0043). *PRDM1* mRNA expression was inversely correlated with *BACH2* in $CD4^+$, $CD8^+$ T cells and $CD19^+$ B cells (r=0.61; 0.71 and 0.65, respectively). Curiously, *PRDM1* was – as expected - significantly up-regulated in CD4+ and CD8+ T cells (p=0.0034; p=0.0017) from B-CLL patients but not in their leukemic B cells. Western blotting analysis demonstrated that *BACH2* and *BLIMP1* (*PRDM1*) protein expressions in the T and B cell subpopulations were significantly correlated with transcript expression.

BACH2-deficient mice have been shown to have an increased numbers of *IL4*-producing $CD4^+$ T cells. We also observed that *BACH2* down-regulation is correlated with increased *IL-4* mRNA expression (r=0.67) but not *IFNγ* in $CD4^+$ T cells. These observations suggest that *BACH2* down-regulation in $CD4^+$ T cells could enhance the expression of effector memory-related genes, particularly Th2, such as *IL-4* and *PRDM1*.

PD-1 mRNA expression was up-regulated in $CD4^+$, $CD8^+$ T cells (p=0.0153 and 0.0214) in the older HD group and also up-regulated in the T cells from B-CLL patients (p=0.0014 and 0.0023) when compared to age-matched HD population. High *PD-L1* mRNA expression was correlated with increased age in HD B cells (p=0.04) with a further increase detected in leukemic B cells (p=0.001). We also observed an inverse correlation between *BACH2* and *PD-1* in $CD4^+$, $CD8^+$ T cells (r=0.62 and 0.68); and between *BACH2* and *PD-L1* in $CD19^+$ B cells (r=0.66).

Conclusion: These data suggest that down-regulation of *BACH2/PRDM1* and up-regulation of *PD1/PD-L1* mRNA expression in major lymphocyte subsets from CLL patients and older healthy controls are significantly correlated with the aging immune cells and could be part of the immunosenescence process

Disclosure of Interest: None Declared

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