CHARACTERIZATION OF A NEW METABOLIC SCORE CORRELATED WITH THE CD38 CELL-SURFACE EXPRESSION AND RESPONSE TO DARATUMUMAB TREATMENT IN MULTIPLE MYELOMA

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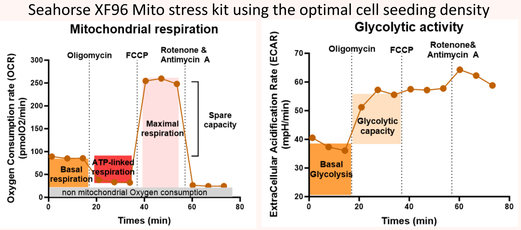
INTRODUCTION AND AIM

Multiple myeloma (MM) is the second most common hematological malignancy characterized by the uncontrolled accumulation of tumor plasma cells within the bone marrow. During the last 10 years, the development of new therapeutics, including the immune based therapies, significantly improved the life quality and survival of patients. However, the clinical heterogeneity of this disease often leads to the development of resistance and relapses. A better understanding, and new strategies to overcome the drug resistance mechanisms linked to Daratumumab remains of major interest for patients care. Among factors that could be involved in myeloma cell resistance to anti-CD38 immunotherapies, we focused on the mitochondrial metabolism, already described as a significant factor influencing response to treatments in several cancers.

METHOD

- Detection of the mitochondrial respiration by measurement of the Oxygen consumption rate (OCR) and the glycolytic activity by measurement of the Extracellular acidification rate (ECAR) with the Seahorse XF96 Mito stress kit using the optimal cell seeding density



- Generation of the Gene expression profile (GEP)-based metabolic score based on 112 genes included 29 glycolytic genes and 83 OXPHOS genes.

Metabolic Score =
∑(Glycolysis genes standardized expression) - ∑(OXPHOS genes standardized expression)

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RESULTS

1. GEP-based metabolic score is representative of the heterogeneous functional metabolic activities in Human multiple Myeloma cell lines (HMCL).

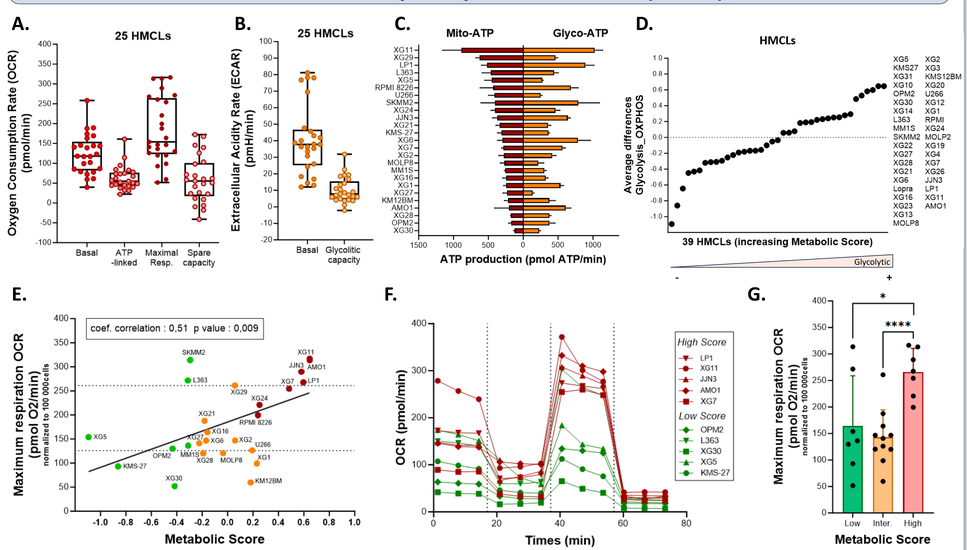

Figure 1: Heterogeneity of the metabolic profiles in HMCLs. A. Basal, ATP-linked, Maximal and Spare OCR are heterogeneous in the 25 HMCLs. **B**. Basal ECAR as well glycolytic capacity are heterogeneous in the 25 HMCLs. **C**. Calculated glycolytic and mitochondrial ATP-production of the 25 HMCLs. **D**. Generation of Metabolic score in 40 HMCLs based on 112 genes including 29 glycolytic genes and 83 OXPHOS genes. **E.** Correlation between functional Maximal mitochondrial Respiration of 25 HMCLs with GEP-Based metabolic score. **F.** OCR representation of the 5 HMCLs with the higher metabolic score compared to the 5 HMCLs with the lower metabolic score. **G.** HMCLs were classified by the quartile method into low, intermediate and high score. HMCLs with a higher metabolic score have higher maximal mitochondrial respiration than HMCLs with in lower metabolic score. *p < 0.05 and ****p < 0.001 analyzed by one-way ANOVA test followed by Tukey's test (means ± SD).

2. High metabolic score values are associated with poor outcomes in MM patients.

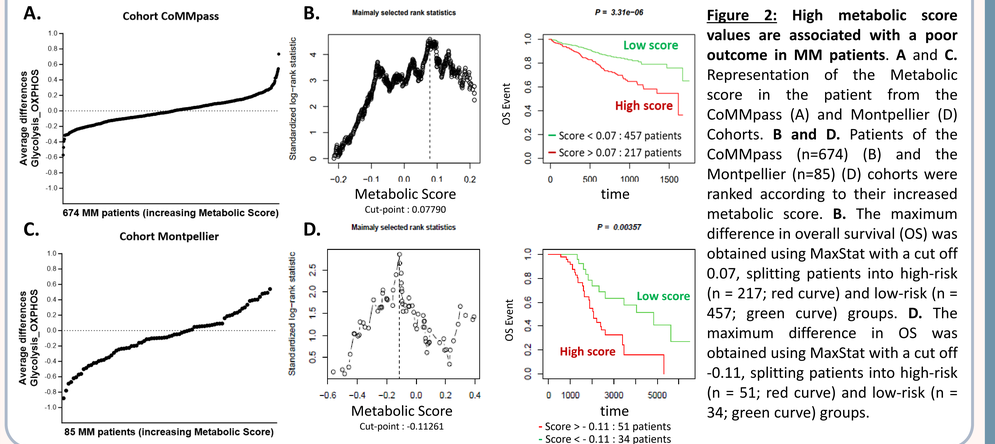

Figure 2: High metabolic score values are associated with a poor outcome in MM patients. **A** and **C.** Representation of the Metabolic score in the patient from the CoMMpass (A) and Montpellier (D) Cohorts. **B and D.** Patients of the CoMMpass (n=674) (B) and the Montpellier (n=85) (D) cohorts were ranked according to their increased metabolic score. **B.** The maximum difference in overall survival (OS) was obtained using MaxStat with a cut off 0.07, splitting patients into high-risk (n = 217; red curve) and low-risk (n = 457; green curve) groups. **D.** The maximum difference in OS was obtained using MaxStat with a cut off -0.11, splitting patients into high-risk (n = 51; red curve) and low-risk (n = 34; green curve) groups.

3. MM patients with low metabolic score show better anti-CD38 Daratumumab treatment responses after relapse and better survival.

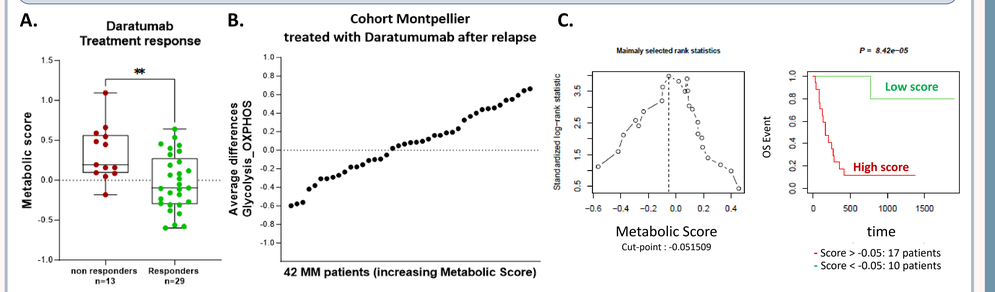

Figure 3: GEP-Based metabolic score as potential prognostic value for Daratumumab treatment. A. MM patients were considered "responders to Dara" if they obtained at least a partial response as a best response to Dara. MM patients were considered "non-responders to Dara" if they had stable or progressive disease. **p < 0.01 was analyzed by two-tailed t-test (means ± SD). **B.** Patients of the Montpellier cohort treated with Dara after relapse (n=42) were ranked according to their increased metabolic score. **C.** The maximum difference in overall survival (OS) was obtained using MaxStat with a cut off -0.05, splitting patients into high-risk (n = 17; red curve) and low-risk (n = 10; green curve) groups.

4. Low CD38 cell surface expression correlates with high functional metabolism in HMCLs and high metabolic score in MM patients.

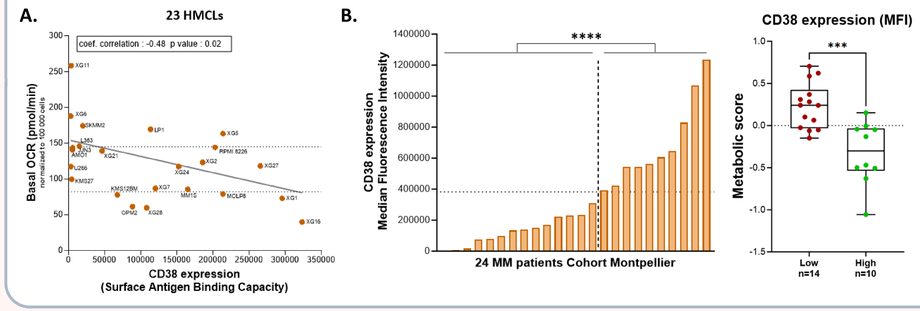

Figure 4: CD38 expression correlates with functional metabolism and metabolic score in HMCLs and MM patients. A Correlation between functional basal mitochondrial Respiration of 23 HMCLs with their respective CD38 expression measure using surface antigen binding capacity by flow cytometry. **B**. CD38 expressions were measured on 24 MM patients by flow cytometry (median fluorescence intensity/MFI). Patients were separated into 2 groups (low and high expression) via their CD38 expression MFI mean. ***p value < 0.001 and ****p value < 0.0001 were analyzed by two-tailed t-test (means ± SD).

CONCLUSIONS

Altogether, our data demonstrated that metabolism dysregulation is associated with a prognostic value in newly diagnosed MM patients. Furthermore, we also reported a link between MM cell metabolism, CD38 expression, and response to anti-CD38 MoAb treatment.