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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Characterization of a New Metabolic Score Correlated with CD38 Cell-Surface Expression and Response to Daratumumab Treatment in Multiple Myeloma

Alizée Steer, PhD[1,2], Elina Alaterre, PhD[1], Djamila Chamlal[1], Emmanuel Varlet[3], Amélie Machura[1], Alboukadel Kassambara, PhD[4], Guilhem Requirand[5], Nicolas Robert[5], Laure Vincent, MD[6], Charles Herbaux, MD PhD[7], Hugues De Boussac, PhD[1], Angélique Bruyer[1], Jerome Moreaux, PhD[8,3,9]

[1] Diag2tec, Montpellier, France
[2] Institute of Human Genetics, CNRS, The French National Centre for Scientific Research, Montpellier Cedex 5, France
[3] Institute of Human Genetics, CNRS, Montpellier, France
[4] Diag2tec, Montpellier, FRA
[5] Department of Biological Hematology, Montpellier University Hospital Center, Laboratory for Monitoring Innovative Therapies, Montpellier, France
[6] Department of Clinical Hematology, Montpellier University Hospital Center, Montpellier, France
[7] Clinical Hematology Department, Montpellier University Hospital, MONTPELLIER, France
[8] Faculty of Medicine, University of Medicine, Montpellier, France
[9] Laboratory for Monitoring Innovative Therapies, Department of Biological Hematology, Montpellier University Hospital Center, Montpellier, France

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 high molecular and clinical heterogeneity of this disease often leads to the development of resistance and relapses. Thus, MM unfortunately remains without definitive treatment in the majority of cases.
Although few studies described the mechanisms of resistance to therapies developed by myeloma cells, a better understanding and new strategies to overcome the drug resistance mechanisms linked to Daratumumab remains of major interest for patients care. Among the factors that could be involved in myeloma cell resistance to anti-CD38 immunotherapies, we focused on the mitochondrial metabolism in MM, already described as a significant factor influencing response to treatments in several cancers.
First, we defined a metabolic score using RNAseq data from different MM models, calculated with the gene expression of 112 genes involved either in the electron transport chain (Oxphos) or glycolysis. Each gene expression value was standardized and the metabolic score was built using the following equation: score= Σ(Glycolysis gene standardized expression) - Σ(Oxphos gene standardized expression). In our unique panel of 40 Human myeloma cell lines (HMCLs), high metabolic score significantly correlated with the functional metabolic profiles assessed by a Seahorse XFe96 analyzer included high mitochondrial and glycolysis activities on 25 HMCLs ($r=0.6$, $p<0.05$).
Moreover, we tested the potential prognostic value of this metabolic score using cohorts of newly diagnosed MM patients treated by high dose of chemotherapy and autologous hematopoietic stem cell transplantation. In the MMRF CoMMpass cohort (674 patients), 32% of the patients with high metabolic score, defined using maxstat algorithm, were associated with a poor outcome (score>0.07; $p<0.0005$). These results were validated in an independent cohort of MM's patient (85 patients, Montpellier cohort), with a significant poor outcome associated with a high score ($p<0.0005$). Furthermore, we calculated the metabolic score in a cohort of MM's patients at diagnosis, who were then treated with anti-CD38 MoAb Daratumumab after relapse (Montpellier cohort N=42). Interestingly, we observed a significant difference between the mean score of patients with progressive or stable disease (n=13, mean score of 0.3380) and the mean score of patients with very good partial response or complete response (n=22, mean score of -0.0703), $p<0.005$). To validate these observations, the potential prognostic value was tested in that cohort: patients with high metabolic score were associated with a poor outcome (score>0.08; $p<0.0005$) suggesting a potential role of metabolism in the response to Dara treatment.

We next questioned the possible link between the CD38 expression level at the surface of MM cells and their metabolic profile. For that purpose, we determined the CD38 surface antigen binding capacity (SABC) on 23 HMCLs representatives of MM heterogeneity. We observed a significant anti-correlation between the CD38 expression and the basal oxygen consumption rates (OCR) ($r=-0.5$, $p<0.05$) quantified with seahorse. Currently, correlations between CD38 expression measured on primary samples from patients with MM (MFI values) and their respective metabolic score are ongoing. However, these data suggest a link between mitochondrial activity, CD38 cell-surface expression and response to anti-CD38 MoAb.
Altogether, our data demonstrated metabolism deregulation 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.

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