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POSTER ABSTRACTS

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

Lipid-Mediated Modulation of DNA Damage Signaling As a Prognostic and Therapeutic Strategy Against Multiple Myeloma

Elvira Garcia De Paco[1,2], *Caroline Soulet*[3], *Guilhem Requirand*[4], *Nicolas Robert*[4], *Guillaume Cartron*[5,6,7], *Laure Vincent, MD*[8], *Charles Herbaux, MD PhD*[9,10], *Maria Moriel-Carretero*[3], *Jerome Moreaux, PhD*[11,12,13,14]

[1] Institute of Human Genetics, Centre National de la Recherche Scientifique, Montpellier, France
[2] Department of Biological Hematology, CHU Montpellier, Montpellier, France
[3] Centre de Recherche en Biologie Cellulaire de Montpellier, Centre National de la Recherche Scientifique, Montpellier, France
[4] Department of Biological Hematology, Montpellier University Hospital Center, Laboratory for Monitoring Innovative Therapies, Montpellier, France
[5] Dept. Biological Hematology, Montpellier University Hospital Center, Montpellier, FRA
[6] Clinical Hematology Department, Montpellier University Hospital Center, Montpellier, France
[7] IGMM UMR 5535 CNRS UM, University of Montpellier, Montpellier, France
[8] Department of Clinical Hematology, Montpellier University Hospital Center, Montpellier, France
[9] Faculty of Medicine, University of Montpellier, Montpellier, France
[10] Clinical Hematology Department, Montpellier University Hospital, MONTPELLIER, France
[11] Faculty of Medicine, University of Medicine, Montpellier, France
[12] Institut Universitaire de France, Paris, France
[13] Institute of Human Genetics, CNRS, Montpellier, France
[14] Laboratory for Monitoring Innovative Therapies, Department of Biological Hematology, Montpellier University Hospital Center, Montpellier, France

Multiple myeloma (MM), characterized by the accumulation of tumor plasma cells in the bone marrow, is the second most common hematologic cancer. Occurrence of chemoresistance invariably leads patients to relapse and results in loss of clinical control over the disease. Cancer cells show a deregulation of different pathways, including lipid metabolism alterations and high genomic instability. Yet, no functional relationship between these two features has been identified. We have shown in a previous work that the metabolism of lipids impacts in how DNA damage is detected, signaled and repaired (Ovejero et al 2023 EMBO J). We reported that breaks in the DNA trigger the birth of lipid droplets (LD), a central lipid-storage organelle, and that this event is key for cells to tolerate this specific DNA damage. Given that MM cells are particularly dependent on DNA repair pathways for survival, we postulated that new therapeutic perspectives would emerge by targeting the formation of LD.

Analysis of the LD formation gene expression profile of a cohort of newly diagnosed MM patients (UAMS-TT2 MM cohort, n = 345) allowed the establishment of a LD ^{score} comprising 13 genes associated with a significant prognostic value after multiple testing correction. The LD ^{score} gene expression-based risk score enabled the identification of MM patients with a poor outcome. The prognostic value of the LD ^{score} was validated in two other independent cohorts of newly diagnosed patients (HM cohort, n = 206; UAMS-TT3 MM cohort, n = 158) and in a cohort of patients at relapse treated with anti-CD38 MoAb (Mtp-Dara, n = 49).

We subsequently studied the presence of LD in primary MM cells obtained from 34 patients. Importantly, we observed a significant positive correlation between the percentage of LD-positive cells and the value of the LD ^{score} (p = 0,02).

This prompted us to investigate the therapeutic interest of interfering with LD formation to target MM cells. To this end, we treated 26 Human Myeloma Cell Lines (HMCLs) with drugs selected on an educated-guess basis and identified positive hits. These results were validated employing a shRNA strategy in selected HCMLs.

Flow cytometry analyses revealed that this regime triggered a cell cycle halt, where cells accumulated in the G_1 phase at the expense of S and G_2. This was accompanied by a decrease in c-MYC expression, as well as an induction of cell proliferation arrest markers such as the G_1-checkpoint CDK inhibitors p21 and p27. Mechanistically, we observed a significant increase in

Chk1 and Chk2 phosphorylations, two downstream events of DNA damage signaling despite that basal DNA damage levels remained unchanged. Together, these data convey the notion that limiting LD formation in MM cell lines boosts the detection of endogenously present DNA damage, thus enforcing a more robust DNA damage signaling which culminates in a drastic loss of proliferative capacity and viability.

Of major importance, we validated the therapeutic interest of this strategy in primary MM cells from patients (n = 19). A significant higher toxicity in MM cells was found compared to normal cells from the microenvironment (tumoral: ****, $p < 0.0001$; normal: ***, p = 0,0006). Moreover, we tested the therapeutic interest of combining this approach with conventional treatments used in MM. Interestingly, we identified a synergistic effect when combined with melphalan, a DNA-alkylating agent used in MM treatment. This synergy was observed in HCMLs and in primary MM cells of patients (n = 7). Furthermore, significant synergistic effects were found in HMCLs by combining with the proteasome inhibitors bortezomib and carfilzomib. Altogether, these data unveil both the LD ^{score} and LD-bearing cell quantification as new prognostic factors in MM, and open new therapeutic perspectives to improve the treatment of MM patients by targeting LD metabolism.

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