MultipleMyelomaHub

General MM

Metabolomic profile of myeloma patients reveals potential new therapeutic targets

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Dysregulated metabolism is a long-described phenomenon of all cancers. In particular, the "Warburg Effect" is the preferred use of anaerobic glycolysis for nutrient production and proliferation in all tumor cells. Metabolic changes have been studied in multiple myeloma (MM) and it was shown that MM cells depend on glucose and glutamine metabolism. Higher levels of certain metabolites were also found in myeloma patients but were lost when patients achieved remission. Alterations in bone marrow (BM) metabolism was found to be an early feature of both monoclonal gammopathy of undetermined significance (MGUS) and MM. Furthermore, targeting glutamine metabolism was found to sensitize cells to Bcl-2 inhibition with venetoclax, and both Lactate Dehydrogenase A (LDHA) and Hypoxia-inducible factor 1-alpha (HIF1α) were found to be targets for drug resistance (eg. bortezomib) under hypoxic conditions in the BM.

Therefore, there is a strong rationale for further analysis of metabolomics in MM. In a study published in PLOS One, Normann Steiner from the Medical University of Innesbruck, and colleagues, examined the metabolomic profile of MGUS patients (pts), newly diagnosed MM pts, and relapsed and refractory (RR) MM pts, and found marked differences between these subsets and healthy controls.

Study Design:

- Pts studied: MGUS = 15 pts, NDMM = 32 pts, RRMM = 19 pts, and healthy controls = 25; pts were defined according to IMWG criteria
- Peripheral blood (PB) plasma levels of 188 endogenous metabolites were assessed by mass spectrometry assay
- Metabolites assessed included: amino acids, biogenic amines, acylcarnitines, glycerophospholipids, sphingomyelins, and hexoses

Key Data:

- Comparisons between healthy controls and MM pts (MGUS+NDMM+RRMM) revealed a distinct metabolic composition of the two populations
- Some differences were observed between MGUS, NDMM, and RRMM pts, but the differences were not as prominent as compared to controls
- Significant overlap between the three patient groups indicates a similar metabolic composition, although intrinsic variations between patients made separating the groups difficult
- Differences in the metabolic profile were evaluated with respect to the known percentage of plasma cells (PCs) in the BM of MM pts
- A total of 18 metabolites were significantly altered between the plasma cell ranges

- These metabolites included: branched-chain amino acids (BCAAs; isoleucine, leucine, and valine), and various medium- and long-chain acylcarnitines (C10, C16 and C18)
- Further statistical analyses were applied to discern differences between the four groups:

Observations in NDMM pts

- Healthy controls *vs* NDMM = 57 metabolites significantly different in NDMM
- Metabolites included: free carnitine (C0), acetylcarnitine (C2) as well as five long-chain acylcarnitines (C14:1, C16, C18, C18:1 and C18:2) all increased in the NDMM group
- Leucine, isoleucine, and valine were in low concentrations, suggesting higher consumption of these metabolites
- Glutamate was significantly increased, compared to healthy controls, suggesting that myeloma cells in the BM either secrete or detoxify glutamate (in line with previous data showing higher levels of glutamate in cancer patients)
- Higher kynurenine/tryptophan ratio was detected (due to increased activity of the kynurenine pathway in which indoleamine 2,3 dioxygenase-1 [IDO1] catalyzes the conversion of tryptophan to kynurenine)
- A total of 8 lysophosphatidylcholines (LysoPCs) were significantly lower
- Of the significantly altered phosphatidylcholines (PCs), 23/25 were increased
- Metabolite differences in acylcarnitines, amino acids, and biogenic amines did not differ between healthy controls, and RRMM or NDMM pts
- In NDMM and RRMM pts, the 13 significantly altered metabolites comprised free carnitine, acetylcarnitine, creatinine, several LysoPCs, and PCs

Observations in RRMM pts

- Healthy controls *vs* MGUS = 36 metabolites significantly different (from a number of different biochemical pathways)
- RRMM *vs* Controls = 32 metabolites significantly altered and long-chain acylcarnitines (C16, C18, C18:1)
- All 3 BCAAs and asymmetric dimethylarginine (ADMA) were increased in healthy subjects
- A higher kynurenine/tryptophan ratio was observed

Observations in MGUS pts

- MGUS *vs* Healthy controls = 36 significant metabolite differences (similar to RRMM and NDMM groups)
- Significantly enriched plasma acylcarnitines (C2, C18, C18:1 and C18:2) as well as kynurenine pathway activation and lower ADMA levels
- Differences between NDMM, RRMM, and MGUS patients were not as prominent as compared to healthy controls group
- NDMM *vs* MGUS = 8 metabolites were significantly altered, including free carnitine, acetylcarnitine, glutamate, ADMA, and 4 PCs species
- RRMM *vs* MGUS patients
- Metabolic profile of pts receiving IMiD-based treatments did not differ significantly from the MGUS group

Conclusions

Differences in the metabolomic profile were identified between MGUS and MM patients compared to healthy controls. The different metabolites identified highlight proteins that could be targeted in myeloma and include the IDO1 enzyme and proteins involved in the glutaminolysis pathway (such as glutamine synthase [GS], cellular glutamine transporter [GLUTs], or oncogenes that regulate this pathway), as well as several others, although further investigations are required to fully establish the link between these metabolites and disease progression. With improved methodologies to identify smaller differences, metabolic profiling may also impact diagnostics and help monitor disease progression.

References

1. Steiner N. *et al*. The metabolomic plasma profile of myeloma patients is considerably different from healthy subjects and reveals potential new therapeutic targets. PLoS One. 2018 Aug 10; 13(8): e0202045. DOI: 10.1371/journal.pone.0202045.