Tumor cells are characterized by high reactive oxygen species (ROS) levels, low mitochondrial content and increased glycolytic capacity. Whereas cancer stem cells are reported to utilize oxidative phosphorylation (OXPHOS) to produce ATP, a metabolic phenotype associated with stemness that constitutes a platform to understand the biology of residual and drug resistant cancer cells.

Previous data:
- Residual multiple myeloma plasma cells (MMPCs)
  - more mitochondria than normal PCs and MMPCs from active disease
  - reduced ROS levels than MMPCs from active disease

To recapitulate the metabolic characteristics of residual MMPCs, myeloma cell lines (MMCLs) were cultured in medium with galactose substituted for glucose to force cells to use oxidative phosphorylation.

- Galactose-conditioned MMCLs:
  - reduced ROS levels
  - increased mitochondrial content
  - Increased sensitivity to drugs that target OXPHOS

Hypothesis: The transition from dormancy to proliferative disease can be detected by determining the metabolic state of residual MMPCs.

INTRODUCTION

Methods

- Detected by FACS:
  - In WBM of primary samples:
    - ROS (DIOCDA),
    - superoxide (DHE),
    - mitochondrial content (Mitotracker)
  - In MMCLs:
    - CD147
    - Glucose uptake (NBDG)

- Serum LDH was used as a marker of glycolytic activity and proliferation.
- Gene expression
  - gene expression profiling (GEP) by microarray
  - qRT-PCR in MMCLs and CD138-selected MMPCs from active disease

The metabolic score (MS) is derived from quartiles for mitochondrial content, superoxide, and LDH. The proportion of the patient population with a high metabolic score increases with disease stage.

RESULTS

Figure 1: A subset of cases with residual MMPCs have elevated ROS levels.

Figure 2: Residual cases with higher ROS levels have increased expression of glycolytic genes.

Figure 3: MM cell lines forced to use OXPHOS have lower glucose uptake, CD147, and HK2 and MYC gene expression.

Figure 4: The metabolic score defines the metabolic state of abnormal PCs and increases with disease stage.

CONCLUSIONS

- Most residual MMPCs have lower ROS and higher superoxide and mitochondrial content.
- A subset of residual MMPCs had higher ROS levels along with elevated Myc, HK2, CD147 and reduced POU2F1 expression, possibly indicating loss of dormancy and transition to active disease.
- Metabolic characteristics of residual disease were recapitulated in galactose-conditioned MMCLs and had reduced Myc, HK2 and CD147 expression and reduced glucose uptake. After Myc inhibition, these parameters were also reduced in MMCLs cultured in standard glucose-containing medium.
- We developed a metabolic score to detect increased glycolytic and proliferative activity and found that it increases with disease stage.
- The metabolic score will be used for precision targeting of residual MMPCs with anti-metabolic drugs and to examine efficacy of predicting progression of residual MM cases based on metabolic changes in prospective studies.

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