P881 CDK7 CONTRIBUTES TO METABOLIC REPROGRAMMING IN MM CELLS THROUGH C-MYC MEDIATED TRANSCRIPTIONAL CONTROL OF GLYCOLYTIC GENES

**Topic:** 13. Myeloma and other monoclonal gammopathies - Biology & Translational Research

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**Background:**

We have recently elucidated the biological role of CDK7 and explore the functional consequence of its inhibition in MM using chemical and genetic approaches. We reported a specific vulnerability in MM cells upon disruption of the CDK7-driven molecular programs, supporting a model where cell cycle and transcriptional deregulation are counteracted by inhibition of CDK7 activity leading to cell cycle arrest and subsequent apoptosis in MM. Importantly, we established that CDK7 positively correlates with c-MYC and E2F1 transcriptional outputs in primary cells from MM patients, suggesting its regulatory role for both transcription factors.

**Aims:**

Bioinformatics analyses of RNA-seq data revealed that CDK7 kinase activity is required for the expression of many components of the glycolytic cascade; in contrast, most genes for OXPHOS were only weakly modulated by YKL-5-124. Interestingly, recent studies have identified CDK7 as an activator of glucose consumption in lung cancer cells, and autosomal dominant polycystic kidney disease. These observations prompted us to delve into the potential role of CDK7 in regulating glucose metabolism in MM cells.

**Methods:**

CDK7 inhibition was achieved with 1. selective covalent inhibitor YKL-5-124; 2. protein degradation dTAG system; 3. inducible KD/KO systems. The transcriptional networks were evaluated by integrated ChIP-seq and RNA-seq data analysis. Metabolic changes were evaluated by ECAR and OCR assessment using Seahorse analyzer.

**Results:**

To evaluate if CDK7 inhibition suppresses glycolysis we assessed control and treated cells during a glycolysis stress test with Seahorse analyzer using extracellular acidification rate (ECAR) as a measure of glycolytic activity. Compared to control, treated cells displayed a significant defect in glycolysis, glycolytic capacity, and glycolytic reserve in a c-MYC dependent manner. These differences in glycolytic activity upon YKL-5-124 treatment were not accompanied by changes in basal oxygen consumption rate (OCR). Similarly to the drug compound, CDK7 protein degradation using dTAG system diminished glycolytic activity, suggesting that CDK7 regulates glycolysis in MM model systems. Evaluation of tumors retrieved from mice after treatment revealed significant reduction in glycolytic activity. Cancer cells catabolize glucose to lactate in aerobic conditions: a sharp time-dependent increase in extracellular lactate release was observed in MM cells over time which was suppressed by YKL-5-124 treatment via regulation of lactate dehydrogenase A (LDHA) expression and enzymatic activity. Together with impairment of aerobic glycolysis, YKL-5-124 treatment resulted in increased ROS levels and induction of apoptotic cell death. The cellular level of ROS is an important oxidative molecule causing endogenous DNA damage. We indeed observed induction of DNA damage as measured by investigation of γH2AX levels after YKL-5-124 treatment. To explore whether YKL-5-124 induced cell death by ROS-mediated mechanisms, we examined the effects of the thiol antioxidant N-acetyl-L-
cysteine (NAC) on MM cells upon YKL-5-124 treatment. NAC treatment prevented ROS production, cell death, apoptosis and DNA damage accumulation induced by CDK7i, indicating a causative link between increased ROS levels upon CDK7i and tumor cell death.

**Summary/Conclusion:** Our data demonstrate that CDK7 through its ability to link cell cycle, transcription and cellular metabolism affects MM cells at several levels, representing an attractive and therapeutically actionable molecular vulnerability in MM.