MULTIPLE MYELOMA DERIVED IL-6 REDUCES FATTY ACID METABOLISM IN THE LIVER BY DOWNREGULATING CD36 AND CPT1A IN HEPATOCYTES

BACKGROUND

Fatty acid metabolism in cancer is altered to promote growth and survival of cancer cells. Multiple Myeloma (MM) cells acquire free fatty acids (FFA) to fuel ATP production by a process known as fatty acid (FA) oxidation (1). Under normal circumstances, the liver processes large quantities of FFA daily and stores only small amounts as triglycerides. This is because when the FFAs are taken up from the plasma, they are processed by re-esterification in the liver. They are then returned to the plasma on one of two forms – either as very-low density lipoprotein (TG-VLDL) which is delivered to muscle or adipose tissue for storage, or as ketone bodies (e.g., acetoacetate or β-OH-butyrate) after FA-oxidation which support metabolism in skeletal muscle and kidneys.

AIMS

The aims of this project were to investigate FFA metabolism in response to MM progression and determine the role of the liver in redirecting FFA to the bone marrow

METHODS

To model MM in vivo we injected 5TGM1$^{(GFP)}$ cells into KaLwRij mice. Blood samples were taken and analysed for FFA content and to measure serum paraprotein levels and verify MM engraftment and IL-6 cytokine levels. Bone marrow was taken and analysed for engraftment using anti-CD138 antibodies and GFP using flow cytometry. Liver tissue was snap frozen and RNA was extracted. Real-time PCR was performed on liver samples to determine expression of genes associated with fatty acid metabolism (CD36, CPT1, PPARA, PPARD and PPARG). For in vitro modelling, primary mouse hepatocytes were co-cultured with conditioned media from 5TGM1 cells or IL-6 cytokine. RNA was then extracted from the hepatocytes and real-time PCR was performed. Seahorse was performed on primary hepatocytes to determine reliance on FFA metabolism.

RESULTS

Analysis of serum from 5TGM1$^{(GFP)}$ engrafted KaLwRij mice showed increased FFA when compared to control animals. Real-time PCR of liver samples showed a significant reduction

in expression of CD36 and CPT1A in MM engrafted animals compared to controls. In vitro modelling showed that primary hepatocytes cultured in conditioned media from 5TGM1 cells had significantly reduced expression of CD36 and CPT1A. We and others have previously shown that IL-6 is upregulated in MM and others have shown that IL-6 can regulate liver FA metabolism (2, 3). Therefore, we explored the role of myeloma derived IL-6 in regulating liver FA metabolism. 5TGM1$^{(GFP)}$ engrafted KaLwRij mice showed increased serum IL-6. Moreover, IL-6 reduced CD36 and CPT1A in primary hepatocytes which was reversed by using the IL-6 neutralising antibody (MP5-20F3). Furthermore, Seahorse analysis showed that primary hepatocytes had decreased reliance on FA oxidation when treated with IL-6.

SUMMARY/CONCLUSION

Here we demonstrate that MM changes FA metabolism in the liver through upregulation of IL-6. Gene expression of FA genes identifies CD36 and CPT1A are down regulated in hepatocytes in response to IL-6. These data suggest that MM is able to redirect FFA away from the liver by down regulating CD36, which mediates FFA uptake in the liver.

REFERENCES

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