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A Metabolic Phenotype in Sarcoma? Repression of Skeletal Muscle Transcription Factor Mondo A (MLX-Interacting Protein)

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Introduction:
MondoA (MLX-interacting protein) is a bHLH transcription factor primarily located in skeletal muscle which drives glucose-dependent pathways such as glycolysis and the expression of TXNIP (thioredoxin-interacting protein). A Mondo-A/TXNIP feedback pathway has been defined previously which is believed to regulate the uptake of glucose by tumours in response to increased glycolysis and production of lactate¹. The aim of this study was to profile MondoA protein expression in muscle-derived sarcomas and to determine how MondoA may interact with pathways associated with the Warburg Effect, lipid metabolism and pathways associated with sarcoma.

Methods:
Immunohistochemical detection and semi-quantitative scoring of Mondo A protein expression was carried out in a commercially available tissue microarray composed of samples of sarcoma of a range of pathologies representing malignant progression versus normal smooth and striated muscle controls (Biomax #S02081). To explore the mechanistic basis of these observations, a statistical analysis of MondoA mRNA expression was carried out using data from a study involving human samples of sarcoma (data mined from Oncomine, Compendia Biosciences)². From this data, the top 200 correlates with MondoA were calculated and Ingenuity Pathway Analysis® used to compile a network for comparison with key pathways involved in sarcoma and muscle development.

Results:
IHC revealed a significant trend for decreased expression of Mondo A in sarcoma relative to normal tissue (One way ANOVA, P =<0.001) (figures 1 and 2A).

Meanwhile, distribution of Mondo A mRNA (figure 2B) also showed a trend for under expression with malignancy, although levels were highest in GIST tumours. MondoA correlates were represented in key pathways associated with sarcoma (P = 8.00E-4) and skeletal and muscle disorders (P = 5.1E-05) and reflective of the function of MondoA as a glucose-responsive transcription factor, with significant representation of gene correlates in pathways involved with energy production (P =3.37E-21 - 1.09E-02), lipid (P = 3.37E-21 - 1.47E-02) and carbohydrate metabolism (P = 4.81E-11 - 1.47E-02). Further network analysis via the Ingenuity Knowledge Base indicates that MondoA interacts with pathways mediated by PPARalpha and gamma, Mix and TXNIP (figure 3).

Conclusion:
MondoA may behave as a tumour suppressor in sarcoma, by interfering with the increased demands for glycolysis and fatty acid production in malignancy. This effect may be partially mediated via the MondoA target gene TXNIP.