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Original Citation

Bishop, Emily, Yusuf, Alex, Stephenson, John and Airley, Rachel (2013) A metabolic phenotype in sarcoma? Repression of skeletal muscle transcription factor mondo A (Mlx- Interacting Protein). In: 2nd International Conference on Tumor Microenvironment and Cellular Stress: Signaling, Metabolism, Imaging and Therapeutic Targets, September 27-October 2, 2013, Corfu, Greece. (Unpublished)

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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 lactate[1]. 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:

Immunohostochemical 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*).

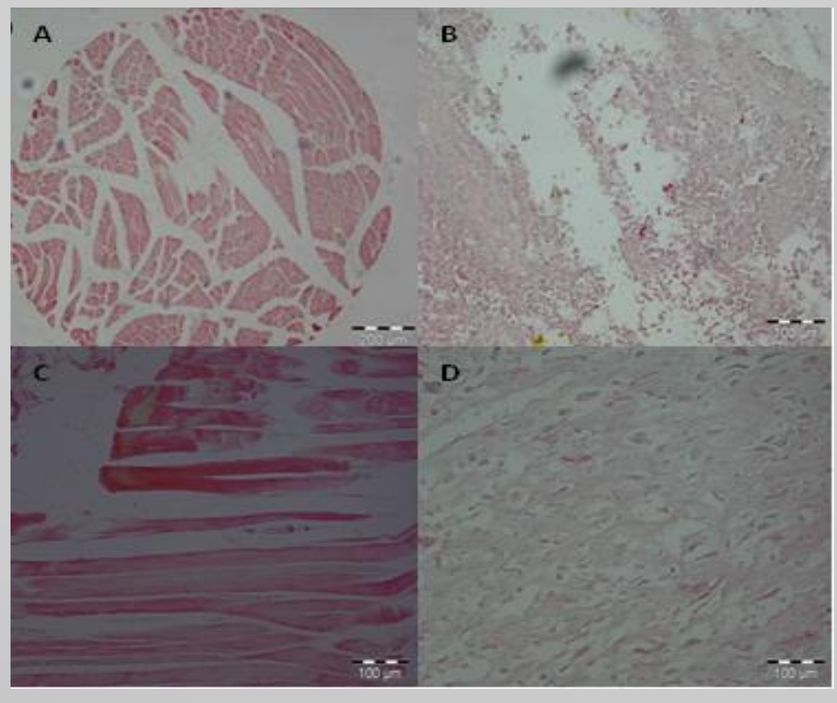

Figure 1: Mondo A (Fast Red) immunohistochemistry showed underexpression of the protein in muscle-derived sarcomas relative to normal tissue. (A) normal smooth muscle; (B) high grade malignant leiomyosarcoma;(C) normal skeletal muscle; (D) pleiomorphic rhabdomyosarcoma.

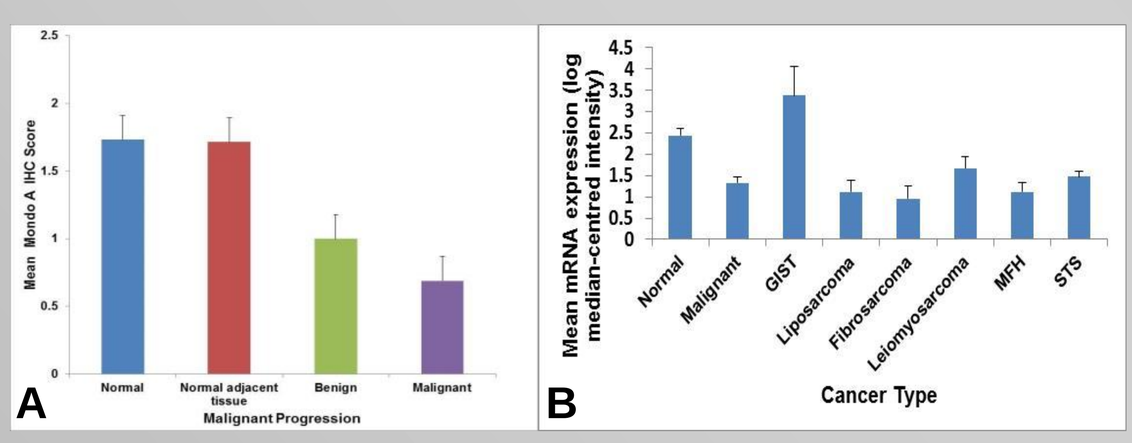

Figure 2: Relationshop between MondoA and malignant progression is shown in (A) and with cancer type in (B).

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, Mlx and TXNIP (*figure 3*).

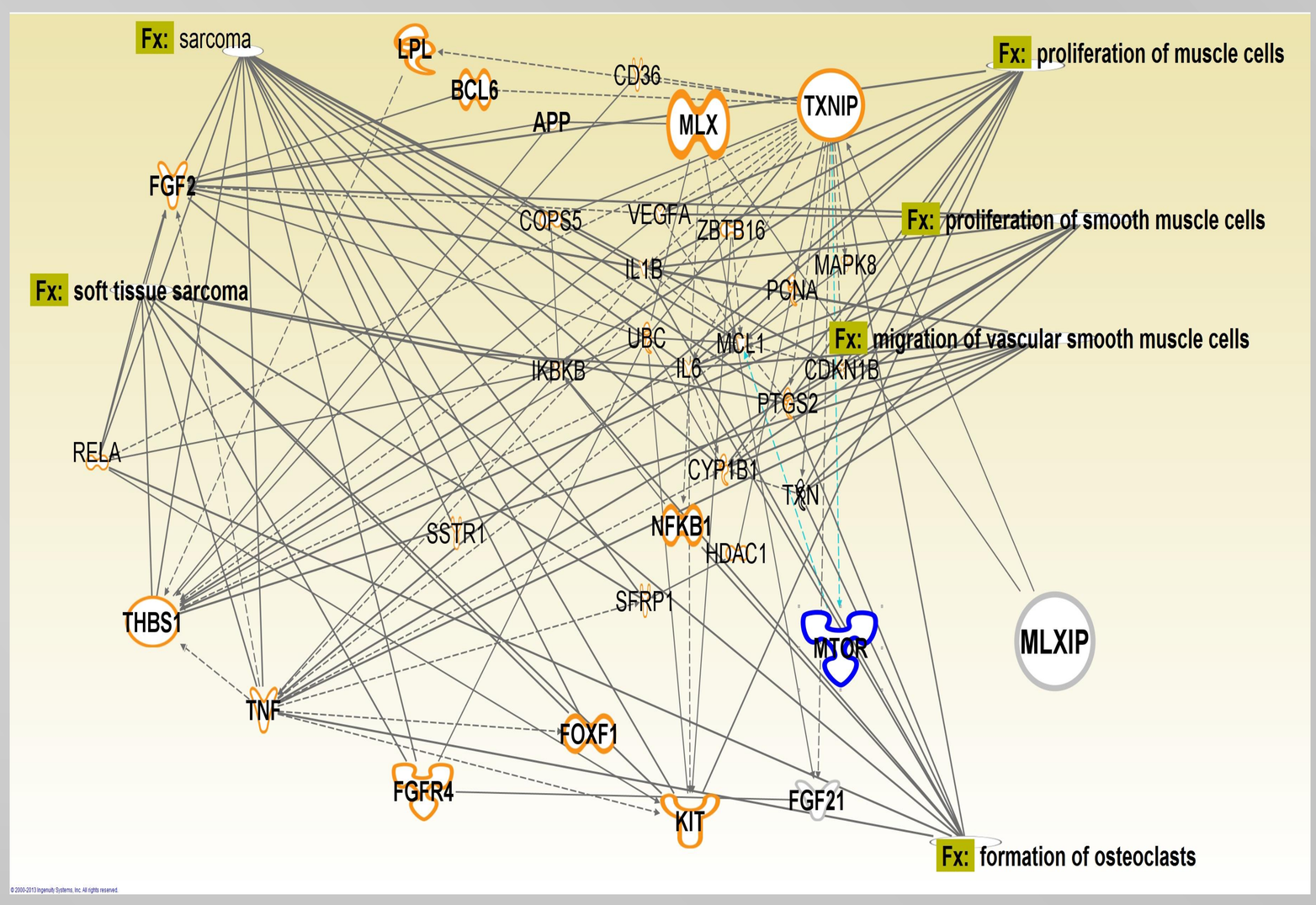

Figure 3: Network analysis (Ingenuity Knowledge Base) showing relationships of MondoA with up- and downstream mediators associated with sarcoma.

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.

References:

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2. Detwiller KY, Fernando NT, Segal NH, Ryeom SW, D'Amore PA, Yoon SS. (2005) Cancer Res, 65:5881-9.