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Can Immunohistochemical characterisation of liposarcoma guide the selection for novel therapy based on the P53 – MDM interactions?

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Background
Inactivation of wild type P53 by its main cellular inhibitors (MDM2 and MDMX) is a well recognised feature of tumour formation in liposarcomas. MDM2 over-expression has been detected in approximately 80% of liposarcomas but only limited information is available about MDMX over-expression. To date, we are not aware of any study that has described the patterns of MDM2 and MDMX co-expression in liposarcomas. Such information has become more pertinent as various novel MDM2 and / or MDMX single and dual affinity antagonist compounds are emerging as an attractive means of potential targeted therapeutic strategies.

Methods
After obtaining the appropriate ethical approvals and with informed consents, we analysed a series of 61 cases of fully characterised liposarcomas of various subtypes by immunohistochemistry to assess the simultaneous expression levels of P53, MDM2 and MDMX.

Results
50 cases over-expressed MDM2 and 42 of these co-expressed MDMX at varying ratios. The relative expression levels of the two proteins with respect to one another were subtype-dependent. This directly affected the detected levels of P53 in two distinct patterns. Diminished levels of P53 were observed when MDM2 was significantly higher in relation to MDMX, suggesting a dominant role for MDM2 in the degradation of P53. Higher levels of P53 were noted with increasing MDMX levels suggesting an interaction between MDM2 and MDMX that results in a reduced MDM2 efficacy in degrading P53. Despite the different genetic alterations involved in the cancerous transformation of the different subtypes of liposarcoma, it is striking that the above patterns applied to all subtypes with a statistically significant negative correlation between MDM2:MDMX ratio and P53 expression ($p<0.001$).

Conclusion
The results suggest that dynamic complex interactions between MDM2 and MDMX proteins may directly affect the cellular expression levels of P53. This therefore invites careful characterisation of these markers in tumours when considering in-vivo experimental evaluation of novel blocker compounds for MDM proteins as a therapeutic strategy to restore wild type P53 functions.

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