Author's response to reviews

Title: Macrophage migration inhibitory factor engages PI3K/Akt signalling and is a prognostic factor in metastatic melanoma

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Author's response to reviews:

Dear Editor,

On behalf of all contributing authors, I submit our attached manuscript entitled “Macrophage migration inhibitory factor engages PI3K/Akt signalling and is a prognostic factor in metastatic melanoma” by Oliveira et al. The work represents original research, is not previously published and has not been submitted for publication elsewhere.

A major theme of our collective team involves understanding the inherent drug resistance of melanoma, a problem representing a major barrier to the efficacy of clinical treatments. The sustained activation of the MAPK and/or Akt pathways is characteristic of most melanomas and this feature has been associated with their inherent drug resistance. At least in terms of the MAPK pathway, this has been recently exploited through the development and application of inhibitors targeting mutated BRAF that occurs in ~50% of patients. The initial success of these agents has re-vitalised the melanoma field but problems have been encountered with the appearance of acquired resistance. Thus the overall approach to melanoma treatment is likely to benefit from identifying alternative molecular targets.

In the present study we examine the role of the atypical cytokine MIF in human melanoma; from the prognostic perspective in clinical specimens and the assessment of its biological role using cultured melanoma cells. Utilising microarray data containing analyses of mRNA expression in melanoma tissues we were able to establish that high levels of MIF mRNA in melanoma was prognostic for faster disease progression. The data utilised contained both
primary and secondary lesions with the effects of poorer outcome appeared in the cases of metastatic disease. These findings likely preclude further investigations of MIF as a predictive marker in primary tumours, but importantly it does establish a clear interest in the biological roles of MIF in melanoma. In particular it suggests that high levels of MIF may act to drive progression in more aggressive cases of the disease.

In complementary work we investigated the possible mechanisms whereby MIF expression may influence the biological behaviour of melanoma cells. We found that depletion of MIF levels using siRNA affected the growth and viability of human melanoma cells. Notably a significant reduction of cells entering S-phase was observed after MIF depletion in a high proportion of melanoma cell lines (4/6). Accompanying alterations in the levels of cell cycle regulatory proteins occurred where MIF depletion changed the growth characteristics. Moreover there was a correlation observed between the effectiveness of MIF knockdown in reducing melanoma cell cycle progression and the effects on the activation status of Akt. This suggests the actions of MIF are significant for a high proportion of melanomas with effects exerted through the Akt pathway.

These findings have implications for treating melanoma through the Akt pathway where elements of the MIF signalling axis comprise therapeutic targets. Additionally as significant effects of MIF depletion were encountered in cells irrespective their BRAF mutational status, targeting MIF signalling in combination with MAPK targeting might also be considered to counter the effects of both oncogenic pathways.

We fully anticipate our work will stimulate the interest of the readership of your journal.

Yours sincerely

Rick Thorne