Introduction

Melanoma is highly aggressive malignancy with an exceptional ability to develop resistance. Inhibitor of apoptosis proteins (IAPs) play a key role in preventing cell death by apoptosis. IAPs are highly regulated by endogenous antagonists (e.g. SMAC) but in melanoma, expression levels of IAPs are generally high and depleting IAPs tended to reduce cell viability, with XAP reduction having the greatest effect [1]. Cancer Stem Cell (CSC) populations are more apoptosis resistant than the bulk cell population and they have been associated with resistance to cancer therapy, relapse and disease progression. Blockade of the apoptotic pathway by up-regulation of anti-apoptotic factors has been implicated in conferring resistance in CSC fractions and increased XAP expression has also been reported in these cells [2-3]. Here we have set out to determine whether our more potent dual cIAP/XIAP antagonists have enhanced apoptosis-inducing capacity on melanoma CSC-like fractions.

First generation of IAP antagonists

- All candidate molecules in development have been derived via peptidomimetic approach based on SMAC peptide sequence (AIP), which contains an alanine warhead and has a selectivity for (AIP) over XAP.

IAP antagonists derived from fragment-based drug discovery

- Balanced cIAP/XIAP
- Non peptidomimetics
- Non alanine warhead
- Oral

At IAP activity in melanoma cell lines and primary tumors

- cIAP degradation observed in all cell lines - sensitive or insensitive
- XIAP degradation in melanoma cell lines is driven by the ability of AT-IAP to switch TNF-α signaling from pro-survival to pro-apoptotic
- TNF-α can be endogenously produced by the cell line
- TNF-α can also be produced by inflammatory cells present in tumour micro-environment

Cancer stem cell populations in melanoma cell lines

- CD133 cells in melanoma show stem-like characteristics (i.e. ability to self-renew and differentiate, and display enhanced tumorigenicity)

Dual antagonist enhances sensitivity of CSC to vemurafenib

- SK-MEL-28 is a BRAF V600E mutant cell line
- Enhanced apoptosis in SK-MEL-28, both total and CSC-fraction, when the dual antagonist Compound 1 is combined with vemurafenib

Conclusions

- AT-IAP and Compound 1 represent a novel class of IAP antagonists with a potent dual cIAP/XIAP antagonist profile
- In vitro live cell line testing suggested significant activity against a panel of melanoma primary tumor and cell lines, which was enhanced on addition of exogenous TNF-α
- Our preliminary studies have shown that AT-IAP has enhanced apoptosis-inducing capacity in melanoma CSC-like fractions
- Combination of IAP antagonist with vemurafenib enhances apoptosis in both total and CSC fractions

References

[1] Engelman et al., Cancer Biology & Therapy, 2011, 12 (1), 47

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