(PS1834) TARGETING THE DNA DAMAGE RESPONSE IN DORMANT MYELOMA CELLS

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background

Multiple myeloma is the second most common haematological cancer in Europe, but it remains incurable due to the prevalence of relapse following therapeutic treatment. Currently approved standard of care therapies often lead to a state of 'minimal residual disease' (MRD), as cancer cells can evade the treatment, causing inevitable relapse. This can be initiated by reactivation of dormant, chemo-resistant myeloma cells. Entry into dormancy is considered a protective mechanism to prolong cellular survival, which may be triggered by DNA damage in myeloma.
No treatments effectively kill dormant cells, so new therapeutics are needed to fill this gap, either to prevent reactivation or to cause complete removal of MRD. Taking advantage of increased levels of DNA damage in dormant myeloma cells may be an unexplored new treatment avenue, with a possibility to exploit changes in the DNA damage response (DDR).

Aims

To determine whether DNA damage levels differ in proliferating and dormant myeloma cells using *in vitro* and *in vivo* (mouse) models.

Methods

Two mouse models were used to measure DNA damage levels. In the first model, ~8-week-old C57BL/KaLwRij immunocompetent mice were i.v. injected with $2x10^6$ DiD-labelled 5TGM1-luc cells and culled 21 days post-injection. In the second model, ~8-week-old NSG immunocompromised mice were i.v. injected with $1x10^6$ DiD-labelled human U266-GFP-Luc cells. When tumour burden was high mice were treated with chemotherapy 50mg/kg lenalidomide and 0.75mg/kg bortezomib. Tumour was monitored via bioluminescent imaging using an IVIS imaging system. Flow cytometry was used to identify dormant myeloma cells by DiD-retention, AXL and p21 expression, and DNA damage was measured by γH2AX staining of bone marrow samples.
In vitro comparisons were made between dormant and proliferating cells cultured for 7 days using flow cytometry, and immunofluorescence staining for γH2AX was performed after FACS sorting for DiD^{Hi} (dormant) and DiD^{Low} (proliferating) cell populations. DNA damage foci were quantified using ImageJ. Activity of DNA damage response inhibitor drugs (olaparib, abemaciclib, berzosertib and Ku55933) on dormant and proliferating myeloma cells was assessed using resazurin viability assay after 1 week of treatment.
Expression of DDR genes were analysed using publicly available single cell RNA seq data (SRA: PRJNA453652).

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Results

NSG and C57BL/KaLwRij models exhibited significantly increased levels of DNA damage (γH2AX+) in dormant compared to proliferating populations. This was supported by *in vitro* experiments where γH2AX foci were significantly higher in the DiD-high (dormant) groups compared to DiD-low (proliferative) in both human and mouse cell lines, indicating dormant myeloma cells have higher levels of DNA damage.
Abemeciclib (CDK4/6 inhibitor), berzosertib (ATR inhibitor) and Ku55933 (ATM inihibitor) dose-dependently inhibited viability in proliferating cells. PARP inhibitor olaparib reduced viability in BRCA deficient 5TGM1 cells, but not U266 cells.
DDR gene expression profiles between dormant and proliferative myeloma cells were comparable. However, gene expression does not represent potential activity levels and low input phospho-proteomics is being used to observe changes in activation between different cellular states.

Summary/Conclusion

Dormant myeloma cells exhibit higher levels of DNA damage across modelling approaches. Thus, targeting the DNA damage response is a promising approach to target chemo-resistant dormant myeloma cells.

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