Loss-of-function of GABARAP drives tumor resistance to bortezomib-induced immunogenic cell death in multiple myeloma

18th International Myeloma Workshop

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Disclosure

- I do not have conflicts of interest
Overcoming immune dysfunction in myeloma

Bortezomib induces calreticulin-dependent immunogenic cell death (ICD) in MM

1. Cell death and DAMPs emission

2. DCs recruitment and maturation

3. T cell recruitment and priming

Gulla A et al. (2021) Blood Cancer Discov
Bortezomib-induced ICD stimulates a potent antitumor immune response \textit{in vivo}.
Clinical benefit of ICD induction in MM patients

To investigate the mechanisms of resistance to BTZ-induced ICD

Gulla A et al. (2021) Blood Cancer Discov
To investigate the mechanisms of resistance to BTZ-induced ICD

- Newly diagnosed MM patients (IFM/DFCI)
  - LongTermSurvival (>5 years) vs. ShortTermSurvival (<1.5 years)
  - differentially expressed genes

- Genes correlated with MM patient OS
- Genes involved in ICD mechanisms

Thielmann Y. et al. (2009) FEBS J.
GABARAP expression levels impact on clinical outcome of MM patients

Patients with low GABARAP, particularly those with del(17p), may not undergo ICD upon BTZ treatment

No patients with del(17p)
BTZ does not induce ICD in low-GABARAP MM cells
GABARAP KO blocks CALR exposure upon BTZ in MM cells

Calreticulin

GABARAP KO

GAPDH

GABARAP

GABARAP add-back

Calreticulin

WT: #709 #993

5 nM BTZ

GABARAP KO + ADD-BACK GABARAP

GAPDH

#6

#7

AMO1

AMO1 W T

AMO1 GABARAP KO

#2 #6 #7

* *
GABARAPKO abrogates phagocytosis by DCs by inhibiting CALR exposure.
GABARAP$^{KO}$ antagonizes BTZ-induced anti-tumor T cell response
GABARAP\textsuperscript{KO} cells treated with BTZ fail to protect against tumor rechallenge \textit{in vivo}.
Conclusions

- Loss-of-function of GABARAP, particularly in high-risk patients with 17p deletion, blocks CALR exposure upon BTZ treatment thus contributing to tumor immune evasion and ICD resistance.

- These studies provide the framework for novel combination treatments to restore anti-MM immunity and improve patient outcome in HR MM.
Acknowledgement

Anderson lab
K. Anderson
T. Hideshima
M. Johnstone
L. Yamamoto
K. Kurata
G. Bianchi
D. Chauhan
Y. Tai
K. Wen
All lab members

Munshi lab
N. Munshi
E. Morelli
M. Kemal Samur
M. Fulciniti
R. Prabhala
S. Talluri
All lab members

Myeloma
Clinical Team
P. Richardson

Translational
Immunogenomic Lab
D. Keskin

Carrasco lab
R. Carrasco
T. Sewastianik

Hematologic Neoplasia
Flow Cytometry
Susan Lazo

All patients of IFM/DFCI clinical study!!