A murine model for immunotherapy against multiple myeloma

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Challenges in myeloma immunotherapy

• Widely disseminated
• Complex tumor stroma
• Tumor cells are actively immunosuppressive
  - B cell origin
  - Key mechanisms not fully established
• Disease relapse is common
• Immunological impact of conventional treatment largely unknown
Why mice?

MOPC315
Mineral-oil-induced plasmacytoma

Serial in-vivo passage
- Bone marrow homing
- Development of paraplegia

MOPC315.BM
Idiotype-specific T cells

Antigen-presenting cell -> Id-specific CD4+ T cell

IFN-γ

T cell receptor transgenic mouse

M315 (Id)

λ2315 light chain

Id peptide recognized on MHC class II
Adoptive T-cell therapy against multiple myeloma

Haabeth et al., Leukemia 2015
Implementation of ACT in current treatment regimens

Open questions:
- T-cell product: CARs, ex vivo-expanded TILs, transgenic TCR?
- Timing of therapy?
- Choice of preconditioning: Melphalan or other chemotherapy? Irradiation?
- Adjunctive treatment: Checkpoint inhibitors, cytokines, IMiDs?
Non-myeloablative melphalan treatment provides a window for T cell therapy

Impact of checkpoint inhibitors

- Heterogeneous expression pattern
- Modest synergy with ACT
- Tumor-intrinsic or microenvironmental effects?
- Other modulatory mechanisms?

** Unpublished data **
CRISPR/Cas9: targeted gene manipulation
Knocking out MHC class II

Haabeth et al., Leukemia 2015
Knocking out MHC class II, cont.

There are APCs in the bone marrow that may be instructed to kill tumor cells

- Which type of cells?
- What is the mechanism of killing?
- Can we find new (*T-cell-independent*) ways of activating them?
Relevant immunosuppressive pathways?

- Mapping relevant pathways in tumor cells and microenvironment
- Ablating individual factors
  - Synergy? Redundance?
  - Effects on spontaneous tumor growth and in immunotherapy setting
Ongoing work

- Identify mechanisms of T-cell immunosuppression in bone marrow by CRISPR/Cas9 screening
- Exploring the potential of TIL-based approaches in myeloma
- Evaluating the effects of IMiDs on T cell phenotype within the bone marrow
Summary: Exciting times!

Treatment regimen

• New and improved T-cell immunotherapy approaches
• New immunostimulatory agents
• Novel drugs with immunomodulatory effects (IMiDs etc.)

Basic research

• Increased understanding of the tumor microenvironment
• Greater understanding of homeostatic mechanisms in T cell responses
• CRISPR/Cas9
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