Ageing and Immune responses to Cancer Vaccination

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Incidence of Cancer

- Incidence: age-related (≥ 50% of patients over 65 years of age)
- Increase in population of elderly
  Increase in mortality
Current Treatment Options and Outcome of Cancer

- Surgical resection or radiation followed by adjuvant treatment or chemotherapy
- Current therapies are ineffective against metastases
- Cancer immunotherapies have an effect on metastases
T Cell Unresponsiveness In Cancer Patients

- Tolerance/Self-antigens
- Genetic instability of tumors: loss of antigen expression
- Immune suppression in the tumor microenvironment
- Ignorance of the age factor
Immune Suppression in the Tumor Microenvironment

- Myeloid-derived suppressor cells (MDSC)
- Tumor-associated macrophages (TAM)
- M2 macrophages
- Foxp3+ macrophages (Joseph Lustgarten)

Manrique et al, JEM 208: 1485-1499, 2011
T cell Unresponsiveness in Elderly

- Decrease in the number of naïve T cells and increase in memory T cells
- Increase in the number of MDSC in the tumor microenvironment at older age
Metastatic Syngeneic Breast Tumor Model 4T1

Injection of tumor cells at young and old age → Development of a breast tumor and metastases

2-4 weeks
Preventive Immunization with pCDNA3.1-Mage-b (improved)

Vaccine: pCDNA3.1-Mage-b  
Thioglycollate: recruitment APC  
GM-CSF: maturation and activation APC  
Immunization: intraperitoneal
Efficacy of Mage-b DNA vaccine

Young mice (3 months)

Old mice (20 months)

n = 15-20 mice
Mann-Whitney p<0.05 significant
Vaccination with Mage-b DNA Induces CD8T cell Responses in vivo at Young but not at Old Age

% of IFN\(\gamma\)-producing cells

Young (3 months)

Old (20 months)

CD8  CD4  Mac  NK  B cells

New Delivery System: *Listeria monocytogenes*

- Triggers potent innate and adaptive immune responses
- Gram positive, facultative, intracellular bacteria
- Phagocytosed by monocytes/macrophages
- Listeriolysin O (LLO), one of the many virulence factors of *LM*, improves immunogenicity
- Enhances antigen presentation and stimulation of naive and memory T cells.
Safety aspects of Listeria (highly attenuated)

- C-terminal site of LLO deleted and mutations in remaining fragment
- Mutations in prfA gene
- Survival time of Listeria bacteria in vivo is only 3-5 days
- Listeria has already used in clinical trials/sensitive for Penicillin and derivates
Immunizations with Listeria-Mage-b

1 preventive/ 2 therapeutic

Vaccine: Listeria-Mage-b
Immunization: intraperitoneal
Listeria Infects Tumor Cells in vivo

Kim et al, 2009, Cancer Res 69: 5860
Myeloid-Derived Suppressor Cells (MDSC)

- Two types: gMDSC (CD11b$^+$Gr1$^{\text{high}}$) and mMDSC (CD11b$^+$Gr1$^{\text{low}}$)

- MDSC strongly reduce T cell activation in the tumor microenvironment, and promote tumor angiogenesis (IL-6, IL-10, TGF$\beta$, Arginase, iNOS, ROS, Stat3, CCL2, CXCL2, MMP-9)