Immunosenescence and cancer
Impact not only for immunotherapy?

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Ageing and Cancer
Age is a major risk factor for many cancers
Usually viewed in the context of the cell biology
but
Cancers are immunogenic, and the immune system can
protect against tumorigenesis
Immunity decreases with age
Decreased immunosurveillance against cancer
contributes to increased disease in the elderly?

Model for immuno-surveillance
The innate immune system first recognises
tumour cells and produces IFN-γ
Inflammatory cascade
causes limited
tumour cell death and
dendritic cells then
transport tumour
products to the
draining lymph node
(Dunn et al., Nature Immunol 2002)

Cancers are immunogenic, and the
immune system can protect against
tumorigenesis
Still controversial but likely to be true

Seminal paper: Adaptive immunity maintains occult cancer in an equilibrium state

Chemotherapy and radiotherapy are effective only
in the presence of an intact immune system?

Chemotherapy and radiotherapy is ineffective in mice without TLR4
TLR4 must be expressed on DC to respond to the „danger“ signal from dying tumour cells
HMGB1 (“alarmin” – nuclear chromatin protein) is the ligand „danger signal“
Breast cancer patients with a TLR4 loss-of-function allele preventing HMGB1 binding relapse more quickly after chemo-radiotherapy

(Apetoh et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy, Nat. Med. 13:1050, 2007)
**Hypothesis:**
All tumours are (initially) immunogenic
Therefore:
Prerequisites for immunosurveillance/immunotherapy of cancer
- Host can respond to tumor antigen
- Antigen is expressed by tumour
- Host immunity damages tumour

**Cancer vaccines**

**Active immunisation:** antigen preparations injected; patient must be immunocompetent
- But the ability to respond is blunted in the elderly

**Adoptive (passive):** antibody or cells infused to patient
- But the aged environment may not support immunity well
- Expanded tumor-specific T cells may already have had to divide too many times in vitro before re-infusion

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**Animal Models – few data available**

Active immunotherapy of cancer is successful in young but not older mice:
- IL-2-transfected mammary adenocarcinoma vaccination protected most young but not old mice against challenge with untransfected cells (Provinciali et al. Gene Ther 7:624, 2000)
- Immunogenic lymphoma rejected by young but not old mice; however, stronger T cell costimulation enables old mice to respond (Lustgarten et al. J Immunol 173:4510, 2004)

**Animal Models – few data available**

Active immunotherapy of cancer is successful in young but not older mice:
- Tumor rejection is efficient in a breast cancer model in young mice, mediated by T cells, but far less efficient in older animals, mediated by innate immunity (Gravekamp et al., Mech Ageing Dev, in press)
- General principle: ageing results in selective loss of adaptive immunity, with better retention of innate
- Hence retention of strong inflammatory responses with age, but now in the absence of the counterbalancing and beneficial effects of the adaptive responses that they normally amplify at younger age may even enhance immunopathology and carcinogenesis.

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**Animal Models of Spontaneous Cancer**

**Less artefactual model:** Her-2/neu transgenic mice spontaneously develop breast cancer; they possess only low avidity T cells specific for Her-2/neu-derived self antigen peptides and are thus a more clinically-relevant model
- Only intratumoral injection of the TLR-9 ligand CpG-ODN plus depletion of T-regulatory cells facilitated tumor control in old mice, but could cure only young mice (Sharma et al. Cancer Immunol Immunother 57:549, 2008)
- Combining this treatment with inhibition of the suppressive factor indoleamine-2,3-dioxygenase (IDO) resulted in 70% mortality – thus, overcoming tolerance and activating anti-tumor responses in young tolerant hosts may kill rather than cure old hosts (Lustgarten, Cancer Immunol Immunother, in press)

**Major challenges for Geriatric Immunotherapy of Cancer**

- Many! Including -
  - Triggering an effective immune response against a pre-existing chronic antigenic stimulatory source
  - Evading the immunoregulatory networks blocking anti-tumor responses which appear to be increased in old individuals (T-regulatory cells, myeloid suppressor cells, IDO levels, inflammatory cytokines)
- These are essentially the same challenges in the young, but the animal models suggest that the problems are greater in the elderly – harder to generate a response, and increased susceptibility to negative effects of therapy
What do we know about human immunosenescence that might help improve chances of successful geriatric cancer control?

Main changes to innate/adaptive immunity interface in ageing

Adaptive immunity over the lifespan

Which immunological parameters are important for successful ageing?

Jönköping OCTO longitudinal studies are determining an “immunological risk profile” predicting mortality in the very old

The IRP is characterised by

- CD4:8 ratio of < 1
- poor T cell proliferative responses
- increased CD8-positive CD28-negative cells
- low B cells
- CMV-seropositivity

CMV seroprevalence by income in the US

CMV seroprevalence very high in the elderly – but nonetheless associated with the IRP

Is there also an association with cancer?

Scattered reports suggest that there might be, but data are scarce:

- With mycosis fungoides and Sézary Syndrome
  (Herne et al., Blood 101:2132, 2003)
- With ovarian cancer (Chan et al., J Clin Pathol 54:48. 2001)
- With cervical cancer (Broccolo et al., J Med Virol 80:147, 2008)
What does CMV do to immunity?

CMV-specific CD8 cells accumulate in the very elderly (>85 yr.)

CD8 cells from HLA-A2 donors bearing a TCR specific for the pp65-HCMV (495-503, NLV) epitope detected in flow cytometry by tetramers

More CMV-specific cells in the IRP category

Age-associated changes to T cell subset distribution

CMV infection is associated with accumulation of the most late-differentiated CD8 cells

.....and decreased CD8+ naive cells

Hypothesis:

Chronic antigenic stimulation by CMV and by cancer antigens is additive and leads to more rapid immune exhaustion and dysbalance in adaptive immunity, which reduces immune capacity for responses to new antigens as well as blunting immune responses (memory) to previously-encountered antigens, including the chronic stressors.
Conclusions

- Elderly are immunocompromised with few naive cells and dysfunctional (exhausted) memory cells, due to chronic antigenic stress and thymic involution
- Persistent infections, especially with CMV, contribute markedly to this immunosenescent state
- Cancer antigens are also likely to have a similar immune-exhausting effect
- CMV (and possibly certain other pathogens) and cancer antigens have additive effects on immune exhaustion

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