Animal models of human oncogenic gamma-herpesvirus infection

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Cell-mediated immune control of EBV

adapted from Taylor et al., Annu Rev Immunol 2015
1. Role of NK cell responses during EBV infection

- Does NK cell depletion alter EBV infection?

- Which program of EBV infection is influenced by NK cell responses?

- Does loss of NK cell mediated immune control predispose for infectious mononucleosis (IM), an immunopathology of massive CD8+ T cell expansion during primary EBV infection?
EBV infection of mice with reconstituted human immune system components

Irradiate new born immunodeficient NOD-scidγc-/- mice with 100cGy

Transplant 1-3x10^5 human CD34+ cells via intrahepatic or intravenous injection

12 weeks

Determine composition of reconstituted human immune system in peripheral blood

intraperitoneal infection with 10^5 RIU EBV for 6 weeks +/- NK cell depletion with αNKp46 antibody

Analyse viral loads, tumor formation and immune compartments longitudinally in peripheral blood and after 6 weeks in the spleen, blood, bone marrow, mesenteric lymph node and tumor microenvironment
NK cell depletion alters lytic EBV infection

wt EBV

BZLF1 KO EBV

Chijioke et al., Cell Rep 2013
NK cell depletion leads to IM-like increased CD8+ T cell expansion during primary EBV infection

Chjioko et al., Cell Rep 2013
Uncontrolled lytic replication leads to weight loss in EBV infected huNSG mice

Chijioke et al., Cell Rep 2013
NK cell depleted mice develop more tumors during EBV infection

NK cell depleted liver

Chijioke et al., Cell Rep 2013
NK cell recognition

Vivier et al., Nat Rev Immunol 2012
Increasing EBV specific immune control by KIR ligand mismatching
Mixed human CD34+ hematopoietic progenitor cell chimeras
Two donors reconstitute side-by-side in huNSG mice

Landtwing et al., J Clin Invest 2016
The NK cell repertoire is not influenced by mismatched HLA in trans

Landtwing et al., J Clin Invest 2016
NK cell education

Höglund and Bodin, Nat Rev Immunol 2010
NK cell education is disarmed by non-cognate HLA in trans

**KIR2DL1**

- **KIR2DL2/3**

- **KIR3DL1**

- **CD94/NKG2A**

*Landtwing et al., J Clin Invest 2016*
Mixed HLA-mismatched chimeras control EBV infection better.

*Data from Landtwing et al., J Clin Invest 2016.*
NK cells are responsible for this improved immune control

Landtwing et al., J Clin Invest 2016
Summary 1:

1. NK cells with an early differentiated NK cell repertoire and HLA mediated education reconstitute in NSG mice and restrict EBV infection in vivo.

2. Plasma virus titers and lytically replicating EBV infected B cells are elevated in NK cell depleted and EBV infected huNSG mice.

3. Loss of NK cell mediated immune control of EBV leads to increased CD8+ T cell expansion during EBV infection, similar to the immunopathology during IM.

4. Lytic replication that is no longer controlled by NK cells leads to weight loss and tumorigenesis in EBV infected huNSG mice.

5. Mixed HLA mismatched NK cell reconstitution allows inefficient KIR engagement and better EBV specific immune control.
In vivo model of EBV infection and immune control

- EBV establishes persistent infection in mice with reconstituted human immune system components. This infection is controlled by T cells with contributions of CD4+ and 2B4+ CD8+ T cells.


- DC targeted vaccination can elicit low level T cell responses and the reconstituted human DC compartment can be investigated for its reactivity towards adjuvant candidates in this in vivo model.

  Gurer et al., Blood 2008; Meixlsperger, Leung et al., Blood 2013

- Innate leucocyte compartments are established and functional. NK cells can target MHC class I negative tumor cells in these mice. These NK cell responses restrict lytic EBV infection and infectious mononucleosis symptoms in vivo.

  Strowig, Chijioke et al., Blood 2010; Chijioke et al., Cell Reports 2013; Landtwing et al., J Clin Invest 2016

- Mutant EBV and novel strain infections phenocopy clinical manifestations in patients, including tumorigenesis. The in vivo model allows to characterize polymorphisms in the viral genome with respect to infection and immune control in vivo.

  White, Rämer et al., J Clin Invest 2012; Tsai et al., Cell Reports 2013
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