Discussion of natural killer cells and innate immunity

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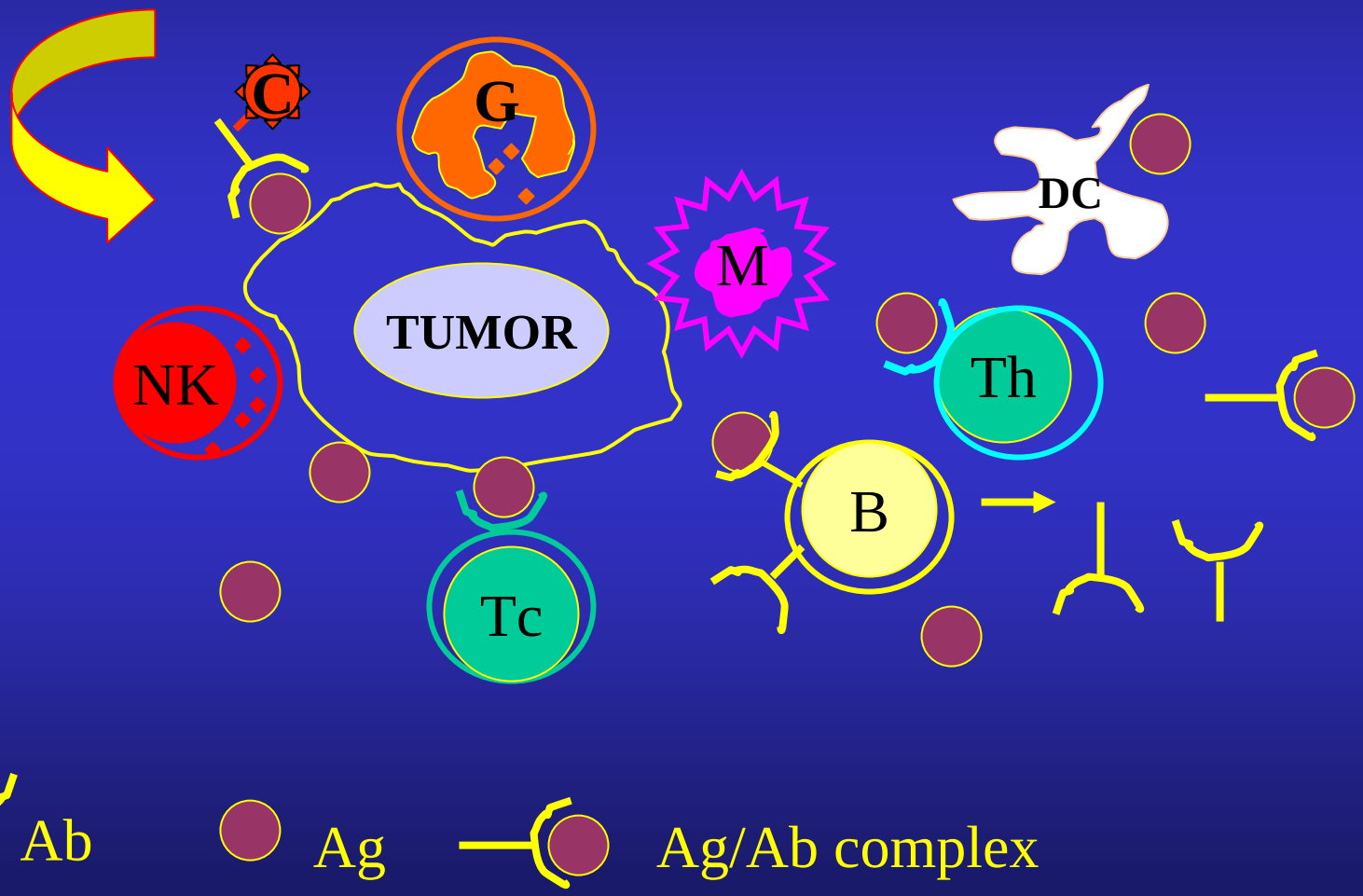
Myths in tumor immunology

- Cancer cells are ignored by the immune system
- Immune responses are directed only against “unique” antigens expressed on tumor cells
- Tumor-specific T cells alone are sufficient for tumor regression
- Tumor are passive targets for anti-tumor responses

Tumor/Immune Cells Interactions

Tumor cell death



NK cells as anti-tumor effectors

- LGL, no TCR, express FcγRIII, other activating receptors and KIRs
- Spare normal cells but kill a broad range of tumor cells *ex vivo* by at least two different mechanisms
- Produce a number of cytokines (IFN-γ, TNF-α)
- Constitutively express IL-2Rβγ and rapidly respond to IL-2 and also to IL-15 and IFNα/β
- Regulated by a balance of inhibitory receptors specific for MHC class I antigens and activating signals
- NK-DC interactions at sites of inflammation

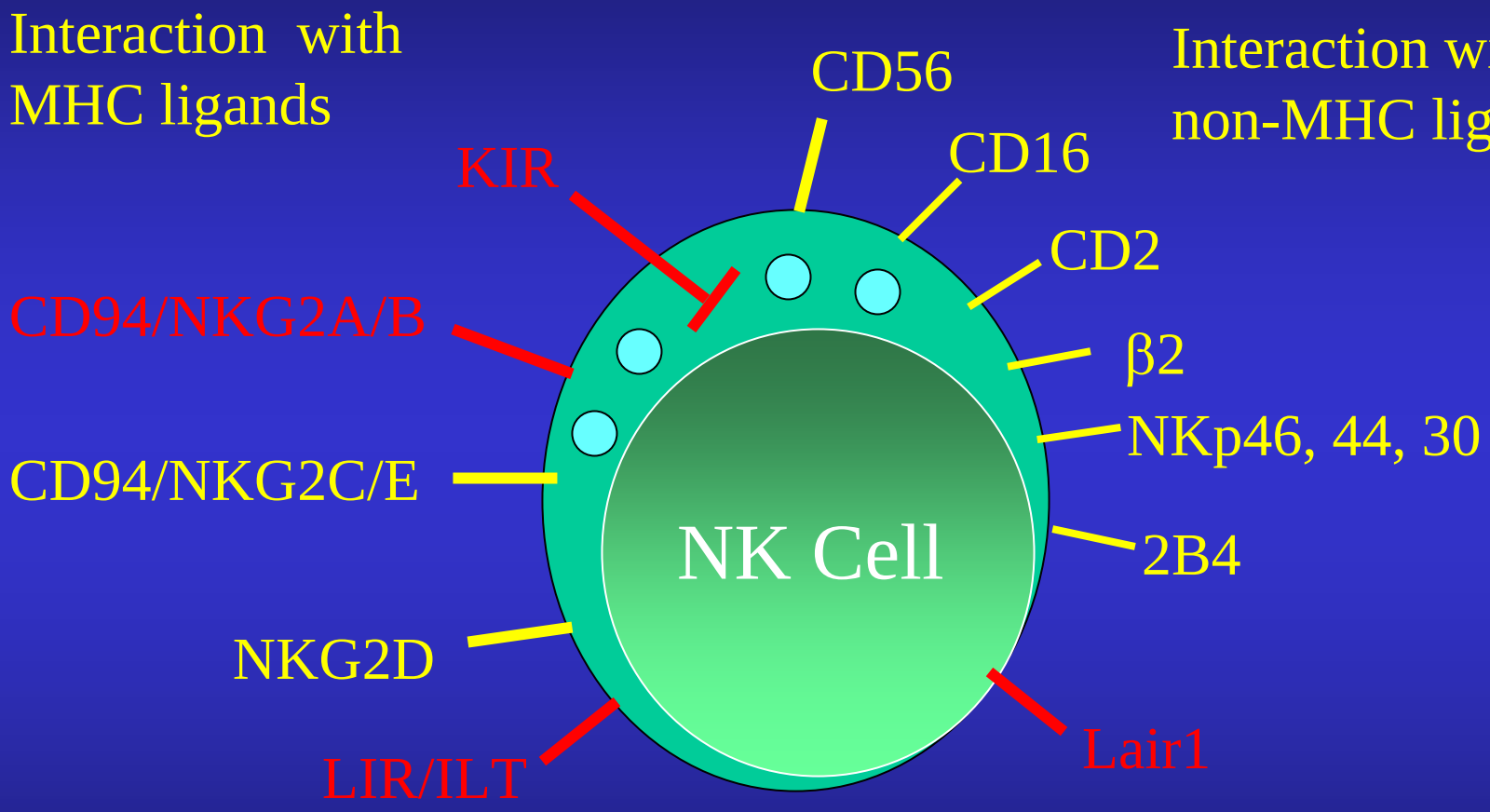
Heterogeneity of human NK cells

- Every NK cell expresses at least one KIR that recognizes a self MHC class I molecule
- Two functionally distinct subsets:

  1) 90% $CD56^{dim}CD16^{bright}$, highly cytotoxic, abundant KIR expression, few cytokines

  2) 10% $CD56^{bright}CD16^{dim/neg}$, produce cytokines, poorly cytotoxic, low KIR expression

Expression of activating and inhibitory receptors on NK cells

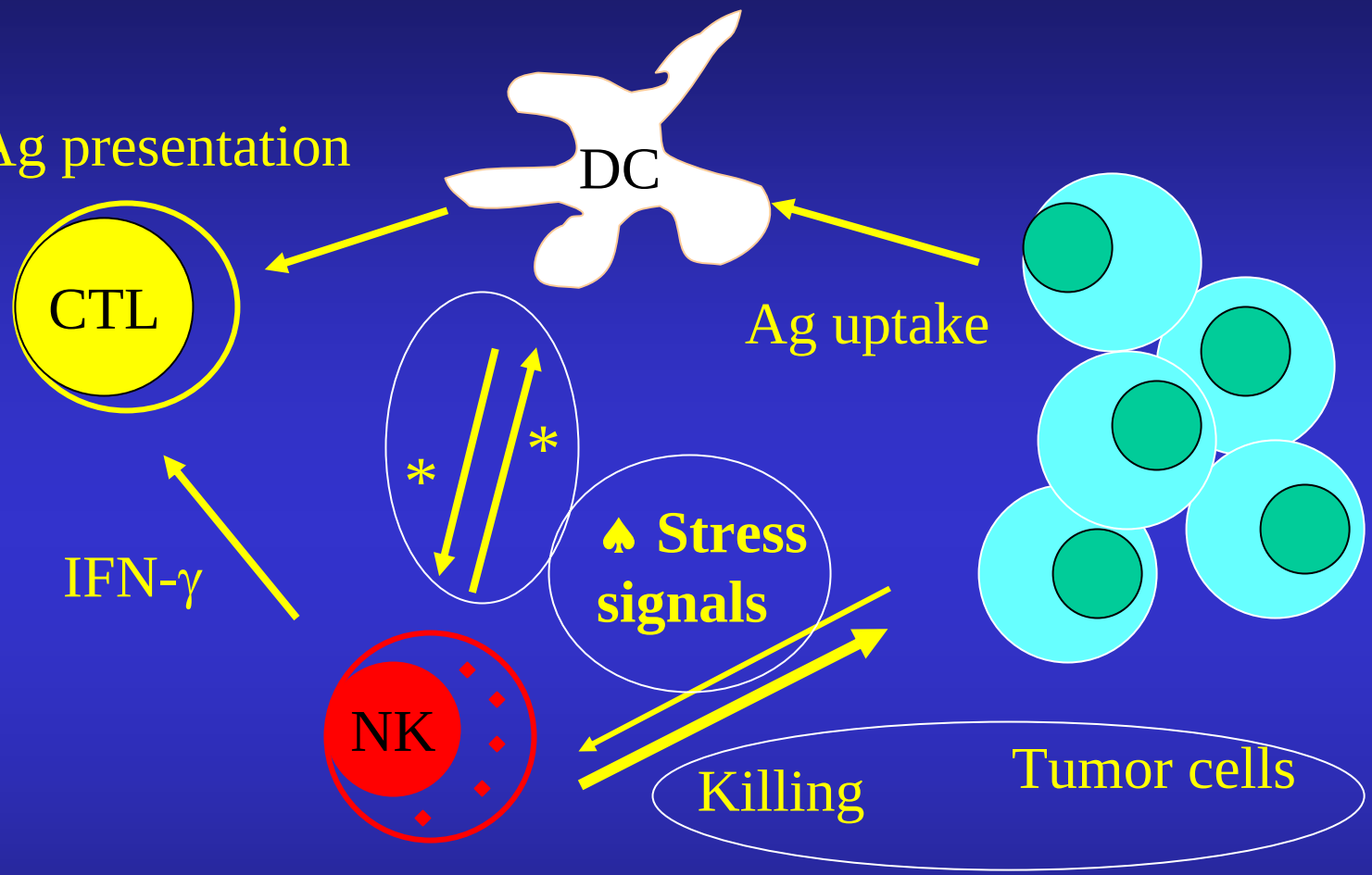


A cell which forms a first line of defense

NK-cell receptors

- NK cells preferentially lyse target cells which downregulate, loose, alter MHC class I molecules
- Ligands expressed by cells with altered or mutated MHC antigens are recognized by activating receptors (NKG2D) and natural cytotoxicity receptors (NKp30, NKp44 and NKp46)
- Inhibitory receptors (KIRs, ILT2/LIR1 and CD94/NKG2A)
- Co-stimulatory molecules (CD28, CD27, 2B4)
- These receptors are expressed on overlapping subsets of NK and memory T cells

NK cells and immune response to tumor cells



* Activation and maturation signals

♠ Down-regulation of MICA or MICB (ligands for NKG2D)

How do tumor cells escape from NK cells?

- Impaired NK-cell function in cancer patients: functional impairment of MIC/NKG2D signaling
- Tumors secrete TGF-β1and plasma levels of this cytokine are elevated in patients with cancer
- Evidence that plasma of cancer patients is responsible for down-regulation of NKGD2 expression on NK cells
- TGF-β1 specifically down-regulated NKGD2 and interfered with NK cytotoxicity
- Blocking of TGF- β1 functions as immunotherapy??
- Not the only mechanism of tumor resistance

Poster # 145 June-Chul Lee et al J. Immunol. 172: 7375, 2004

How to augment NK activity against tumor targets??

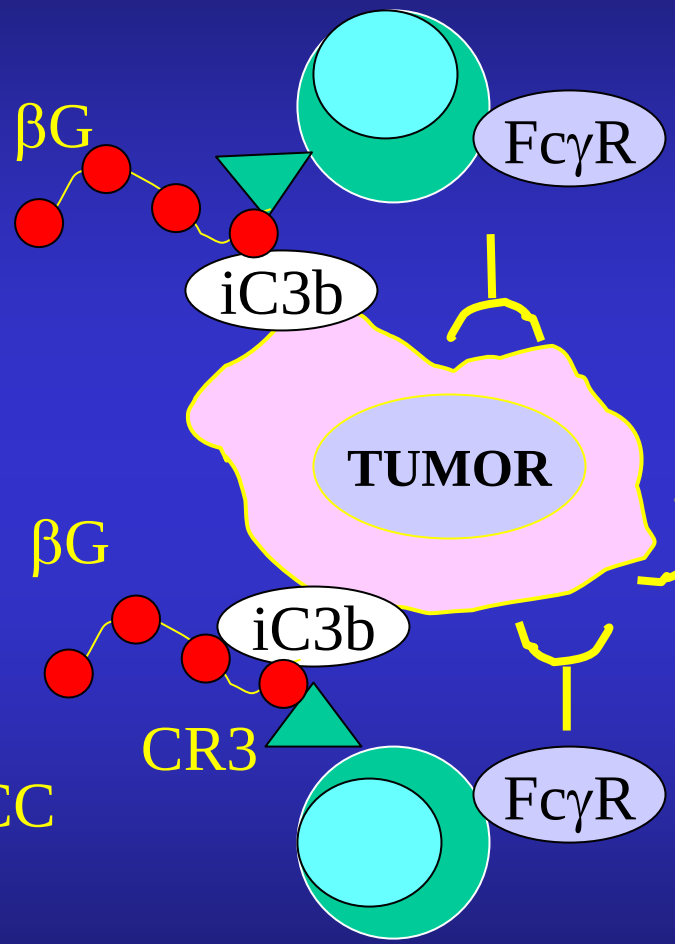
- The granule pathway and the death ligand pathway (TNF-α, FasL,TRAIL)
- Liver-infiltrating NK cells constitutively express TRAIL and are responsible for elimination of metastases
- PS-341(bortezomib) is a proteasome inhibitor which sensitizes tumor cells to TRAIL-mediated killing: it up-regulates expression of DR5 on tumor cels
- One of the mechanisms proposed is via reduction of cFLIP, which binds to death domains and inhibits the signaling cascade leading to apoptosis. So remove the inhibitor of apoptosis, and this makes tumor cells more susceptible to A-NK cells

Poster# 144: William Hallett et al

Drug-resistant neuroblastomas are sensitive to A-NK cells and A-NK Cells + IC *in vitro* & *in vivo*

- Expression of NKG2D ligands (MICA, MICB, ULBP1-3) on neuroblastoma cells correlated with A-NK cytotoxicity
- NKG2D expresssion was up-regulated on A-NK cells
- Abs against NKG2B blocked cytotoxicity against tumor
- Anti-GD2/IL-2 immunocytokine (IC) +IL2 + A-NK cells was more effective in tumor- growth inhibition than A-NK cells alone *in vitro* and *in vivo*
- Targeting of ANK cells to neuroblastoma with the IC as a therapeutic strategy

Anti-tumor effector mechanisms of mAbs



ADCC
Phagocytosis or
Cytotoxicity

C1q
CDC Cytotoxicity

CR3-DCC

Effector cells: NK cells, granulocytes, monocytes, M∅

Poster # 147 Gordon Ross et al

Lessons learned from the poster presentations

- Evidence that innate immunity plays an important role in anti-tumor defense
- Tumors develop strategies to evade effector cells mediating innate immunity
- Receptor-ligand interactions are critical for regulation of activation/inhibition signals
- Therapies targeting various aspects of innate immunity and combinations of innate and specific immunotherapy are promising and likely to provide a novel generation of anti-tumor therapies