HLA expression: implications for immunotherapy

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Anti-tumor Immune response

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells

MHC class I (HLA)

Immune effectors
- Cytotoxic T lymphocytes
- NK cells

Chen DS, Immunity, 2013
Recognizing self from non-self, and altered self

- MHC: Major histocompatibility complex or Human leukocyte antigens (HLA)
- Surface glycoproteins displaying diverse peptides derived from internal proteins
- Polygenic family, polymorphic and co-dominantly expressed

**MHC class I**
- Regulate CD8 T cell and NK cell activation (cytotoxic)
- Associate to peptides generated in the cytosol
- Constitutively expressed by all nucleated cells
  - **MHC class Ia (HLA-A, -B, -C):** Highly polymorphic
  - **MHC class Ib (HLA-E, -G, -F):** low polymorphism

**MHC class II** (HLA-DR, -DP, -DQ)
- Regulate CD4 T cell activation (helper)
- Constitutive expression restricted to professional antigen presenting cells (DC, Ma, B cells)
- Load and display peptides generated in the endocytic pathway
  - Highly polymorphic.
HLA class Ia regulation of cytotoxic lymphocyte effectors

Groups of HLA class Ia
Peptide independent

Inhibit

Kill

HLA class I allele and peptide dependent

Tumor Foreignness
Aberrantly expressed proteins
Neoantigens

KIR family

TcR

Tumor cell

HLA-A

HLA-B

HLA-C

NK

T

Ignorance
HLA class Ib regulation of cytotoxic lymphocyte effectors

- HLA-E
- HLA-G

Inhibit Inhibit

CD94/NKG2A LILRB1/ILT2
Altered MHC phenotypes in tumors

N. Aptsiauri, Canc Res, 2013
Frequency of MHC class I altered expression

- Total HLA antigen loss
- Selective HLA class I allospecificity loss

**HLA class Ia**

**HLA class Ib**

**M Campoli, Oncogene, 2008**

HLA altered expression has been found in 60-90% of tumors depending on their histological type
Molecular defects underlying MHC class I altered expression in tumors

**IRREVERSIBLE:** Structural gene abnormalities

- **Chr.6:** Loss of Heterozygosity (LOH)
  - Mutations of MHC class I Heavy chain genes

- **Chr.15:** LOH and mutations in β2m gene

- IFN transduction pathway: JAK/STAT pathway blockade

**REVERSIBLE:** Regulatory defects

- Transcriptional Regulation: Coordinated down-regulation of HLA-A, -B, -C or APM
- Hypermethylation of HLA class I genes
- Oncogenic activation (HER2, c-myc, adenovirus): down-regulation of HLA class I genes

Adapted from Garrido F, IJC, 2010
Immunoselection of tumor variants with HLA class I alterations and immunotherapy

Immune modulatory mAbs (PD-1/PD-1L, CTLA-4, 4-1BB, OX40)
Adoptive T cell therapy
Vaccination

Adapted from Garrido F, IJC, 2010
Primary, adaptive and acquired resistance to cancer immunotherapy (PD-1, CTLA-4))

Sharma P, Cell, 2017
Marabelle A, Cancer Discovery, 2017
Gabriel Abril-Rodriguez and Antoni Ribas, Cancer Cell, 2017
The “cancer immunogram”

HLA class I expression as predictive biomarker of response to immunotherapy?

• Difficulty inherent to HLA polymorphism and multiple targetable checkpoints

<table>
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<th>HLA Class I</th>
<th>Gene</th>
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Technique combination

• IHQ: Quantitative approach to analyse HLA-I expression in tumor cells. Combined with flow cytometry.
  mAb to broadly recognizing “all” HLA class Ia molecules (discriminating from HLA class Ib molecules)
• Identification of the specific molecular defects underlying HLA-I alteration (microdissection and RT-PCR, microsatellite analysis for LOH detection, DNA sequencing)
• Discrimination between reversible versus irreversible alterations to decide putative complementary therapies
Case A, x200

Case B, x200

HC10: free HLA-B, HLA-C heavy chains

Case C, x200

Dr. Federico Rojo
Thank you for your attention