The particular biology of lymphomas in immuneprivileged sites

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Definition of immune privilege/immune privileged sites

Sites which tolerate the introduction of antigens without eliciting an inflammatory immune response

Classical immune privileged sites:
- CNS (blood-brain barrier)
- Testis (blood-testis)
- Eyes
- Placenta and fetus

**Immune Deviation**

- Eye
- Testis
- CNS
- Placenta/fetus

**Immunological tolerance**
- T-cell anergy
- Sertoli cell barrier
- Microglia/macrophages
- Vitreous fluid
- Anterior Chamber Immune Deviation

**Limited immune cell entry**
Classical and presumed immune privileged/restricted site lymphomas

Inflammatory reaction

Pyothorax-associated LBCL
Fibrin-associated LBCL
Intravascular LBCL
Fluid-overload-associated LBCL

PCNSL
PTL
BIA-ALCL

Systemic immunodeficiency

Local immunological tolerance

Limited immune cell entry
Typical features of primary testicular and CNS large B-cell lymphoma

- Localized disease at presentation
- Poor prognosis
- Complicated disease management
- Dissemination within the compartment (testis-testis, CNS-CNS) and between compartments (testis ↔ CNS), but rare systemic dissemination

PCNSL

PTL

Not all large B-cell lymphomas are diffuse large B-cell lymphomas. The current situation.
Diffuse large B-cell lymphoma at immune-privileged sites
Immunophenotypical characteristics of IP-LBCL

CD10

MUM1

HC10 – MHC class 1

BCL6

HLA-DR – MHC class 2

Antigens used in Cell-of-origin Classification

Weighted Mean Frequency of Positive Expression

Twa et al Blood Reviews 2018;12:249-255
PTL and PCNSL have a different CNA profile compared to DLBCL.
Loss of MHC class I and II is mediated by various mechanisms

Beta2microglobulin mutational spectrum (10%)

Various translocations in PCNSL (10%)
Structural alterations at 9p24 – PD-ligand locus

9p24.1/PD-L1/PD-L2 FISH in PCNSL in the HOVON105 clinical trial

Total number of evaluable cases: 87

Roemer et al, in preparation
PDL1 expression is not fully explained by genetic alterations
Immune escape in PTL/PCNSL

- Invisibility for the immune system - absence of MHC class I and/or class II
- Suppression of anti-tumor T-cell response - activation of PD1-PDL1

Genetic alterations
- Copy number alterations
- Translocations
- Disruption of 3'UTR

Oncogenic signaling
- JAK2, MYC, RELA
- STAT, JUN, EGFR, CDK5, RAS, ALK

Inflammatory signaling
- IFN-γ, -α, -β
- TLR3, TLR4
- Interleukins
- TNF-α
- TGF-β

Viral infection
- EBV
- HHv8
- ... microRNAs
- miR-513
- miR-155
- miR-217
- miR-34a
- miR-200
- miR-142-5p
- miR-152
- miR-93
- miR-570

Post-translational regulation
- CMTM4, 6
- CDK4
- GSK3B
- B3GNT3

Absence of CD37 expression

PDL1

HLA-DR

Mutational spectrum of PTL/PCNSL – constitutive NFkB activation

The spectrum of alteration in PTL/PCNSL has similarities to ABC-DLBCL but also differs essentially.
Molecular classification of DLBCL beyond cell-of-origin

COO classification:  
- ABC  
- GCB  
- Unclassified

**C0**  
- MYD88  
- CD79B

**C5**  
- NOTCH1

**C1**  
- BCL6
- NOTCH2

**C3**  
- BCL2
- EZH2

**C4**  
- TP53  
- CDKN2A

**C2**  
- MCD  
- N1  
- BN2  
- EZB  
- Other GCB  
- Other ABC  
- Other Unclass

Chapuy et al Nat Med 2018;24:679-690  
Schmitz et al NEJM 2018;378:1396-407
The relationship between cluster C5 and features of IP-DLBCL

9/11 cases with testis/CNS involvement

immune evasion characteristics
(B2M, CD70, FAS, PDligand SV)

immune evasion characteristics
(CD83, CD58, CD70)

Chapuy et al Nat Med 2018;24:679-690
Conclusions

Immune privileged site LBCL are characterized by a highly characteristic genetic landscape

- Constitutive NFkB activation via BCR and TLR pathways
- Immune escape via complementary genetic and regulatory mechanisms

- Share genetic features with nodal-type ABC-DLBCL, novel “cluster C5”- DLBCL and “MCD”-DLBCL
- Share genetic features with classical Hodgkin lymphoma/primary mediastinal B-cell lymphoma
- The precise relationship between these classes remains to be elucidated
- The mechanism behind the preferential genotype/phenotype is still unknown

- Specific features of Immune privileged site LBCL impact on treatment options
  - NFkB/BTK inhibition – e.g. ibrutinib
  - Checkpoint inhibition – e.g. nivolumab/pembrolizumab
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