Characterize Tumor Infiltrating Immune Repositories with TRUST

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Immune System Recognizes Antigens by Generating Diverse Repertoires from V(D)J Recombination

• V(D)J recombination creates diverse T cell and B cell receptor repertoires for antigen recognition and immune activation

• Hypervariable CDR3 sequences important for antigen recognition, but unmappable to the reference human genome
TRUST for Tumor Immune Receptor Repertoires

Li et al, Nat Genet, 2017

https://bitbucket.org/liulab/trust/
TRUST Accurately Reconstructs CDR3s and Identifies Isotypes Validated by BCR-seq

CDR3 reconstruction

CDR3+constant gene(Isotype)

Hu et al, Nat Genet, 2019
Frequent Tumor BCR Somatic Hypermutations

Hu et al, Nat Genet, 2019
Frequent Tumor BCR Ig Class Switches

Breast Invasive Carcinoma

Skin Cutaneous Melanoma

Ig isotype

Class switches

Hu et al, Nat Genet, 2019
IgG Class Switches are Enriched in Tumors Compared to Normal

• B lymphocytes and cancer: a love-hate relationship
  • Yuen et al, Trends Cancer. 2016

Only consider cancer types with > 10 normal RNA-seq samples
CDR3 diversity, IgA/G switches normalized to total called CDR3 clusters

Hu et al, Nat Genet, 2019
Tumors with B Cell IgG1/2/3 Switches Show Increased Natural Killer Cell Activities (CD16a)

Hu et al, Nat Genet, 2019
Patients with Amplified MICA but High IgG1/3 Switches Show Survival Benefits

• Potential immune evasion of ADCC through MICA amp and cleavage
• Potential IgG1/3 class switched MICA auto-antibodies in MICA amplified tumors are associated with better survival

Hu et al, Nat Genet, 2019
Ongoing work: TRUST4 Assembles Complete BCRs/TCRs Including CDR1/2 Regions

**FZ-116: IGHV3-23 + IGHJ6 + IGHJ6**

**TRUST4**

**TRUST3**
Conclusions

- TRUST is an accurate and sensitive computational tool for detecting BCR/TCR from RNA-seq data
- We observed strong selection of somatic hypermutations and diverse preferences on the immunoglobulin subclass switches
- We observed immunoglobulin subclasses relate to natural killer cell activities and survival rate.
- Next version of TRUST (TRUST4) reports full-length BCRs/TCRs including CDR1 and CDR2 regions efficiently
- The immunoglobulin heavy chain sequences identified by TRUST are potentially useful resources for future development of B cell related immunotherapies
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