IO17 | Large Scale Bioinformatics for Immuno-Oncology

Neoantigen prioritization

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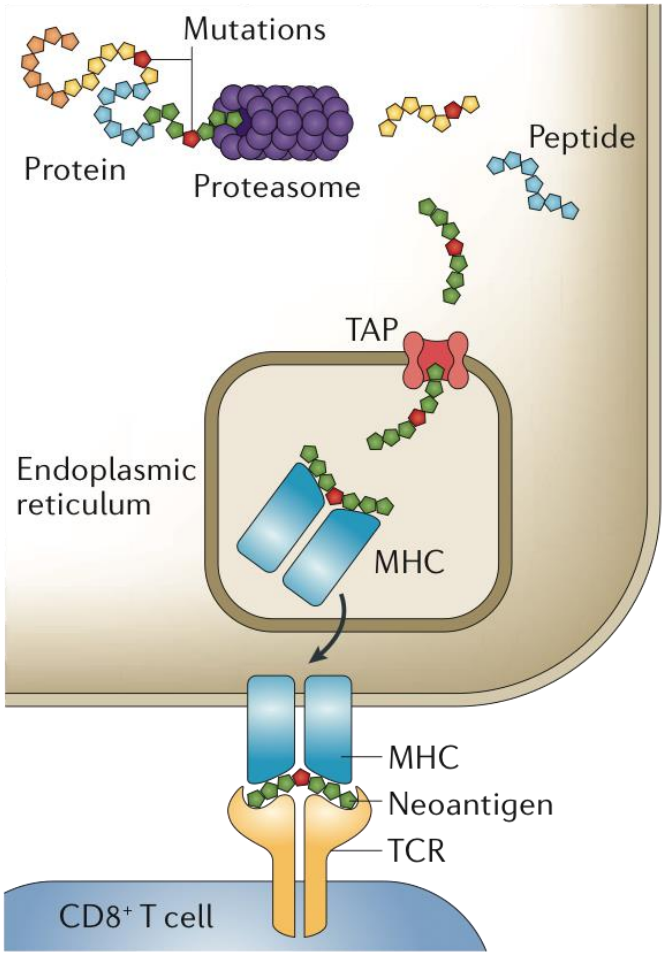
Peptide-MHC binding affinity



Peptide-MHC binding is the most selective event in the process of antigen presentation

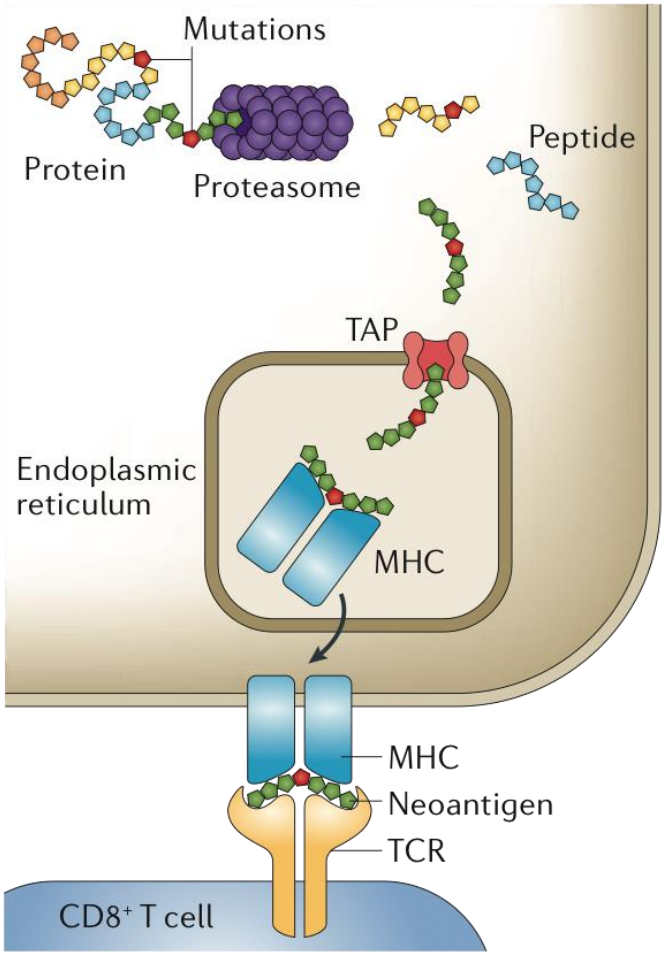
Binding affinity

IC_{50} (or percentile rank for unbiased representation of MHC alleles)

Low IC_{50}/rank → strong binding affinity

H Hackl*, P Charoentong*, F Finotello* et al. Nature Reviews Genetics, 2016

Peptide-MHC binding stability



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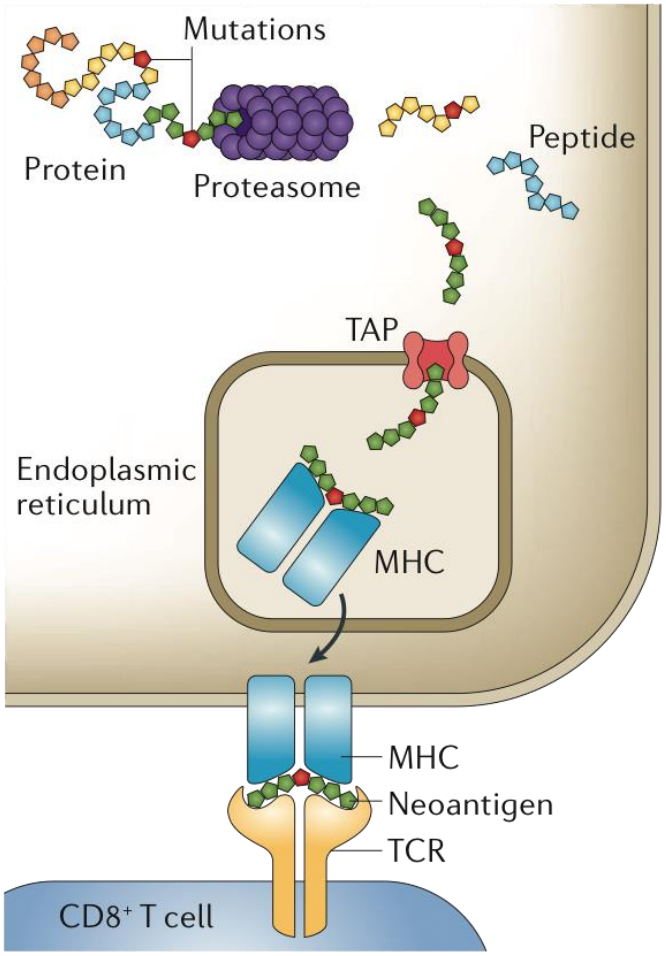
Binding stability

The neoantigen must be retained on the cell surface until the arrival and binding T cell

Binding stability can be predicted with netMHCstab (K Jørgensen et al., Immunology, 2014)

H Hackl*, P Charoentong*, F Finotello* et al. Nature Reviews Genetics, 2016

Antigen processing



Peptide-MHC binding is the most selective event in the process of antigen presentation

… but the preceding steps of antigen processing also have a role in the MHC-I pathway!

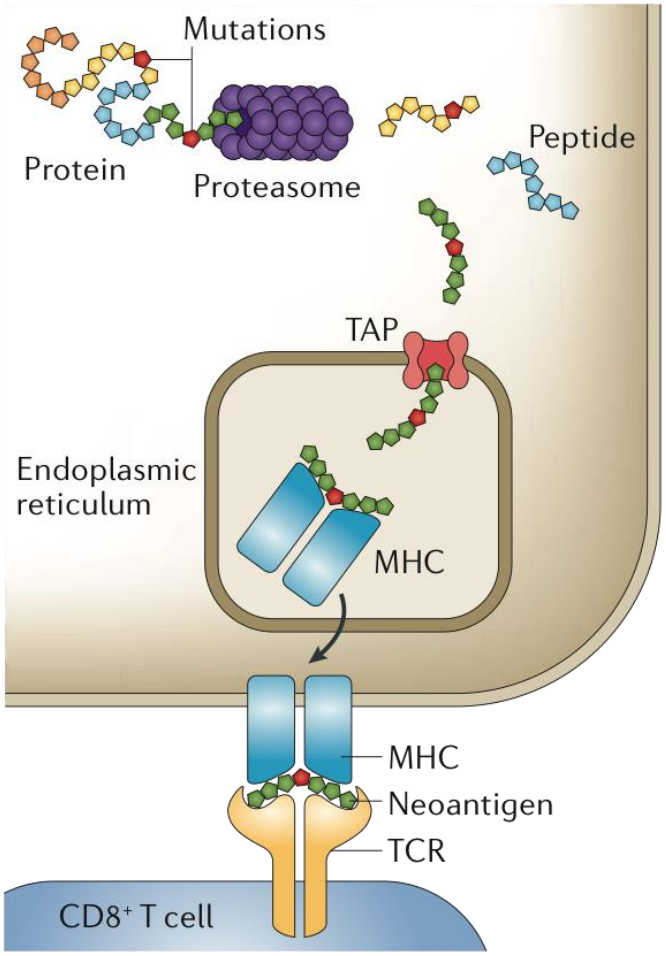
Proteasomal cleavage: converts large proteins into smaller peptides

TAP transport: transport of the peptide into the endoplasmic reticulum by transporter associated with antigen processing (TAP)

Prediction algorithms are available, but have limited performance (B Linus and O Kohlbacher, Genome medicine, 2015)

H Hackl*, P Charoentong*, F Finotello* et al. Nature Reviews Genetics, 2016

T-cell propensity



The binding of peptides to MHC-I molecules is not sufficient to elicit an immune response…

…it must be recognized by the CD8+ T lymphocyte

T-cell reactivity or propensity: propensity of T cells to recognize antigens bound to MHC molecules

Prediction of T-cell propensity is probably the most difficult task for the identification of neoantigens recognized by T cells

H Hackl*, P Charoentong*, F Finotello* et al. Nature Reviews Genetics, 2016

Neoantigen expression

Timiner default pipeline filters candidate neoantigens considering the **expression** of the gene they originate from.

However, in tumors with a high mutation rate, up to 50% of mutations are typically not expressed in RNA

The “sensitive filtering” module of TIminer pipeline allows selecting expressed neoantigens considering the **allele-specific expression** (i.e. the RNA-seq coverage of mutations)

Strategy:

1. Sensitive (re)mapping of the RNA-seq reads with HiSat2 (D Kim et al., Nature Methods 2015)
2. Computation of the RNA-seq read coverage for each mutation with GATK (A McKenna, et al., Genome Res, 2010)
3. Filtering of mutated peptides with a read coverage ≥5 counts

Strategies for neoantigen prediction and prioritization

Method	Predictions	URL	Ref
FRED 2	Mutated peptide (from SNPs and indels), HLA typing, proteasomal cleavage, TAP transport, peptide-HLA binding affinity, peptide prioritization, and vaccine design	http://fred-2.github.io	(Schubert et al., 2016)
INTEGRATE-neo	HLA typing, mutated peptide (from gene fusions), peptide-HLA binding affinity	https://github.com/ChrisMaherLab/INTEGRATE-Neo	(Zhang et al., 2017)
MuPeXI	Mutated peptide (from SNPs, frameshift mutations, and indels), peptide-HLA binding affinity, peptide prioritization considering also gene expression, allele frequency, and protein self-dissimilarity	http://www.cbs.dtu.dk/services/MuPeXI/	(Bjerregaard et al., 2017)
NetCTL	Proteasomal cleavage, TAP transport, peptide-HLA binding affinity, and combined score for peptide prioritization	http://www.cbs.dtu.dk/services/NetCTL	(Larsen et al., 2007)
NetEpi	Peptide-HLA binding affinity and stability, T-cell propensity, and combined score for peptide prioritization	http://www.cbs.dtu.dk/services/NetTepi	(Trolle and Nielsen, 2014)
pVAC-seq	Mutated peptide (from SNPs), peptide-HLA binding affinity, and peptide prioritization considering also NGS read coverage and gene expression	http://github.com/griffithlab/pVAC-Seq	(Hundal et al., 2016)

E Tappeiner, F Finotello et al., Bioinformatics, 2017