

Two distinct approaches in cancer immunotherapy

- Enhancement
 - Hypothesis: Pts do not produce sufficient intrinsic immunity
 - To enhance **normal** immune response systemically
- Normalization
 - Hypothesis: Pts produce sufficient intrinsic immunity that is impaired in the TME
 - To repair **defective** immunity in the TME

两种不同的肿瘤免疫治疗

- **癌种免疫增强疗法**

- 假设：Pts不能产生足够的内在免疫力
- 增强正常免疫反应

- **系统正常化**

- 假设：Pts产生足够的内在免疫力，在TME中受损
- 修复TME中有缺陷的免疫力

Cancer patients who benefit from immunotherapy

- Enhancement:
 - Cytokines: Type I IFN, <1% (Mel, RCC, lymphoma); IL-2, <1% (Mel, RCC)
 - Immune checkpoint: Anti-CTLA4: <1% (Mel)
 - Vaccine: Sipuleucel-T, <1% (Prostate Ca)
 - Adoptive cell therapy: CAR-T, <1% (B lymphoma)
- Normalization:
 - Anti-PD-1/PD-L1: ~25% (>20 solid and liquid tumors)

不同免疫疗法受益的肿瘤患者对比

● 免疫增强疗法：

- 细胞因子：I型IFN， < 1%（黑色素瘤， 肾癌， 淋巴瘤） IL-2， < 1%（黑色素瘤， 肾癌）
- 免疫检查点：抗CTLA4： < 1%(黑色素瘤)
- 肿瘤疫苗：Sipuleucel-T, < 1%（前列腺癌）
- 细胞治疗：CAR-T， < 1%（B细胞淋巴瘤）

● 免疫正常化疗法：

- PD-1/PD-L1抗体： > 25%（ > 20种实体肿瘤和血液肿瘤）

Lessons learned from anti-PD therapy

- To identify **tumor-induced** immune evasion mechanisms
- Immune evasion happens mainly in the **tumor microenvironment** (TME)
- To target the “**master switch**” which can reprogram immunity

抗PD-1治疗的感悟

- 识别肿瘤诱导的免疫缺陷
- 免疫逃逸主要发生在肿瘤的微环境（TME）
- 免疫治疗要靶向性的针对优势通路

The “normalization” approach is NOT the same as the “immune checkpoint blockade” (ICB)

- ICBs may block normal immune inhibitory mechanism, but not tumor-induced immune evasion mechanisms
- ICBs may not modulate the TME as main mechanism of action
- ICBs may not target the “master switches” in the TME

免疫正常化的疗法和免疫检查点抑制是不同的

- ICBs同时也作用于正常的免疫抑制机制，但是不能完全阻止肿瘤引起的免疫逃逸机制（CTLA-4）
- ICBs的主要作用可能不是调节TME,而是全身的免疫抑制
- ICBs的作用的通路可能不是主要的免疫通路

The ICBs fail frequently in single agent clinical trials on solid tumors (2020)

- Anti-LAG3*
- Anti-ICOS
- IDO inhibitors
- Anti-TIM3
- Anti-TIGIT
- Anti-PD-1H (VISTA)
- Anti-CD47
- Anti-A2AR
- PDL2Ig
- Anti-B7H3*
- Anti-CSF1
- Anti-CSF1R
- Anti-TGF β R
- Anti-TGF β
- Anti-B7-H4

ICBs在实体肿瘤的单药临床试验几乎都没有阳性结果 (2020)

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- Anti-B7H3*
- Anti-CSF1
- Anti-CSF1R
- Anti-TGF β R
- Anti-TGF β
- Anti-B7-H4

Advanced human cancer is highly heterogenic in the TME

- **Genetic instability and/or Epigenetic modulation**
 - Angiogenesis
 - Metabolism
- **Treatment-induced evolution**
- **Immune heterogeneity**

晚期肿瘤病人的TME具有高度的异质性

- 遗传不稳定性和/或表观遗传调节

- 血管生成

- 代谢

- 标准治疗诱导的肿瘤进化

- 免疫异质性

Our strategy to search immune normalizers in the TME

- Non-inflamed cancer:
 - Physical barrier: endothelial cell permeability, cell adhesion
 - Chemical barrier: hypoxia, low pH, chemokine availability, metabolites
- Inflamed cancer:
 - Immune cell survive
 - Proliferate and expansion
 - Memory formation

TME正常化的探索

- 无炎症反应的肿瘤

- 物理屏障：内皮细胞的渗透性、细胞粘附性

- 化学屏障：细胞缺氧、低PH、化学基质，趋化因子、肿瘤细胞内部代谢物

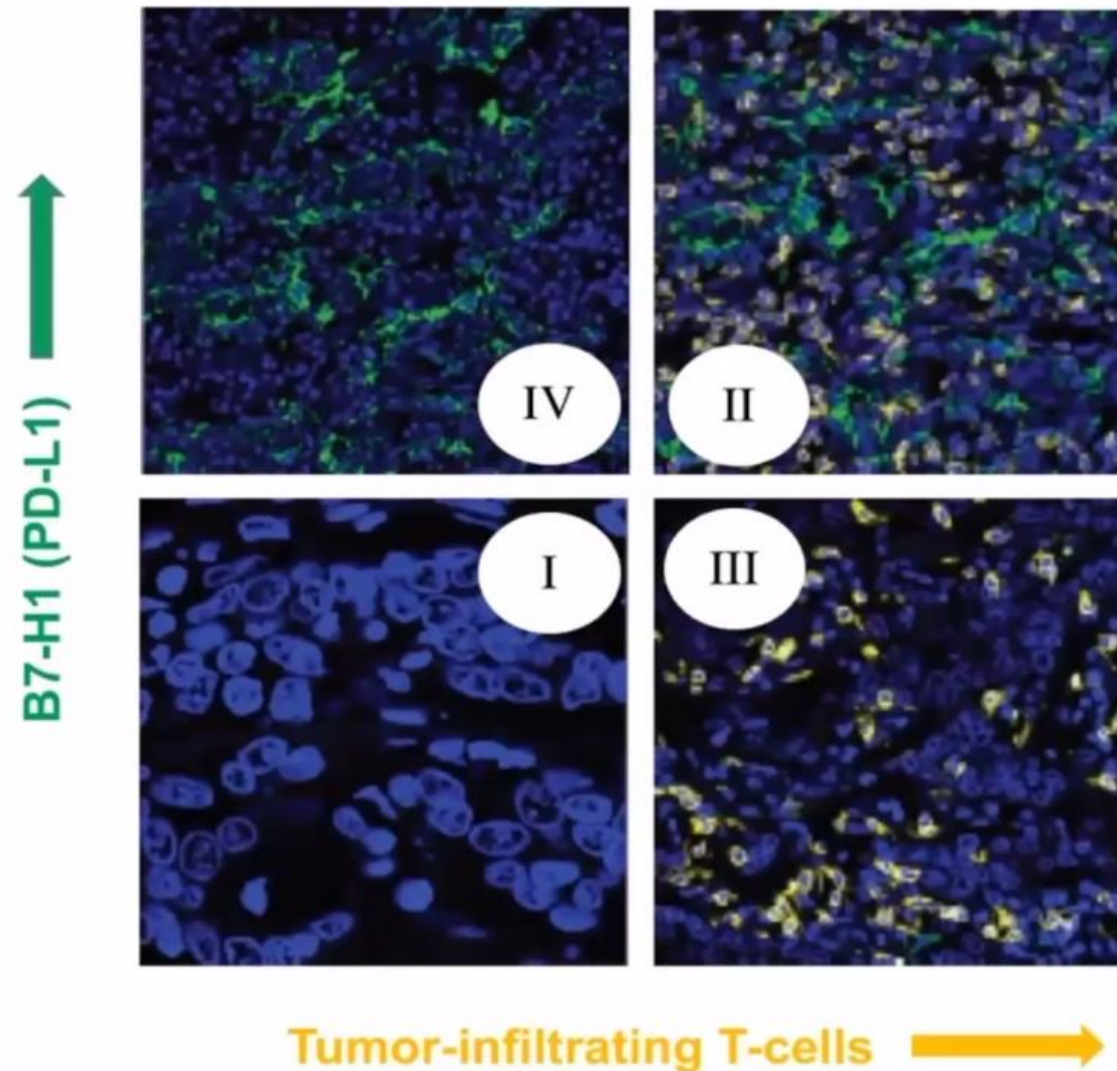
- 有炎症反应的肿瘤

- 免疫细胞的存活

- 增殖和扩张

- 记忆的形成

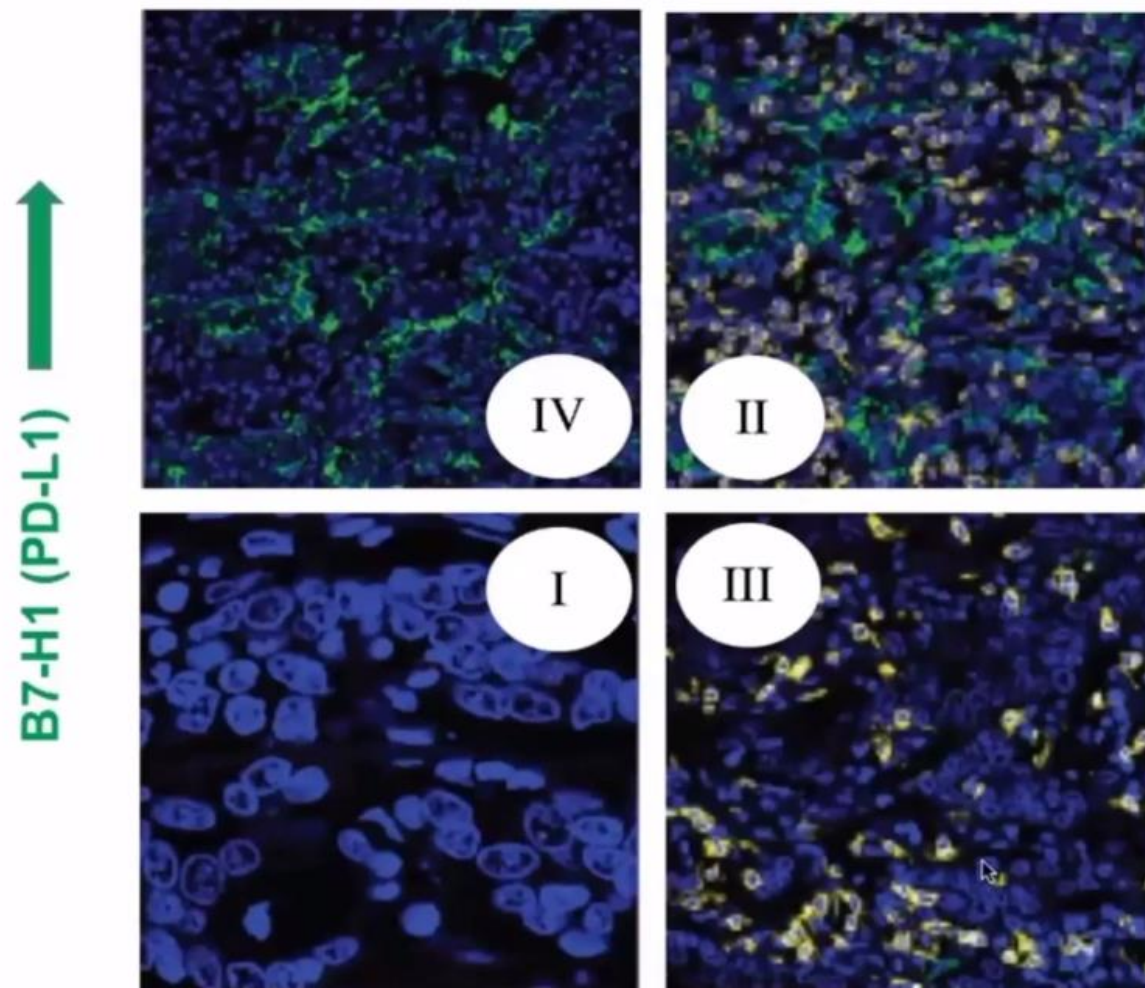
TIME* classification of human cancer



*Tumor Immunity in MicroEnvironment
#Blue=DAPI, Green=PD-L1, Yellow=TILs

Taube J et al, *Sci Transl Med* 2012
Sznol M & Chen L, *Clin Can Res* 2013
Zhang Y & Chen L, *JAMA Oncol* 2016

基于“免疫微环境”的肿瘤分类



TIME Classification of Advanced Human Cancer

	I	II	III	IV
	DN	DP	TIL+	B7-H1+
Melanoma (n=256*)	39%	45%	16%	<1%
Lung Ca (n=457**)	45%	17%	26%	12%
Bladder Ca (n=126*)	21%	32%	40%	7%
Colon Ca (n=816*)	27%	14%	13%	46%
Gastric Ca (n=105**)	40%	22%	25%	13%
Breast Ca (n=167*)	49%	17%	32%	2%
TNBC (n=215*)	37%	18%	30%	15%
(n=2,142)	37%	24%	26%	13%

***Surgical specimens** (Taube et al, *Sci. Transl. Med.* 2012, Obeid et al, *Oncolimmunol.* 2016, Zhang et al, *Peer J*, 2017, Hamada et al, *Oncoimmunol.* 2018, Ju et al, *Oncotarget* 2017, Kim et al, *Sci Rep* 2017, AiErken et al, *IJBS* 2017)

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PD-L1/PD-1 FGL1/LAG3 Siglec-15

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Vascular normalizers
Chemokine antagonists

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血管正常化
趋化因子拮抗剂

Cancer immunotherapy

- **Enhancement cancer immunotherapy**
 - “Unlimited” targets
 - Raise immunity to supra-normal level
 - Severe toxicity
- **Normalization cancer immunotherapy**
 - Restores immunity to a controlled level
 - Targeting the TME, less toxicity
 - Many targets are yet to be discovered

肿瘤的免疫疗法

- 增强免疫疗法

- 无限靶点
- 将免疫力提高到超正常水平
- 严重毒性

- 免疫正常化疗法

- 将免疫力恢复到受控水平
- 靶向性针对主要通路-毒性低
- 许多靶向通路还未发现

Trending on cancer immunotherapy

- Normalization vs. enhancement
- Molecule-based classification
 - Beyond traditional pathology
- Mechanism-based treatment
 - Targeting complimentary mechanisms

肿瘤免疫治疗的趋势

- 免疫微环境正常化VS免疫增强
- 肿瘤分子分类
 - 超越传统病理学
- 基于肿瘤发病机制的治疗
 - 针对主要发病通路的治疗