The function and mechanism of demethylase TET2 in breast cancer

去甲基化酶TET2在乳腺癌中的作用及机制研究

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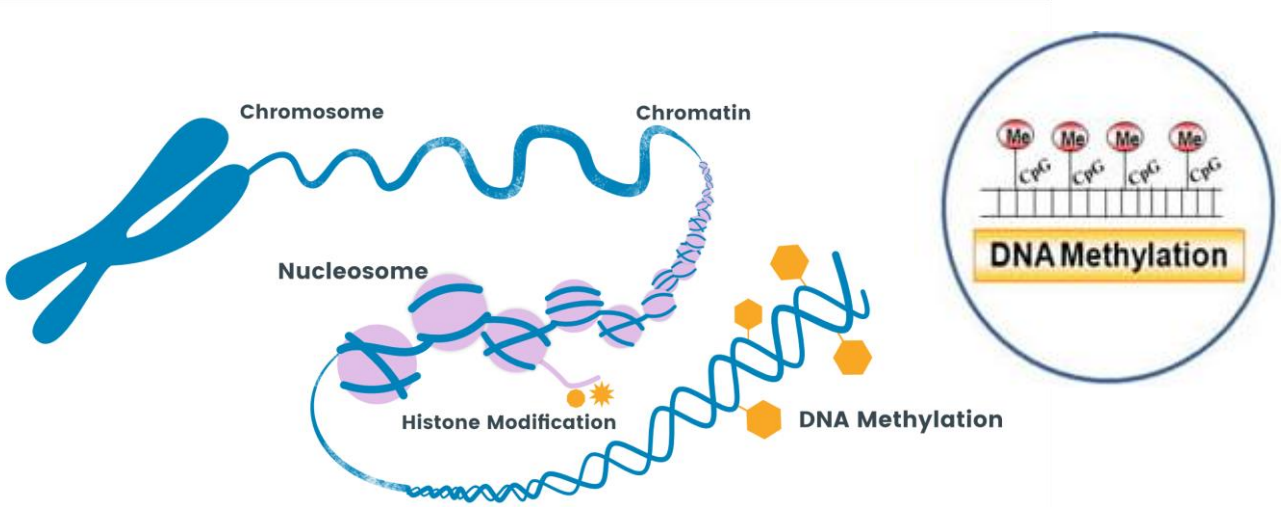
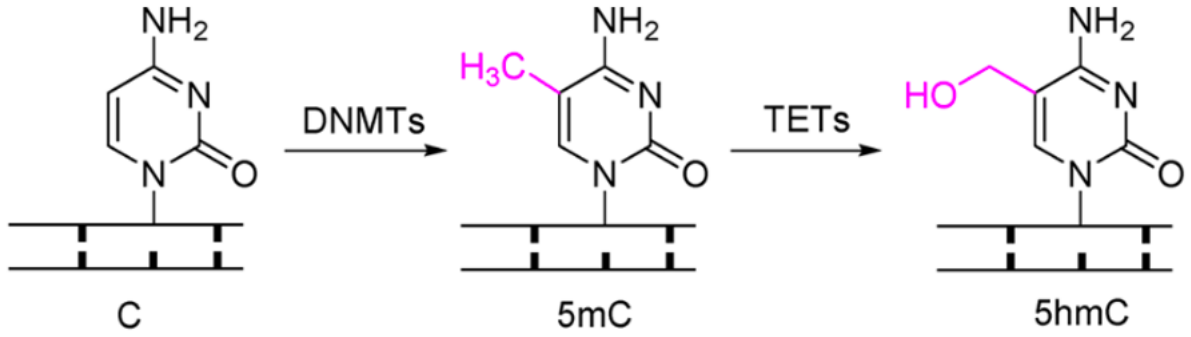
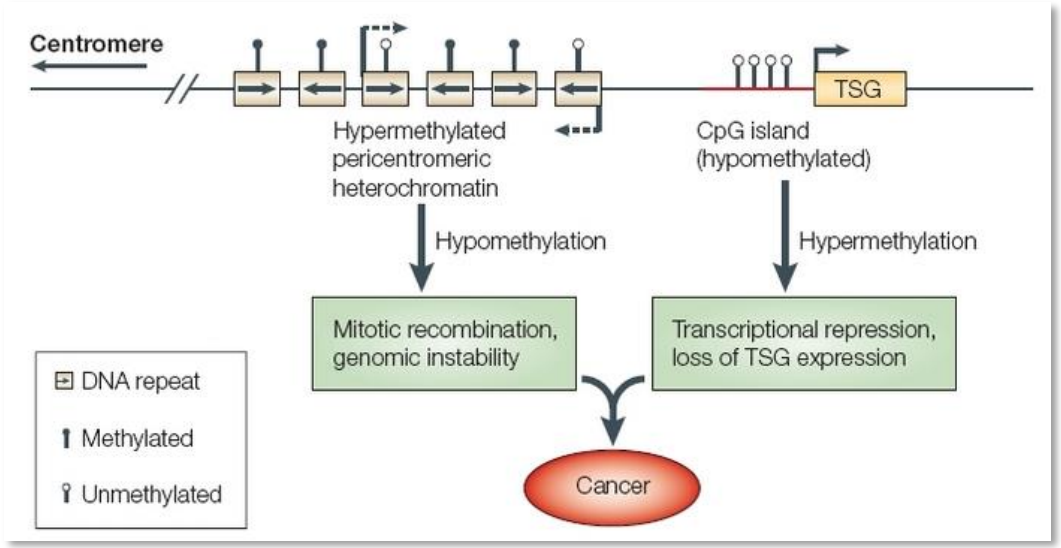
DNA甲基化修饰



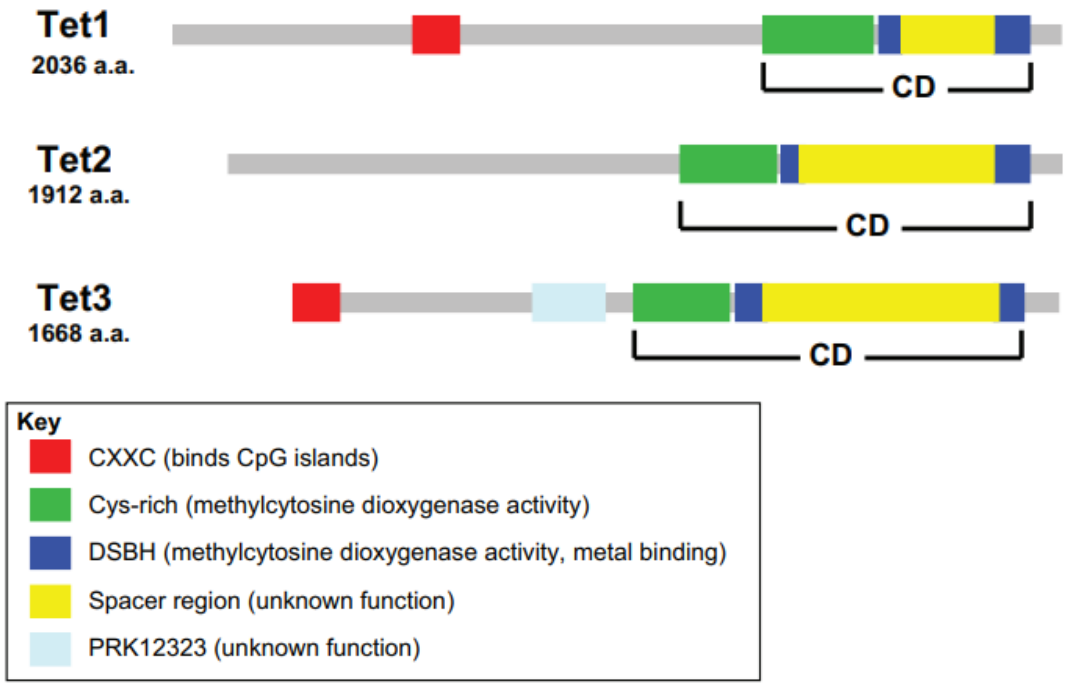


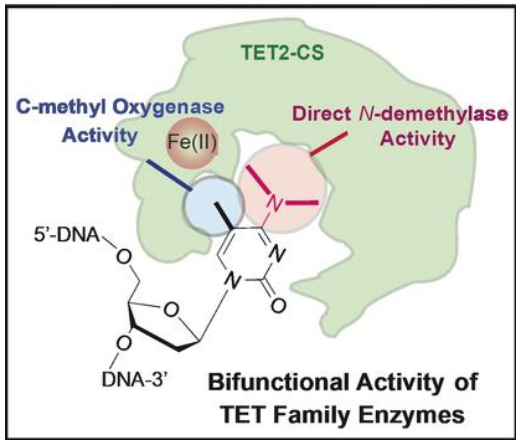
DNA甲基转移酶介导DNA甲基化修饰，TET酶介导DNA去甲基化

- DNA甲基化是最常见的表观修饰方式之一，主要发生在基因组的CpG区域；
- DNA甲基化往往导致基因表达“沉默”；
- DNA甲基化和去甲基化过程由专门的酶控制，受到严格的调控；
- DNA甲基化异常与胚胎发育、染色体稳定性、癌症、自身免疫病等过程有关。



(ten-eleven translocation, TET) 十-十一易位双加氧酶蛋白家族





Xiaoji Wu, et al, Nature Review, 2017

- TET家族包括3个成员：TET1、TET2、TET3，在人和鼠中均保守存在；
- 结构上主要包含：CXXC结构域、Cys富集基序和一个酶活结构域；
- 催化核心DSBH结构域在人和鼠中高度保守，主要功能是将Fe(II) 和5-甲基胞嘧啶聚集在一起进行氧化，而富含半胱氨酸的结构域包裹着DSBH核心以稳定整体结构并和DNA相互作用。

TET2

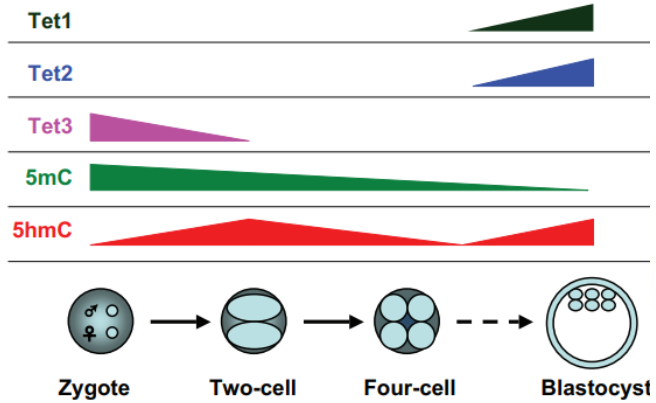
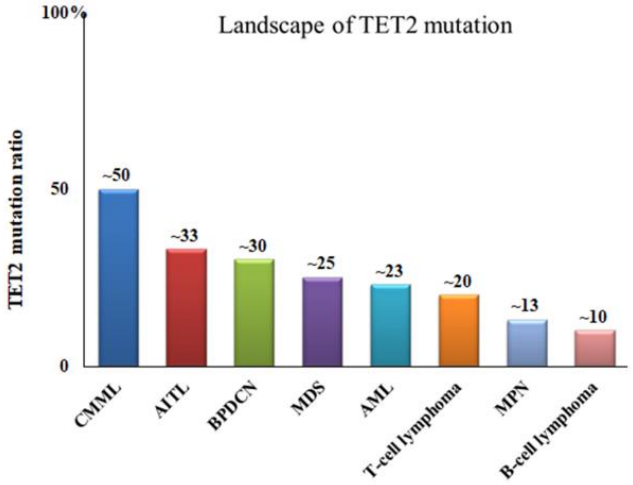
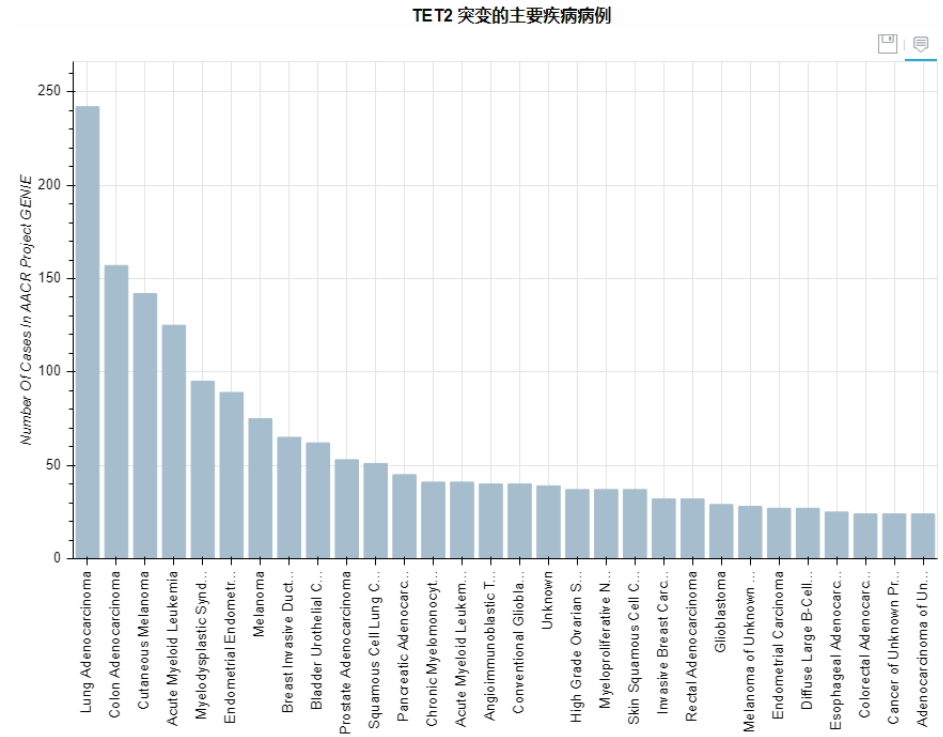


Table 1. Phenotypes of Tet knockout mice

Genotype	Preimplantation development	Postimplantation development	Postnatal development
Tet1$^{-/-}$	Normal	Small body size	Small body size
Tet2$^{-/-}$	Normal	Normal	Spontaneous myeloid leukemia
Tet3$^{-/-}$	Normal	Normal	Neonatal lethality
Tet3$^{mat-/pat+}$	Normal, but blockage in paternal genome reprogramming	A high frequency of degeneration and variable multi-organ abnormalities	Neonatal lethality and small body size

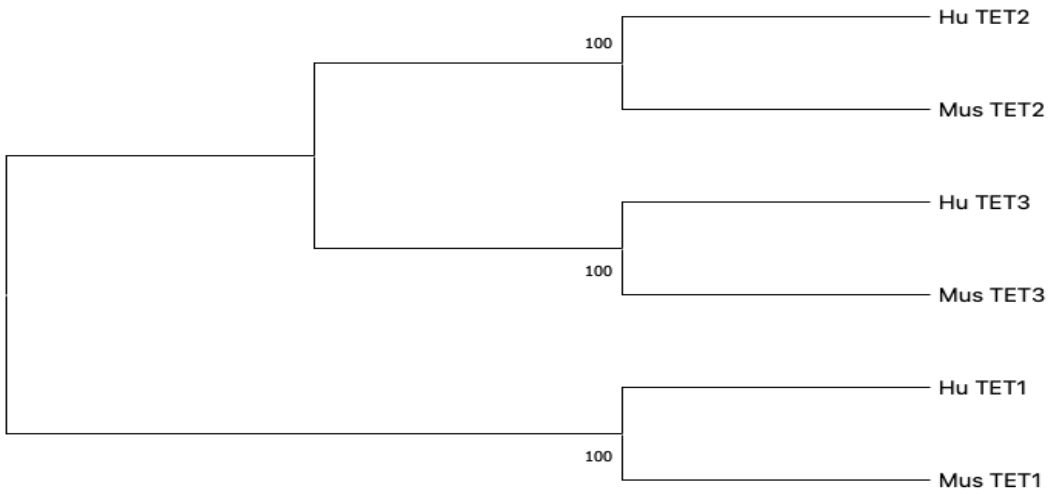




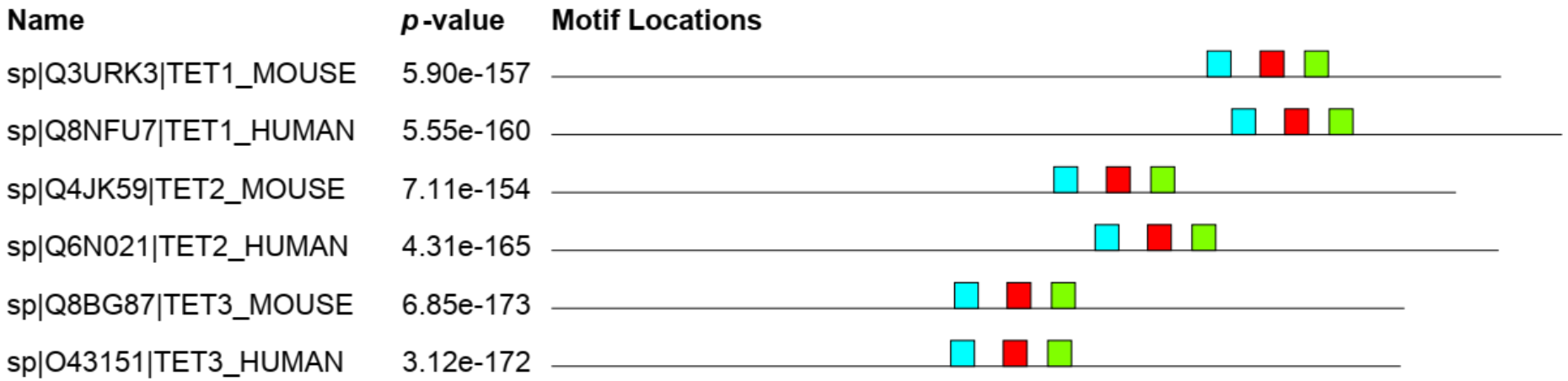
- TET1、TET2和TET3在功能上很大的冗余性和代偿性，在发育的不同阶段以及不同组织中差异表达；
- TET1在胚胎发育和体细胞中均广泛表达，TET3主要在发育阶段表达；
- TET2主要在造血系细胞中表达，许多研究证明了造血细胞中TET2突变与血液瘤的发生发展有密切的联系；
- 近年来的研究表明，多种肿瘤中也都存在明显的TET2突变和异常表达，提示TET2在癌症发生中发挥广泛作用。

TET家族系统发生树构建

编号	登陆名	蛋白质登录号	RefSeq 登陆号	基因名	蛋白长度	物种
Mus TET1	TET1_MOUSE	Q3URK3	NP_001240786.1	Methylcytosine dioxygenase TET1	2007	Mus musculus (Mouse)
Hu TET1	TET1_HUMAN	Q8NFU7	NP_085128.2	Methylcytosine dioxygenase TET1	2136	Homo sapiens (Human)
Mus TET2	TET2_MOUSE	Q4JK59	NP_001333665.1	Methylcytosine dioxygenase TET2	1912	Mus musculus (Mouse)
Hu TET2	TET2_HUMAN	Q6N021	NP_001120680.1	Methylcytosine dioxygenase TET2	2002	Homo sapiens (Human)
Mus TET3	TET3_MOUSE	Q8BG87	NP_001334242.1	Methylcytosine dioxygenase TET3	1803	Mus musculus (Mouse)
Hu TET3	TET3_HUMAN	O43151	NP_001352951.1	Methylcytosine dioxygenase TET3	1795	Homo sapiens (Human)



TET家族蛋白基序分析

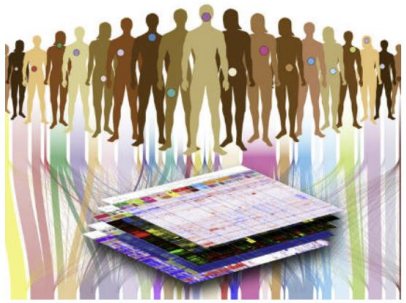


TCGA: The Cancer Genome Atlas Program: 癌症基因组图谱计划

The Cancer Genome Atlas Program

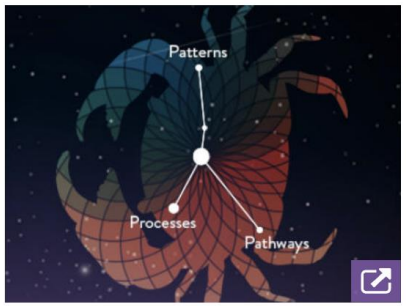
The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. This joint effort between NCI and the National Human Genome Research Institute began in 2006, bringing together researchers from diverse disciplines and multiple institutions.

Over the next dozen years, TCGA generated over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data. The data, which has already led to improvements in our ability to diagnose, treat, and prevent cancer, will remain publicly available for anyone in the research community to use.



TCGA Outcomes & Impact

TCGA has changed our understanding of cancer, how research is conducted, how the disease is treated in the clinic, and more.

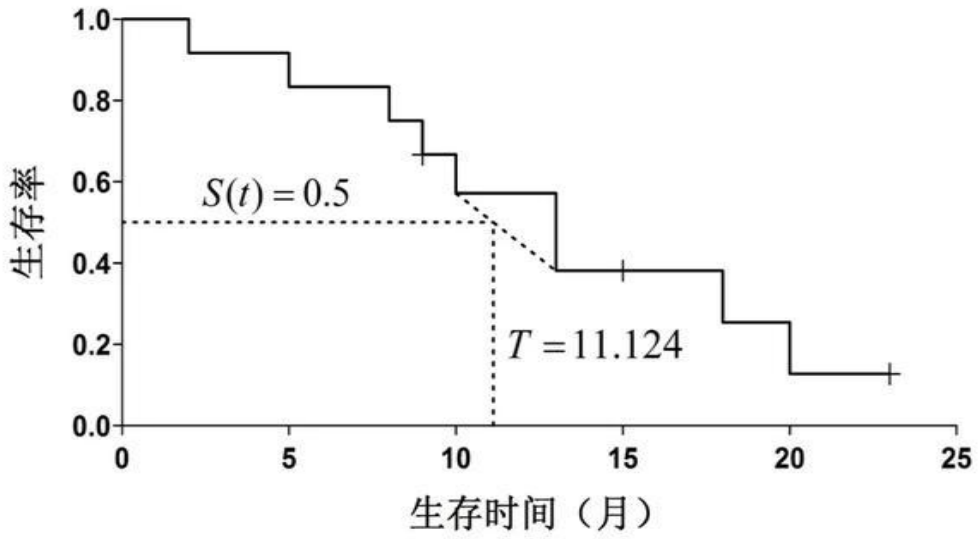


TCGA's Pan-Cancer Atlas

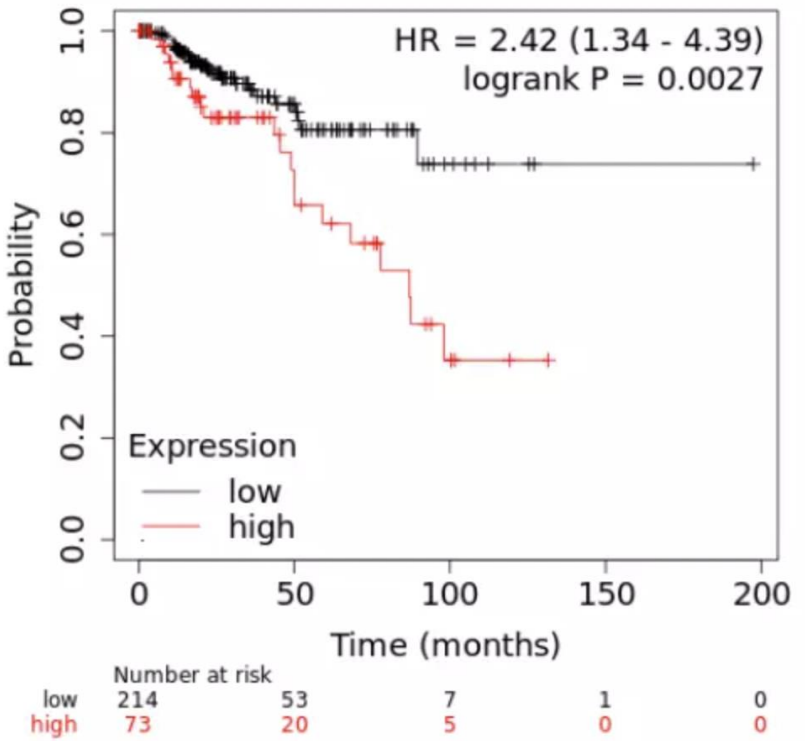
A collection of cross-cancer analyses delving into overarching themes on cancer, including cell-of-origin patterns, oncogenic processes, and signaling

- TCGA数据库是由美国国家癌症研究所（NCI）和国家人类基因组研究所（NHGRI）合作建立的癌症研究项目，收集和整理癌症相关的各种组学数据，目前共收录了33种癌症类型，并且数据免费公开，为癌症研究提供了极大的便利。
- 官方网站是：https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
- 数据库中包括临床样本信息，以及多组学的测序数据，包括了基因组，转录组，表观遗传，蛋白组等各个组学数据

Kaplan-Meier 生存曲线



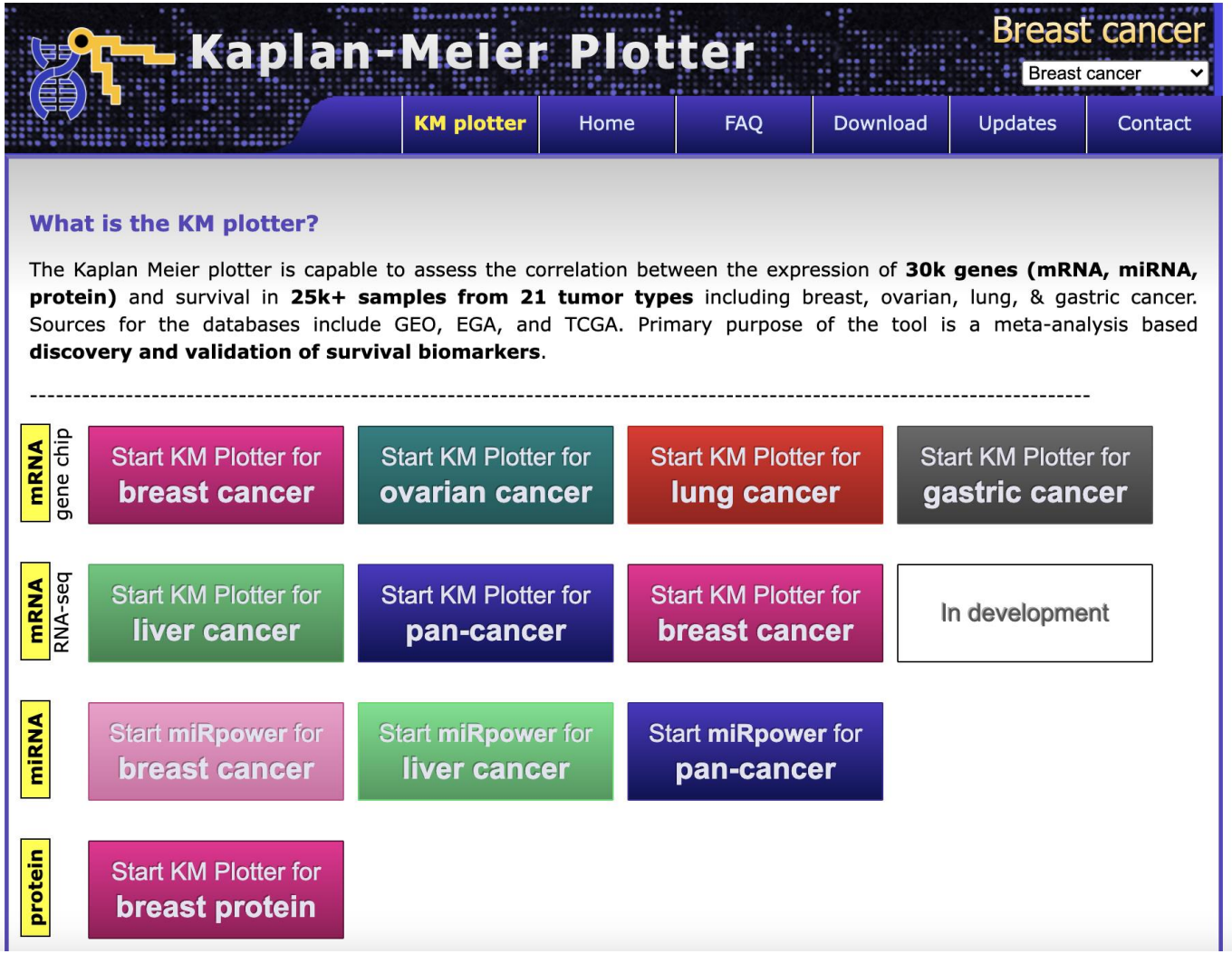
$$\hat{S}(t)=\frac{t\text{时刻仍存活的患者数}}{\text{观察总患者数}}$$



- KM法即乘积极限法（product-limit method），是现在生存分析最常用的方法，是由Kaplan和Meier于1958年提出，因此称Kaplan-Meier法，通常简称KM法。KM法是这样估计生存曲线：首先计算出活过一定时期的病人再活过下一时期的概率（即生存概率），然后将逐个生存概率相乘，即为相应时段的生存率。

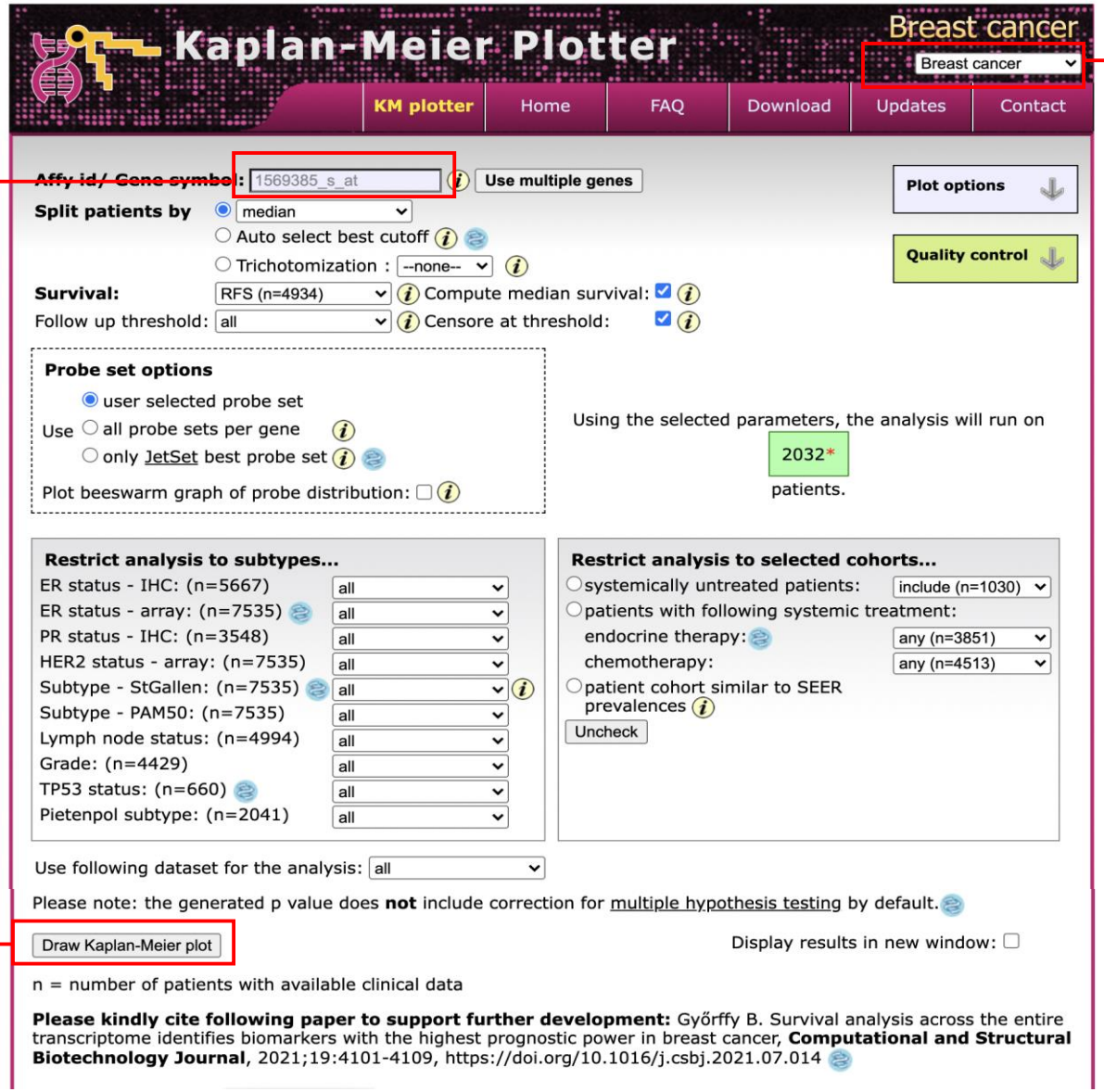
- 在比较生存曲线时，可以对比同样时间不同组病人的存活率，曲线靠上的病人存活率更高，因此曲线在上方代表病人具有更好的生存。

Kaplan Meier Plotter在线分析软件



- Kaplan Meier Plotter在线分析软件能够评估来自 21 种肿瘤类型（包括乳腺癌、卵巢癌、肺癌和胃癌）的2万5个样本中3万个基因（mRNA、miRNA、蛋白质）的表达与病人生存之间的相关性。
- 数据库的来源主要是TCGA数据库。
- 该工具的主要目的发现和验证肿瘤生存生物标志物。
- 网站为：https://kmplot.com/analysis

Kaplan Meier Plotter在线分析软件使用



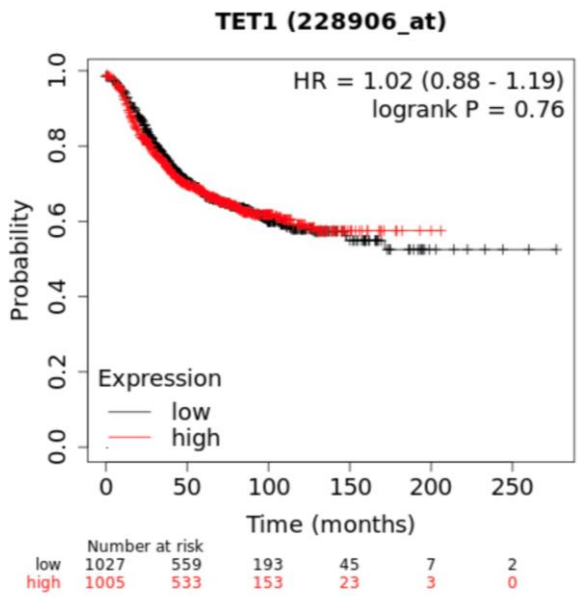
癌症种类

输入基因名或ID

绘制生存曲线

乳腺癌病人中，TET2高表达病人生存更差

P value: 0.7639



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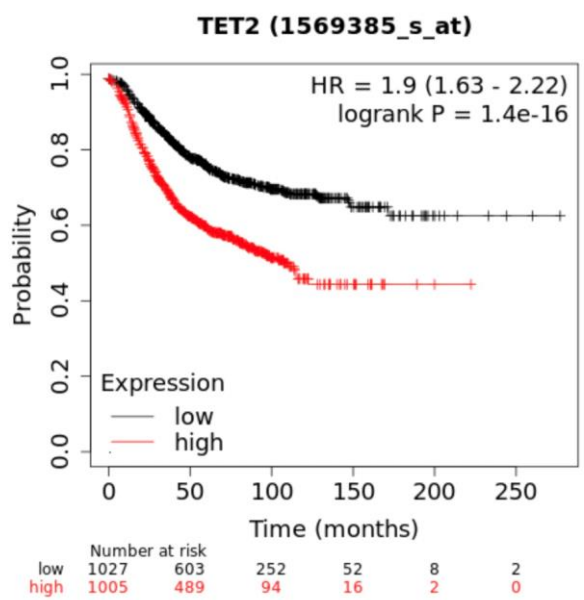
Upper quartile survival

Low expression cohort (months)	High expression cohort (months)
40.3	36.96

P value: 1.4e-16



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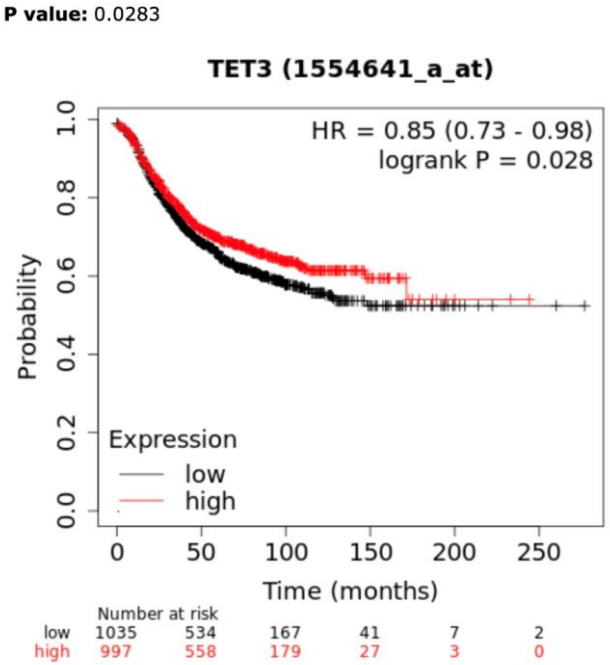
Upper quartile survival

Low expression cohort (months)	High expression cohort (months)
61.2	27.96

P value: 0.0283



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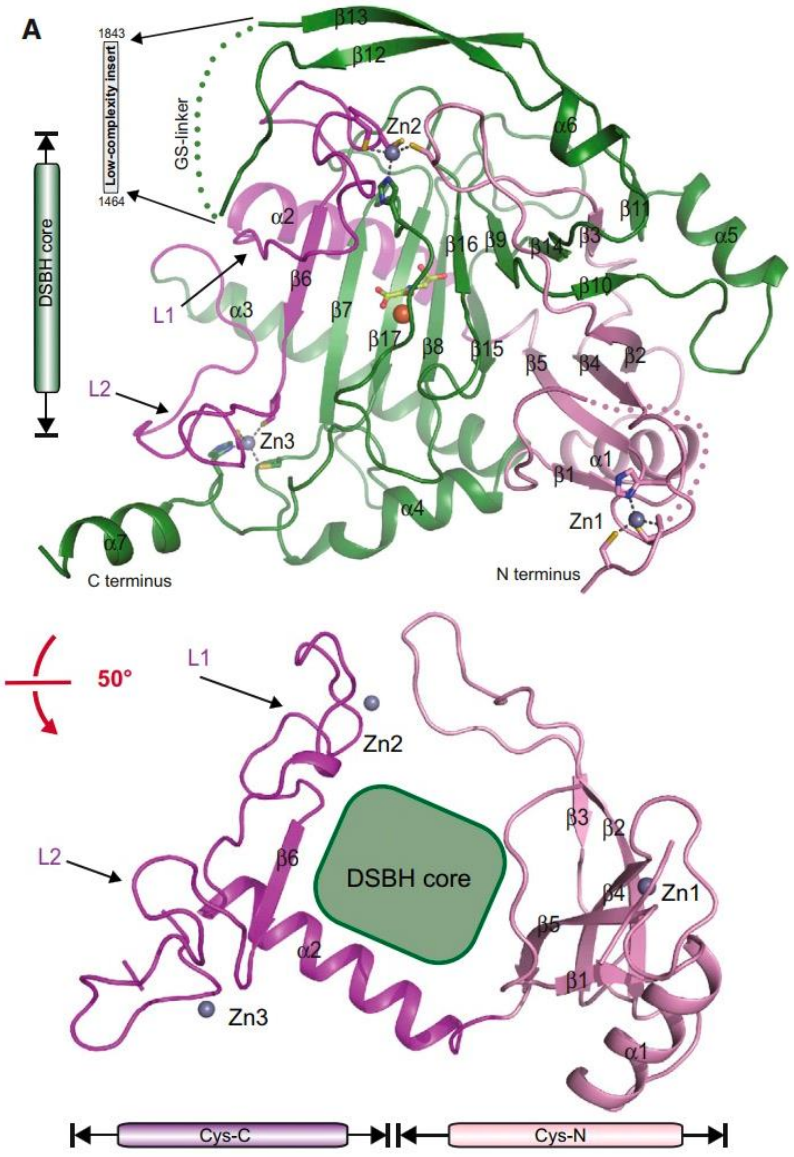
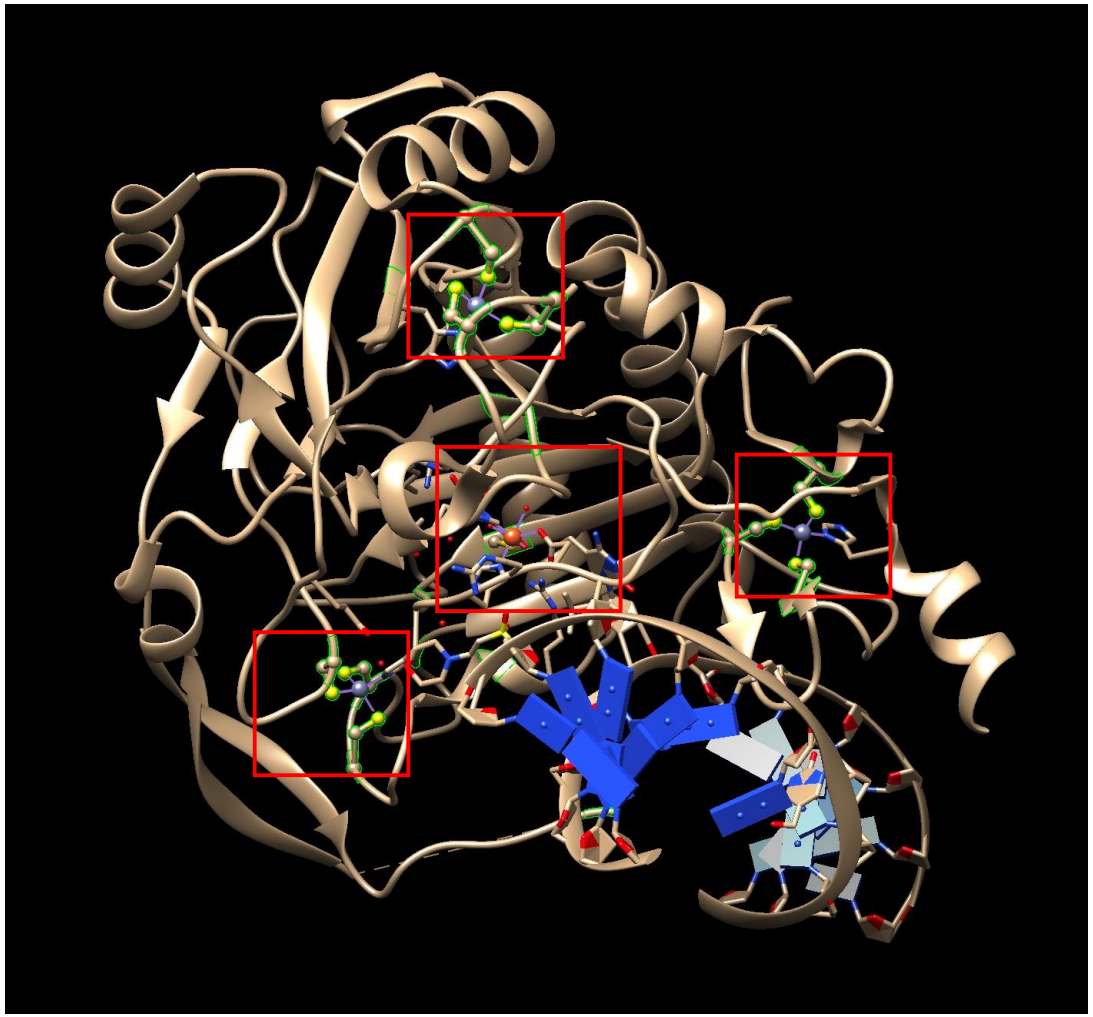
Upper quartile survival

Low expression cohort (months)	High expression cohort (months)
35.09	42

Kaplan-Meier Plotter

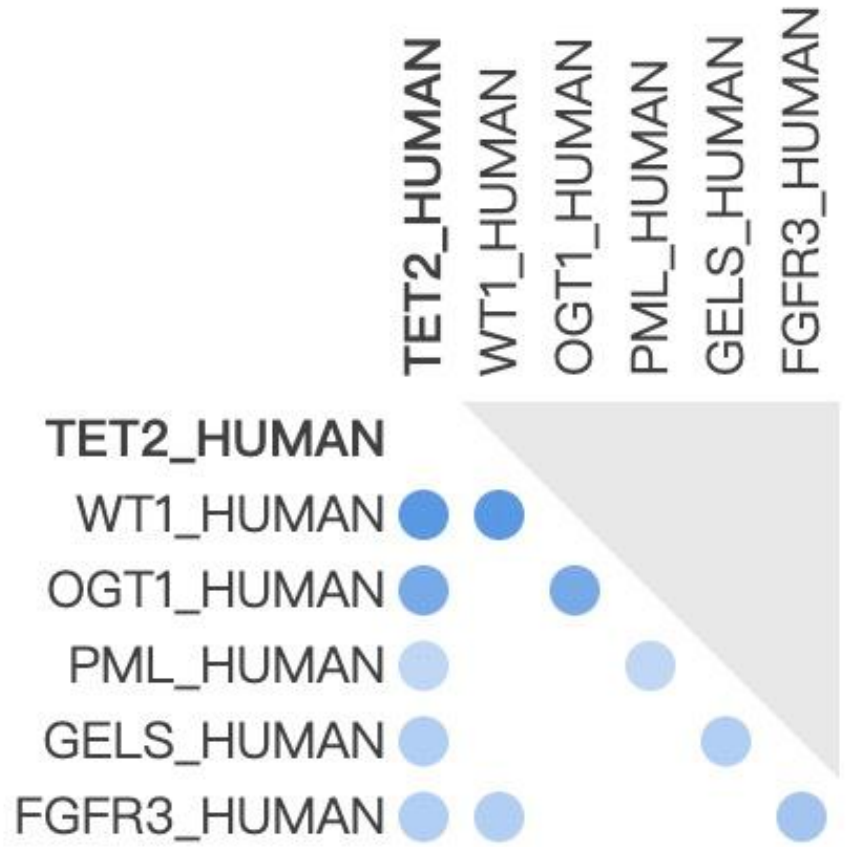
TET2核心结构域分析





Lulu Hu et. al., Cell , 2013

TET2 相互作用蛋白分析



Q6N021与5种蛋白质有二元相互作用

Interactors	Cell resource	Function
2-HG	Human cell line	Competitive inhibitor of 2-OG
Vitamin C	Mouse ESCs	Enhances TET2 enzymatic activity
miR-22	Mouse hematopoietic cells	Inhibits TET2 gene expression
miR-29, miR-125 and miR-101	Human and mouse hematopoietic cell lines	Inhibits TET2 gene expression
EBF1	Human cell line	Binding partner of TET2 to regulate DNA methylation
WT1	Human and mouse hematopoietic cell lines	Recruits TET2 to specific genomic loci for 5mC hydroxylation
OGT	Human cell line and mouse ESCs	Being recruited to chromatin for histone modification and gene transcription
VprBP	Human cell line and mouse ESCs, MEFs	Promotes TET2 binding to DNA through monoubiquitylation
IDAX	Human cell line and mouse ESCs	Promotes TET2 protein degradation in a caspase-dependent mechanism

- TET2和OGT对DNA和组蛋白的双重表观遗传修饰共同参与基因转录调控
- WT1招募TET2到特定的基因组位点进行5mC羟基化

Pan, et. al, IUBMB Life, 2015

2022 Thanks ~

G02组