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刘默芳, 同济大学生命科学与技术学院院长聘特聘教授, 长期致力于RNA调控与精子发生及男性不育研究。国家杰出青年科学基金、国家“万人计划”领军人才、新基石研究员、东方英才团队等人才项目获得者, “十四五”科技部重点研发计划项目负责人。以通讯作者(含共同)在*Science*、*Cell* (2篇)、*New Engl J Med*、*Nat Cell Biol*、*Mol Cell*、*Dev Cell*、*Cell Res*等发表论文40余篇, 成果入选“国家重点研发计划重大科技成果”“中国生命科学十大进展”“中国科学院科技亮点成果”(2次), 受邀发表*Nat Rev Mol Cell Biol*长文综述, 系统总结了piRNA研究进展。多次受邀在Keystone、EMBO、Gordon等重要国际学术会议上作大会报告, 组织EMBO、CSHA等重要国际学术会议, 目前担任《中国科学: 生命科学》副主编和*Cell Res*、*J Biol Chem*、*Biol Reprod*等期刊编委, 以及中国生物化学与分子生物学会RNA专业委员会主任。曾获上海市自然科学奖一等奖、全国妇幼健康科学技术奖自然科学一等奖、谈家桢生命科学创新奖、上海市巾帼创新奖等荣誉。

癌/睾丸抗原的促癌机制研究新进展

金纯辉¹, 刘默芳^{1,2*}, 赵爽^{3*}

(1 国科大杭州高等研究院, 生命与健康科学学院, 杭州 310024; 2 同济大学生命科学与技术学院, 上海 200092; 3 中国科学院分子细胞科学卓越创新中心(生物化学与细胞生物学研究所), 上海 200031)

摘要: 癌/睾丸抗原基因在生理条件下特异性在睾丸中表达, 参与调控雄性生殖发育与分化; 这类基因常在肿瘤细胞中被异常激活, 以癌基因的角色促进肿瘤发生、转移、耐药及复发等生物学过程。癌/睾丸抗原成员根据其基因定位可分为X染色体编码和非X染色体编码两大类。大量研究发现, 癌/睾丸抗原具有较强的自发免疫原性, 能够引发体液免疫和细胞免疫反应。特别是, 癌/睾丸抗原基因在正常体细胞中不表达或极低表达, 这一特性使其成为肿瘤免疫治疗领域极具潜力的靶点。本文将总结癌/睾丸抗原的促癌机制及其在肿瘤中被异常激活的机制研究新进展, 并探讨靶向癌/睾丸抗原的抗癌药物研发及临床应用。

关键词: 癌/睾丸抗原; 肿瘤发生; 肿瘤微环境; 免疫治疗

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Cancer/testis antigens in carcinogenesis: Mechanisms and frontiers

JIN Chun-Hui¹, LIU Mo-Fang^{1, 2*}, ZHAO Shuang^{3*}

(1 School of Life Science, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Hangzhou 310024, China; 2 School of Life Science and Technology, Tongji University, Shanghai 200092, China; 3 CAS Center for Excellence in Molecular Cell Science, Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences-University of Chinese Academy of Sciences, Shanghai 200031, China)

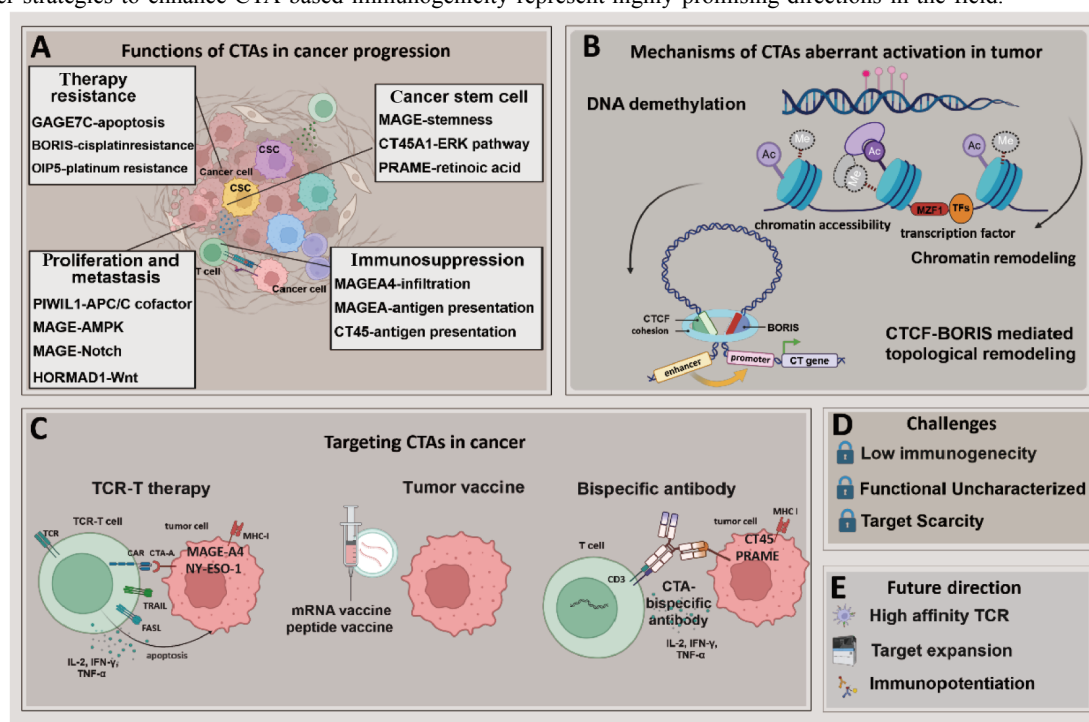
Abstract: Cancer/testis antigens (CTAs) are restrictively expressed in testis but aberrantly activated in tumors, functioning in regulating male germline development and promoting carcinogenesis. As oncogenic regulators, CTA members are widely involved in tumor initiation, invasion, metastasis, chemo-resistance and relapse, while their intrinsic immunogenicity and

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*通信作者: E-mail: szhao01@sibcb.ac.cn(赵爽); mfliu@tongji.edu.cn(刘默芳)

somatic silencing make them ideal targets for cancer immunotherapy. Here, we summarize recent advances in understanding of the molecular mechanisms underlying CTAs' oncogenic functions and aberrant activation in cancers, and discuss CTA-targeting therapeutic strategies and clinical translation. Since the identification of the first CTA, MAGE-A1, in 1991, numerous immunogenic germline-specific tumor-associated antigens have been discovered with the development of serological analysis of cDNA expression libraries (SEREX). Based on their genomic loci, CTAs are classified as X-encoded (X-CTAs) and non-X-encoded (non-X-CTAs). X-CTAs, such as GAGE, SSX, MAGE, and NY-ESO-1, are organized in ordered tandem/inverted repeats in X-chromosome, showing high conservation across species but their roles remaining unclear yet in male reproduction. Non-X-CTAs, such as PIWI and TDRD families, display tumor-promoting functions during carcinogenesis and well-established roles during male germline development. Aberrant activation of CTA genes in tumors is tightly linked to epigenetic reprogramming (DNA demethylation, histone acetylation, chromatin accessibility) and complex regulation by transcription factors, regulatory RNAs, and even other CTAs. Notably, CTA expression is heterogeneous across tumor types, subpopulations and stage-specific in some malignancies, endowing cancer cells with phenotypic plasticity and adaptive advantages. Notably, CTAs play various roles during tumorigenesis, which have been evident to activate oncogenic signaling, modulate post-translational modification and degradation of key signaling molecules, sustain cancer stemness, regulate tumor-microenvironment crosstalk, mediate immune escape throughout tumor progression and etc. Collectively, recent studies demonstrate that CTAs function as critical regulators in malignant tumor progression. Given their intrinsic immunogenicity and testis-restricted expression pattern, CTAs represent ideal targets for cancer immunotherapy. Meanwhile, an extensive pattern of alternative splicing and genetic alterations in cancer cells generate a large repertoire of potential antigenic peptides derived from CTA genes. Nevertheless, current clinical trials and applications are largely limited to a few prominent targets, such as NY-ESO-1. Hence, systematically investigating the immunogenicity of CTAs and developing proper strategies to enhance CTA-based immunogenicity represent highly promising directions in the field.



Key words: cancer/testis antigens; carcinogenesis; tumor microenvironment; immunotherapy

癌/睾丸抗原(cancer/testis antigen, CTA)的表达具有高度特异性,仅在男性睾丸生殖细胞、胎盘及多种肿瘤细胞中表达,正常体细胞几乎不表达,是“肿瘤特异性极强”的抗原家族,已成为肿瘤免疫治疗的核心靶点。传统放化疗因对机体损伤显著、易诱发耐药,在肿瘤临床治疗中面临严峻挑战,推动靶向治疗与免疫治疗已成为当前研究热点。尽管肿瘤发生、转移及

耐药均受驱动基因调控,但受癌细胞高度可塑性、肿瘤干细胞及免疫抑制微环境等多重因素影响,单纯靶向驱动基因的临床获益仍十分有限^[1-4]。T细胞免疫治疗通过激活或改造自体T细胞,实现对肿瘤细胞的精准识别与清除,是当前最具潜力的个体化治疗策略。CTAs因仅在睾丸组织生理性表达,成为TCR-T细胞治疗的理想靶点。自黑色素瘤中首次发现

MAGE-A1以来,大量研究证实CTAs在多种恶性肿瘤中异常高表达并参与调控肿瘤增殖等恶性表型。目前,FDA已批准靶向MAGE-A4的TCR-T疗法(Tecelra)用于既往接受过化疗,且HLA-A*0201、HLA-A*0202、HLA-A*0206、MAGE-A4阳性的不可切除或转移性滑膜肉瘤患者。相关临床研究结果显示,接受治疗的滑膜肉瘤患者客观缓解率为39%,45.6%的患者免疫应答持续至少6个月^[1]。多项针对其他CTAs的临床试验亦在开展,充分展现了其临床转化价值。

与此同时,越来越多的机制研究发现CTAs参与RNA代谢、离子稳态等关键生物学过程,其异常表达与DNA甲基化及表观遗传紊乱密切相关,提示精子发生程序异常激活在体细胞癌变中具有重要意义。本文系统综述肿瘤细胞中睾丸特异性CTAs异常表达的分子机制与促癌功能,为靶向CTAs的肿瘤免疫治疗提供理论支撑。

1 癌/睾丸抗原的发现

Boon课题组在1991年发现病程进展良好的黑色素瘤患者具有识别自体肿瘤的杀伤性T细胞(cytotoxic T-lymphocyte, CTL),并利用基因克隆技术成功鉴定到癌症抗原基因*MZ2-E*,编码基因为MAGE1^[2-4]。后续的研究发现MAGE1在睾丸及胎盘中特异性表达,后被命名为MAGE-A1^[3,5]。利用肿瘤患者CTL扩增及cDNA文库转染体外激活CTL的鉴定系统,鉴定到MAGE-A2、MAGE-A3、BAGE及GAGE等肿瘤新抗原基因^[6-9]。这些肿瘤抗原生理条件下仅在雄性生殖系中表达,因此被命名为癌/睾丸抗原^[10-12]。随着cDNA表达文库血清学分析(serological analysis of cDNA expression libraries, SEREX)技术的开发,研究人员鉴定了大量具有免疫原性且生殖系特异表达的肿瘤相关抗原(tumor associated antigen, TAA),包括SSX蛋白家族(synovial sarcoma/X breakpoint)、SCP1(synaptonemal complex protein 1)和强免疫原性蛋白NY-ESO-1(New York esophageal squamous cell carcinoma 1)等。表1总结了靶向癌/睾丸抗原的TCR-T细胞临床试验。

1.1 位于X染色体上的癌/睾丸抗原

癌/睾丸抗原根据编码基因所在染色体可分为X染色体编码的癌/睾丸抗原(X-CTA)和非X染色体编码的癌/睾丸抗原(non-X-CTA)。位于X染色体上的癌/睾丸基因(cancer testis gene, CT genes)以重复和

反向重复的形式有序排列形成癌/睾丸抗原家族,如GAGE、SSX、PAGE和XAGE等癌/睾丸抗原基因位于Xp11区域^[13-15],MAGE及NY-ESO-1则位于Xq28区域^[2,16](图1)。位于X染色体的癌/睾丸抗原基因序列在物种间保守性较高,但在雄性生殖中的功能及作用机制尚缺乏系统性研究(表2)。

大部分X染色体来源癌/睾丸抗原主要在精原细胞及初级精母细胞中表达,部分在胚胎发育及精原干细胞中表达^[17]。MAGEA家族共有12个成员,MAGE-A1在性分化后的生殖细胞中开始表达,在处于增殖状态的生殖细胞中高表达^[18]。MAGE-A4在精原干细胞及所有精原细胞中均有表达^[19,20],MAGEA家族基因整体敲除导致小鼠睾丸变小、精母细胞发生p53依赖的细胞凋亡^[21]。MAGEB家族共有4个成员,MAGE-B2作为RNA结合蛋白抑制G3BP的mRNA翻译,调控小鼠精原干细胞的自我更新^[22],而MAGE-B4对于小鼠精子发生及雄性生育是非必需的^[23]。SSX1基因属于灵长类特有基因(primate specific genes, PSGs),在少弱精症及畸形精子症患者样本中鉴定到SSX1基因突变,基于非人灵长类的研究证明SSX1敲除导致精子形态异常、活力下降^[24]。NY-ESO-1表达于精原细胞和初级精母细胞,被认为与精原细胞的增殖相关^[18]。

目前发现,10%以上的X染色体基因在睾丸及肿瘤组织中共表达,部分基因在滋养层表达。MAGE蛋白家族在黑色素瘤中被鉴定为肿瘤新抗原,其成员在结直肠癌、肺癌、前列腺癌、乳腺癌等众多癌症组织中表达,并与癌症干细胞(cancer stem cells, CSCs)的富集密切相关^[25]。NY-ESO-1在几乎所有检测的脂肪肉瘤样本中表达^[26],在80%以上的神经母细胞瘤和滑膜肉瘤患者组织中表达,在其他大部分实体瘤中也有不同程度的表达^[27-30]。这些研究显示,X-CTA在肿瘤组织中的表达具有广谱性,提示其参与肿瘤进展的早期调控事件。

1.2 非X染色体来源的癌/睾丸抗原

大量非X染色体来源的癌/睾丸抗原的鉴定得益于转录组测序及蛋白质组分析技术的进步。PIWI是生殖系特异性Argonaute蛋白家族,结合生殖细胞特异性piRNA,对雄性生殖细胞发育至关重要^[31-34]。研究发现该家族4个成员,PIWIL1(HIWI)、PIWIL2(HILI)、PIWIL3和PIWIL4(HIWI2),均在人类癌组织中高表达。PIWIL1在胰腺癌、胃癌、结直肠癌、胶

表1 靶向癌/睾丸抗原的TCR-T细胞临床试验
Table 1 Clinical trials of TCR-T therapy targeting CTAs

靶点基因	HLA亚型	分期	联用药物	适应证	NCT
NY-ESO-1/LAGE-1A	HLA-A*02	I	环磷酰胺 氟达拉滨 纳武利尤单抗 阿地白介素	Ⅳ期或局部晚期实体瘤	NCT02775292
NY-ESO-1	HLA-A*0201	Ⅱ	环磷酰胺 氟达拉滨 阿地白介素	NY-ESO-1阳性转移性肿瘤	NCT01967823
NY-ESO-1	HLA-A*0201 HLAA*0205 HLA-A*0206	I / Ⅱ	环磷酰胺 氟达拉滨	复发/难治性卵巢癌	NCT01567891
NY-ESO-1	HLA-A*02	I	环磷酰胺 氟达拉滨	滑膜肉瘤	NCT01343043
NY-ESO-1	HLA-A*02	Ⅱ	环磷酰胺 氟达拉滨	晚期/转移性黏液样/圆细胞脂肪肉瘤	NCT02992743
NY-ESO-1/LAGE-1A	HLA-A*02	Ⅱ	环磷酰胺 氟达拉滨	晚期实体瘤	NCT03967223
NY-ESO-1/LAGE-1A	HLA-A*02	I	环磷酰胺 氟达拉滨 ±帕博利珠单抗	晚期/复发非小细胞肺癌	NCT03709706
NY-ESO-1/LAGE-1A	HLA-A*02	I / Ⅱ	环磷酰胺 氟达拉滨	既往治疗后晚期/转移性滑膜肉瘤	NCT06048705
NY-ESO-1/LAGE-A	HLA-A*02	I / Ⅱ	环磷酰胺 氟达拉滨	既往治疗后晚期滑膜肉瘤	NCT05943990
MAGE-A4	HLA-A*02	I	环磷酰胺 氟达拉滨	复发/难治实体瘤	NCT03132922
MAGE-A4	HLA-A*02	Ⅱ	环磷酰胺 氟达拉滨	晚期/转移性滑膜肉瘤	NCT04044768
MAGE-A4	HLA-A*02	Ⅱ	环磷酰胺 氟达拉滨 帕博利珠单抗	复发或转移性头颈鳞癌	NCT04408898
MAGE-A4	HLA-A*02	Ⅱ	环磷酰胺 氟达拉滨 ±纳武利尤单抗	卵巢癌	NCT05601752
PRAME	HLA-A*02:01	I / Ⅱ	环磷酰胺 氟达拉滨 ±纳武利尤单抗	复发/难治实体瘤	NCT03686124
PRAME	HLA-A*02:01	Ⅲ	环磷酰胺 氟达拉滨	既往治疗后不可切除或转移性皮肤黑色素瘤	NCT06743126
MAGE-A1	HLA-A*02:01	I	环磷酰胺 氟达拉滨	晚期实体瘤	NCT03441100
MAGE-A4/8	HLA-A*02:01	I	环磷酰胺 氟达拉滨	晚期实体瘤	NCT03247309
CT83	HLA-A*01:01	I	环磷酰胺 氟达拉滨 阿地白介素	转移/复发难治上皮肿瘤	NCT05035407
CT83	HLA-A*01:01	I	环磷酰胺 氟达拉滨 阿地白介素	转移性胃/乳腺/宫颈/肺癌等	NCT05483491
MAGE-C2	HLA-A2	I / Ⅱ	丙戊酸 5-氮杂胞苷 阿地白介素	晚期黑色素瘤或复发/转移性头颈鳞癌	NCT04729543
MAGE-A10	HLA-A*02:01 HLA-A*02:06	I	环磷酰胺 氟达拉滨	尿路上皮癌、黑色素瘤或头颈癌	NCT02989064

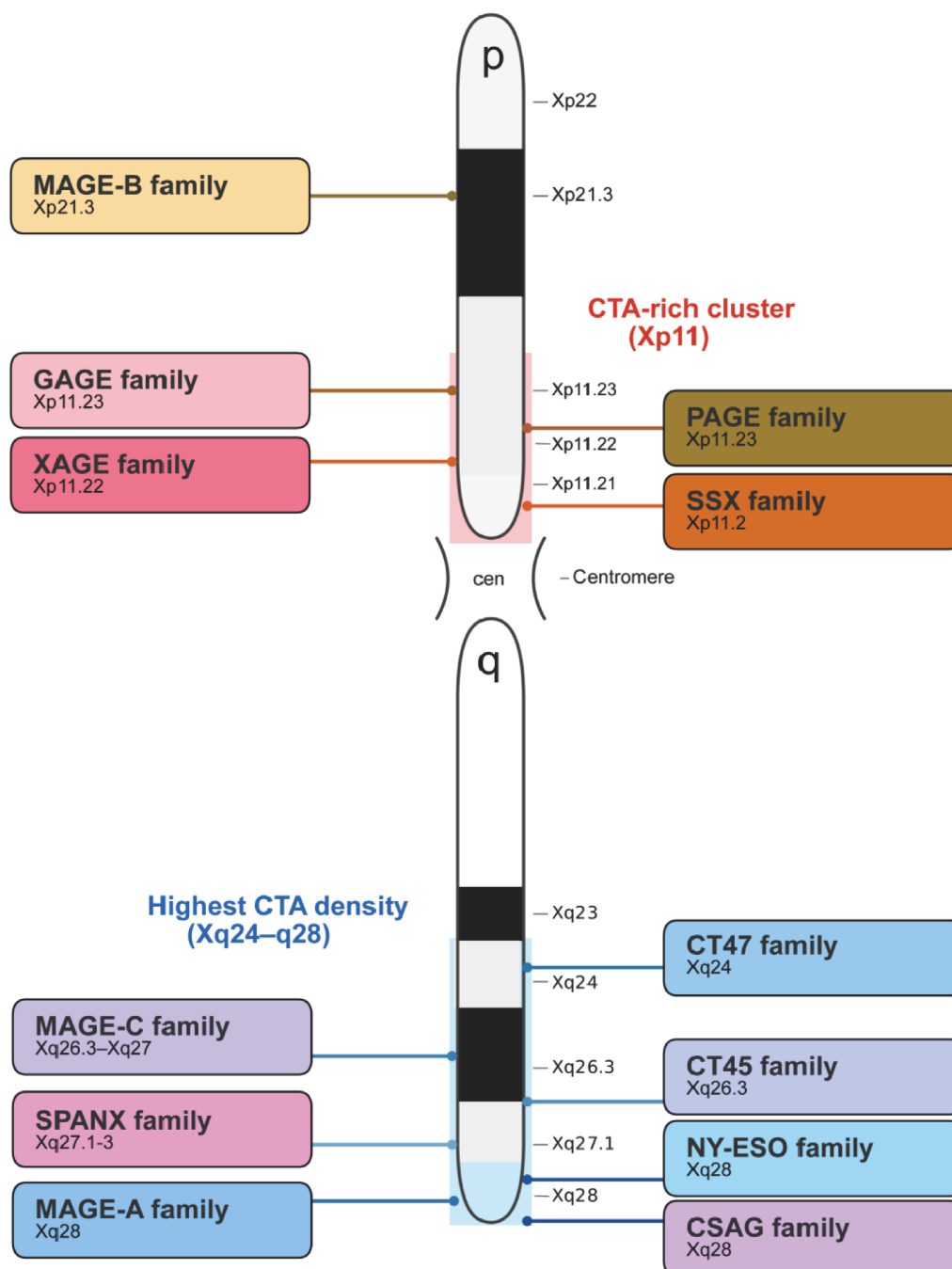


图1 癌/睾丸抗原家族基因在X染色体上的分布

Figure 1 Distribution of CTA gene families on the X chromosome

质瘤、宫颈癌及肝癌等组织中异常高表达^[32,35-37]。我国科学家发现PIWIL1以非piRNA依赖的方式促进癌细胞增殖及转移^[38,39]。PIWIL2在结直肠癌、肝癌、宫颈癌等组织中表达上调^[40,41], PIWIL3和PIWIL4则被报道在膀胱癌和胰腺癌等少数组织中高表达^[41-43]。此外,参与piRNA生成的TDRD家族蛋白也是重要的CTAs。TDRD1蛋白在约68%的前列腺癌样本中高表达^[44], *TDRD4* mRNA水平在部

分肝癌样本中显著升高并与CD133表达水平正相关^[44,45]。在结直肠癌患者组织芯片中,还发现*TDRD1*、*TDRD5*、*TDRD9*存在多个突变,这些突变可能与结直肠癌的病变相关^[46]。YBX2在胚胎发育早期阶段及睾丸组织中特异性表达,参与mRNA翻译过程。子宫内膜癌及肝癌组织中YBX2高表达,通过调控靶基因稳定性促进癌细胞增殖^[47-49]。肺癌细胞中HORMAD1高表达,激活WNT/ β -catenin通路

表2 X染色体癌/睾丸抗原家族的表达及功能

Table 2 Expression patterns and indicated functions of X-CTA

CT基因家族	家族成员	染色体位置	表达癌症类型	功能
MAGE-A	12	Xq28	黑色素瘤等实体瘤	促进细胞周期、抗凋亡;增强mTOR信号
MAGE-B	6	Xp21.3	黑色素瘤等实体瘤	增强细胞应激耐受;促进肿瘤细胞增殖
MAGE-C	3	Xq26~27	多发性骨髓瘤及部分实体瘤	促进肿瘤细胞增殖
GAGE-A	8	Xp11.23	黑色素瘤等实体瘤	抗凋亡;增强化疗耐药
GAGE-B	8	Xp11.23	黑色素瘤等实体瘤	参与抗凋亡与应激耐受
PAGE	5	Xp11.23	前列腺癌及其他肿瘤	降低ROS并增强氧化应激下细胞增殖;促进化疗及放疗耐药
SAGE	1	Xq26.3	肉瘤、食管癌等	免疫原性,免疫治疗靶点;致癌功能研究有限
XAGE	6	Xp11.22	肺腺癌、部分乳腺癌等	参与促增殖、迁移侵袭表型
CAGE	1	Xp22.11	胃癌等实体瘤	介导奥希替尼耐药并增强侵袭性
NY-ESO-1	3	Xq28	黑色素瘤、滑膜肉瘤等	促进ERK1/2活化;增强失巢凋亡耐受
SSX	6	Xp11.2	滑膜肉瘤等	干扰Polycomb复合体组织、解除其靶基因抑制
CSAG	2	Xq28	黑色素瘤等实体瘤	与获得性紫杉醇耐药相关
SPANX	10	Xq27.1~3	黑色素瘤等实体瘤	调控Lamin A/C影响核结构;促进肿瘤增殖
IL13RA1	1	Xq24	霍奇金淋巴瘤及部分胃癌、结直肠癌	介导IL-13/IL-4信号参与肿瘤增殖及转移
FTHL17	1	Xp21.2	结直肠癌	功能未知
NXF2	1	Xq22.1	急性白血病、三阴性乳腺癌及部分鳞癌	功能未知

调节上皮-间充质转换(epithelial-mesenchymal transition, EMT),促进癌细胞增殖及远端转移^[50,51]。Wang等^[52]联合转录组及蛋白质谱分析19个癌症组织相关癌/睾丸抗原,共鉴定到870个睾丸及肿瘤特异性高表达的基因,包括蛋白质编码基因和非编码基因;最后鉴定出300多个高可信度的蛋白质编码基因,发现不同肿瘤表达的癌/睾丸抗原具有明显的异质性。这些最新的研究提示,非X染色体来源的癌/睾丸抗原表达具有一定的肿瘤组织特异性。另一方面,非X染色体癌/睾丸抗原在精子发生中的功能较为明确,为进一步探索其促癌功能提供了线索。

2 癌/睾丸抗原促癌的功能与机制

癌/睾丸抗原因其限制性表达模式及潜在的免疫治疗价值成为新的研究热点。作为一类新的肿瘤相关标志物,CTAs通过调节肿瘤相关信号通路、细胞周期、细胞连接等参与癌细胞增殖及迁移过程,深入研究还发现部分CTAs在肿瘤耐药、免疫抑制微环境形成中发挥重要作用。本节将从促癌信号通路、肿瘤干细胞维持及肿瘤微环境/耐药三个主要方面对癌/睾丸抗原促癌功能及分子机制进行概述。

2.1 癌/睾丸抗原激活促癌信号通路

体细胞内在的信号转导异常是细胞癌变的重要驱动因素,进化上保守的Notch、Wnt及Hedgehog信号通路在癌细胞中通常处于失调状态,促进肿瘤微环境

调控上皮-间充质转换、循环肿瘤细胞(circulating tumor cells, CTCs)的定植等。癌/睾丸抗原可通过增强癌症相关信号通路激活发挥促癌功能。MAGE-A1与转录调控因子SKIP(Ski interacting protein)互作招募HDAC1,抑制NOTCH1的转录激活^[53]。GAGE-7C高表达促进肿瘤细胞启动对IFN- γ 、化疗药物及放疗的抗凋亡途径^[54]。NY-ESO-1通过增强ERK1/2通路活性,促进癌细胞失巢凋亡耐受^[55]。肺癌细胞中LDHC的高表达会提高AKT和GSK-3 β 的磷酸化水平,从而激活PI3K/AKT/GSK-3 β 癌基因信号通路^[56]。HORMAD1促进AKT及GSK-3 β 磷酸化,激活 β -catenin的细胞核定位,增强WNT/ β -catenin信号通路活性^[51]。

此外,还有部分癌/睾丸抗原通过调控相关信号分子的修饰和降解发挥功能。MAGE蛋白家族成员的MHD结构域具有TRIM28/KAP1等泛素连接酶结合活性,MAGE-C2增强泛素连接酶活性,促进DNA修复,抑制细胞凋亡^[57]。MAGE-C2还可以与转录因子STAT3相互作用,抑制STAT3多聚泛素化及蛋白酶体依赖的降解程序,促进STAT3磷酸化及下游基因转录^[58]。Yang等^[59]发现,MAGE-A11通过招募HUWE1,促进剪接与多聚腺苷酸化因子亚基PCF11泛素化修饰及降解,导致癌细胞可变腺苷酸化(alternative polyadenylation, APA)紊乱,癌基因及抑癌基因mRNA 3'UTR缩短,促进癌细胞增殖。刘默芳课题组发现胰腺癌中PIWIL1作为APC/C泛素

连接酶的共激活因子促进靶蛋白的降解,促进癌细胞肝转移^[38]。PIWIL1还可与UPF1相互作用调节mRNA的降解,促进胃癌细胞恶性增殖^[39]。

2.2 癌/睾丸抗原维持肿瘤细胞干性

大量研究发现血液肿瘤及实体瘤中存在一类与肿瘤起始、复发相关的,具有自我更新能力的肿瘤干细胞。肿瘤干细胞在转录和表观遗传层面与胚胎干细胞、成体干细胞存在显著相似性,胚胎/生殖程序性调控异常激活可能是肿瘤干性维持的重要机制^[60]。部分癌/睾丸抗原参与肿瘤干细胞的维持。MAGE-A3在膀胱癌干细胞中高表达,促进癌症干细胞在体内的增殖^[60-62]。MAGE-C1在多发性骨髓瘤CD34⁺干细胞和未成熟B细胞中高表达,提示MAGE-C1可能在肿瘤早期发生中发挥重要作用^[63]。乳腺癌细胞中CT45A1表达显著激活ERK和CREB信号通路,增强癌细胞干性及成瘤能力^[64]。癌细胞中高表达的PRAME可与维甲酸受体(retinoic acid receptor, RAR)结合并阻断维甲酸诱导的受体激活及干性相关基因转录,提示PRAME可能参与维持癌细胞干性^[65]。有限稀释实验证明,TEX19对癌细胞的自我更新及克隆形成是必要的。TEX19在结肠癌早期阶段开始表达,为早期腺癌形成所必需^[66]。YBX2/CT45调控轴促进子宫内膜癌干细胞群维持及紫杉醇耐药,其表达水平与临床患者分级显著正相关^[48]。

近年来的研究发现,MAGEA、NY-ESO-1等在鳞状上皮不典型增生组织中表达^[67]。非浸润性乳腺导管原位癌(ductal carcinoma in situ, DCIS)是侵袭性乳腺癌的前体病理阶段,病理学证据显示MAGEA在乳腺导管原位瘤及良性增生组织中高表达^[68]。KK-LC-1在胃癌早期组织中表达^[69]。MAGE-A3/A6-TRIM28复合物通过AMPK信号通路调控与胰腺癌起始密切相关的细胞自噬^[70,71]。这些研究提示癌/睾丸抗原可能通过调控肿瘤干细胞自我更新及其他机制参与细胞癌变及癌症起始过程,但仍有待体内功能实验的进一步验证。

2.3 癌/睾丸抗原在肿瘤微环境调控及细胞耐药中的作用

免疫抑制微环境是癌细胞难以被免疫系统彻底清除的关键因素之一,肿瘤细胞自身及微环境异常共同导致传统化疗及免疫治疗失败。研究发现,癌/睾丸抗原也参与癌细胞-微环境互作。黑色素瘤免疫治疗队列研究表明,X染色体q28区域的MAGEA

基因簇高表达预示CTLA-4治疗耐受,提示癌/睾丸抗原表达可能与免疫微环境及抗原加工呈递相关^[72]。MAGE-A4通过促进MAGE-A4反应性浆细胞(MAGE-A4 responsive plasma cells, MARPs)积累,抑制巨噬细胞、树突状细胞和T细胞的浸润和活化,同时促进免疫抑制微环境的形成,导致肿瘤进展和转移^[73]。CT45来源的HLA I类抗原肽-TCR复合物进一步增强毒性T细胞对肿瘤细胞的清除能力^[74],提示癌/睾丸抗原在免疫治疗中的潜力。GAGE-7C促进IFN- γ 和Fas介导的肿瘤细胞凋亡耐受。同时,GAGE-7C高表达增强紫杉醇及 γ 射线引发的细胞凋亡^[54]。非小细胞肺癌中BORIS抑制顺铂诱导的DNA损伤,而BORIS敲低可增强DNA损伤并提高对顺铂的敏感性^[75]。对TCGA数据库的分析显示,OIP5在膀胱癌中高表达,并与患者预后显著相关。进一步的研究发现OIP5促进患者顺铂耐药^[76]。CAGE通过调控miR-181-5p/S1PR1轴促进胃癌化疗耐药^[77]。此外,减数分裂联会复合物组分SYCP3在部分原位肿瘤中表达,抑制RAD51介导的同源重组,破坏有丝分裂细胞的染色体完整性^[78]。

上述研究提示,癌细胞中异位表达的睾丸特异性基因通过DNA损伤修复、转录调控、信号转导、蛋白质修饰降解以及肿瘤细胞与微环境互作、免疫逃逸等不同维度的多种机制调控肿瘤进展,在肿瘤发生发展的全过程中均发挥重要作用,是临床诊治的潜在靶点。

3 癌/睾丸抗原异位激活的分子机制

在正常睾丸组织中,基因表达呈现高度时序化的特征,从而确保精原细胞增殖、减数分裂启动、精子形成与成熟等阶段的正常进行。癌/睾丸抗原在不同肿瘤类型、不同癌细胞亚群中被异常激活,在部分肿瘤中还呈现分期特异性表达。癌/睾丸抗原的异位激活及亚细胞特异性表达为癌细胞提供了表型可塑性与适应性储备。明确癌/睾丸抗原异位激活及细胞亚群特异性表达的机制有助于理解肿瘤演化的分子基础及关键事件。

3.1 DNA去甲基化与癌/睾丸抗原异位表达

DNA甲基化可直接干扰转录因子与目的DNA的结合;同时甲基化CpG岛结合蛋白(methyl-CpG-binding proteins, MBDs)可募集染色质重塑共抑制复合物进一步阻止基因表达^[79]。因此,DNA甲基

化通常伴随基因表达沉默。在生理条件下,癌/睾丸抗原在睾丸组织中特异性表达,体细胞中的基因启动子及CpG岛处于高度甲基化状态^[80]。癌细胞中MAGE蛋白家族基因启动子区DNA处于低甲基化水平^[81]。在肺癌细胞中,5-Aza-dc处理后,NY-ESO-1表达沉默的癌细胞再次转录活跃^[82]。体外实验表明地西他滨处理刺激细胞表达NY-ESO-1,提示NY-ESO-1在卵巢癌细胞中异质性表达与启动子甲基化状态相关^[83],提示免疫治疗策略设计初期,目的蛋白表达异质性是继免疫原性外的另一关键考量。在胃癌细胞系中,地西他滨诱导XAGE-1启动子去甲基化并促进其表达^[84]。对其他癌症的研究也都发现,DNA甲基化抑制剂地西他滨、阿扎胞苷处理促进癌/睾丸抗原启动子去甲基化及表达上调^[85,86]。这些研究证明,DNA甲基化是癌/睾丸抗原在睾丸组织中限制性表达的主要原因,癌细胞中全局性DNA去甲基化是其异位激活的关键条件。

3.2 组蛋白修饰与癌/睾丸抗原异位表达

DNA去甲基化是癌/睾丸抗原在肿瘤中表达的首要条件,其转录活跃水平则与相关基因区域染色质开放程度及组蛋白修饰改变密切相关。组蛋白甲基化、HDAC介导的组蛋白去乙酰化及多梳家族蛋白在早期胚胎发育、癌症调控中发挥重要作用。癌/睾丸抗原在体细胞中的沉默状态与DNA甲基化、多梳蛋白抑制复合物招募呈正相关,而抑制组蛋白赖氨酸甲基化可显著促进MAGE-A1、NY-ESO-1等CTAs的表达^[87]。膀胱癌及黑色素瘤中的研究表明,MAGE基因簇的表达激活由DNA去甲基化与组蛋白乙酰化共同介导,HDAC抑制剂刺激MAGE-A1基因的瞬时激活^[88]。在肺癌细胞中敲低KMT6、KDMI及KDM5B基因可显著增强地西他滨介导的癌/睾丸抗原转录激活,提示DNA去甲基化与组蛋白甲基化共同调控癌/睾丸抗原的异位激活^[87]。这些证据表明癌/睾丸抗原的激活是在DNA去甲基化的基础上,由组蛋白修饰及转录抑制复合物共同控制。表观遗传重编程是肿瘤发生早期的关键事件^[89],肿瘤驱动基因及表观遗传修饰酶促使癌变细胞组蛋白修饰发生全局性改变^[90,91],但部分癌/睾丸抗原仍呈组织特异性表达,提示其他因子参与癌/睾丸抗原的精确表达。

3.3 癌/睾丸抗原异位激活的次级调控

相较于X染色体癌/睾丸抗原的激活主要受控于

基因簇的甲基化状态,非X染色体来源的部分基因表达调控则更为复杂。转录因子MZF1促进黑色素瘤中PRAME表达^[92]。胶质母细胞瘤中E2F1与OIP5启动子结合促进其表达,提示细胞周期在癌/睾丸抗原表达中的作用^[93]。有趣的是,激活后的OIP5以正反馈的形式参与E2F1的表达调控。miR-200b与CAGE形成反馈调节机制,调控血管生成及肿瘤侵袭^[94]。miR-874通过结合UTR区域靶向抑制肝癌细胞中HCA587/MAGE-C2的表达^[95]。

此外,ChIP实验发现NY-ESO-1启动子上对CpG甲基化不敏感的CTCF/BORIS结合位点,CTCF结合导致基因沉默,BORIS结合则促进NY-ESO-1重新激活^[96],提示染色质拓扑结构改变也参与CTAs在肿瘤细胞中的异位激活。BORIS对NY-ESO-1的激活则为增强癌/睾丸抗原免疫原性提供潜在新策略。MAGE-A1可与CTCF、DNMT3A形成复合物甲基化BORIS启动子,提示癌/睾丸抗原间的调控关系^[97]。肝细胞癌中TRIM28抑制蛋白酶体对MAGE-C2的降解^[98],前列腺癌中p14-ARF则促进MAGE-A11蛋白降解^[99]。这些研究证明癌/睾丸抗原异位激活不仅受到基因组及染色质开放程度的调控,特定细胞状态下的转录因子及蛋白质水平调控也参与癌/睾丸抗原的激活。

4 总结与展望

正常体细胞中处于沉默状态的性腺发育、精子发生及减数分裂相关基因的异常激活在表观遗传、转录及翻译水平促进肿瘤恶性表型相关的基因表达及信号通路活跃。因为具备自体免疫原性及睾丸限制性表达,癌/睾丸抗原是免疫治疗的理想靶点。同时,由于癌细胞中活跃的可变剪接事件及基因突变,产生大量的癌/睾丸抗原来源的潜在抗原肽。目前对于癌/睾丸抗原机制的研究越来越深入(图2),但仅有MAGE-A4相关的TCR-T产品获批临床应用,其他进行中的临床试验仍局限于NY-ESO-1等明星靶点,这凸显出当前对癌/睾丸抗原免疫原性仍缺乏系统性研究。靶向癌/睾丸抗原的优势主要体现在较低的体细胞毒性,但值得注意的是,临床治疗中需要考虑癌/睾丸抗原表达异质性、HLA分型限制等决定TCR-T实际疗效的关键因素。同时,针对癌/睾丸抗原免疫原性增强的技术开发也将是未来的研究方向之一。

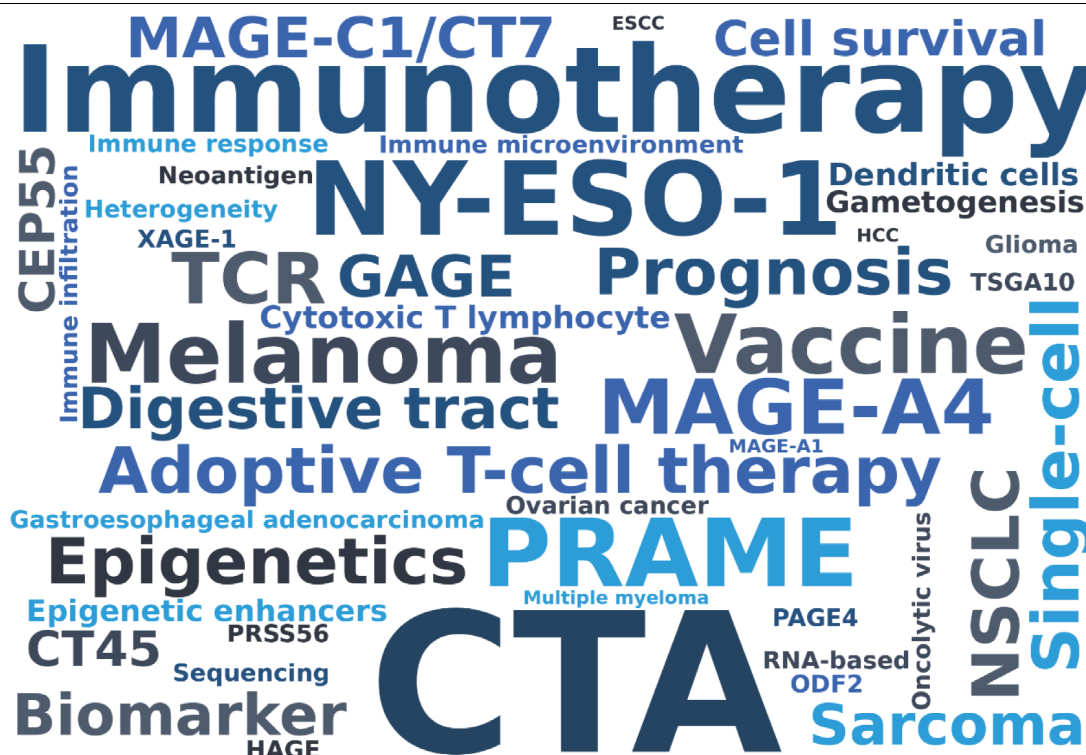


图2 癌/睾丸抗原研究热点词云

Figure 2 Keyword cloud of research hotspots in CTA

参考文献

- [1] Barnett KK, Johnson AR, Das A, et al. FDA approval summary: afamitresgene autoleucel for adults with HLA-restricted, MAGE-A4-positive unresectable or metastatic synovial sarcoma after prior chemotherapy. *Clin Cancer Res*, 2025, 31: 3112–7.
- [2] van der Bruggen P, Traversari C, Chomez P, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. *Science*, 1991, 254: 1643–7.
- [3] Coulie PG, Weynants P, Lehmann F, et al. Genes coding for tumor antigens recognized by human cytolytic T lymphocytes. *J Immunother Emphasis Tumor Immunol*, 1993, 14: 104–9.
- [4] Knuth A, Wölfel T, Klehmann E, et al. Cytolytic T-cell clones against an autologous human melanoma: specificity study and definition of three antigens by immunoselection. *Proc Natl Acad Sci U S A*, 1989, 86: 2804–8.
- [5] Juretic A, Spagnoli GC, Schultz-Thater E, et al. Cancer/testis tumour-associated antigens: immunohistochemical detection with monoclonal antibodies. *Lancet Oncol*, 2003, 4: 104–9.
- [6] Gaugler B, Van den Eynde B, van der Bruggen P, et al. Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes. *J Exp Med*, 1994, 179: 921–30.
- [7] Chomez P, De Backer O, Bertrand M, et al. An overview of the MAGE gene family with the identification of all human members of the family. *Cancer Res*, 2001, 61: 5544–51.
- [8] Boon T, Cerottini JC, Van den Eynde B, et al. Tumor antigens recognized by T lymphocytes. *Annu Rev Immunol*, 1994, 12: 337–65.
- [9] Kawakami Y, Robbins PF, Rosenberg SA. Human melanoma antigens recognized by T lymphocytes. *Keio J Med*, 1996, 45: 100–8.
- [10] Chen YT, Boyer AD, Viars CS, et al. Genomic cloning and localization of CTAG, a gene encoding an autoimmunogenic cancer-testis antigen NY-ESO-1, to human chromosome Xq28. *Cytogenet Cell Genet*, 1997, 79: 237–40.
- [11] Chen YT, Old LJ. Cancer-testis antigens: targets for cancer immunotherapy. *Cancer J Sci Am*, 1999, 5: 16–7.
- [12] Old LJ, Chen YT. New paths in human cancer serology. *J Exp Med*, 1998, 187: 1163–7.
- [13] De Plaen E, Arden K, Traversari C, et al. Structure, chromosomal localization, and expression of 12 genes of the MAGE family. *Immunogenetics*, 1994, 40: 360–9.
- [14] Türeci O, Sahin U, Schobert I, et al. The SSX-2 gene, which is involved in the t(X;18) translocation of synovial sarcomas, codes for the human tumor antigen

- HOM-MEL-40. *Cancer Res*, 1996, 56: 4766–72.
- [15] Liu XF, Helman LJ, Yeung C, et al. XAGE-1, a new gene that is frequently expressed in Ewing's sarcoma. *Cancer Res*, 2000, 60: 4752–5.
- [16] Chen YT, Scanlan MJ, Sahin U, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc Natl Acad Sci U S A*, 1997, 94: 1914–8.
- [17] Chen YT, Chiu R, Lee P, et al. Chromosome X-encoded cancer/testis antigens show distinctive expression patterns in developing gonads and in testicular seminoma. *Hum Reprod*, 2011, 26: 3232–43.
- [18] Gjerstorff MF, Kock K, Nielsen O, et al. MAGE-A1, GAGE and NY-ESO-1 cancer/testis antigen expression during human gonadal development. *Hum Reprod*, 2007, 22: 953–60.
- [19] Di Persio S, Saracino R, Fera S, et al. Spermatogonial kinetics in humans. *Development*, 2017, 144: 3430–9.
- [20] Aubry F, Satie AP, Rioux-Leclercq N, et al. MAGE-A4, a germ cell specific marker, is expressed differentially in testicular tumors. *Cancer*, 2001, 92: 2778–85.
- [21] Hou S, Xian L, Shi P, et al. The Magea gene cluster regulates male germ cell apoptosis without affecting the fertility in mice. *Sci Rep*, 2016, 6: 26735.
- [22] Lee AK, Klein J, Fon Tacer K, et al. Translational repression of G3BP in cancer and germ cells suppresses stress granules and enhances stress tolerance. *Mol Cell*, 2020, 79: 645–59.e9.
- [23] Li N, Yu J, Zhou M, et al. MAGE-B4, a binding partner of PRAMEF12, is dispensable for spermatogenesis and male fertility in mice. *Biochem Biophys Res Commun*, 2023, 675: 46–53.
- [24] Liu C, Si W, Tu C, et al. Deficiency of primate-specific SSX1 induced asthenoteratozoospermia in infertile men and cynomolgus monkey and tree shrew models. *Am J Hum Genet*, 2023, 110: 516–30.
- [25] Weon JL, Potts PR. The MAGE protein family and cancer. *Curr Opin Cell Biol*, 2015, 37: 1–8.
- [26] Hemminger JA, Ewart Toland A, Scharschmidt TJ, et al. The cancer-testis antigen NY-ESO-1 is highly expressed in myxoid and round cell subset of liposarcomas. *Mod Pathol*, 2013, 26: 282–8.
- [27] Gyurdieva A, Zajic S, Chang YF, et al. Biomarker correlates with response to NY-ESO-1 TCR T cells in patients with synovial sarcoma. *Nat Commun*, 2022, 13: 5296.
- [28] Odunsi K, Jungbluth AA, Stockert E, et al. NY-ESO-1 and LAGE-1 cancer-testis antigens are potential targets for immunotherapy in epithelial ovarian cancer. *Cancer Res*, 2003, 63: 6076–83.
- [29] Saillard M, Cenerenti M, Reichenbach P, et al. Engineered CD4 TCR T cells with conserved high-affinity TCRs targeting NY-ESO-1 for advanced cellular therapies in cancer. *Sci Adv*, 2025, 11: eadu5754.
- [30] Pan Q, Weng D, Liu J, et al. Phase 1 clinical trial to assess safety and efficacy of NY-ESO-1-specific TCR T cells in HLA-A*02:01 patients with advanced soft tissue sarcoma. *Cell Rep Med*, 2023, 4: 101133.
- [31] Gou LT, Kang JY, Dai P, et al. Ubiquitination-deficient mutations in human Piwi cause male infertility by impairing histone-to-protamine exchange during spermiogenesis. *Cell*, 2017, 169: 1090–104.e13.
- [32] Zhao S, Gou LT, Zhang M, et al. piRNA-triggered MIWI ubiquitination and removal by APC/C in late spermatogenesis. *Dev Cell*, 2013, 24: 13–25.
- [33] Dai P, Wang X, Gou LT, et al. A translation-activating function of MIWI/piRNA during mouse spermiogenesis. *Cell*, 2019, 179: 1566–81.e16.
- [34] Wang X, Lin DH, Yan Y, et al. The PIWI-specific insertion module helps load longer piRNAs for translational activation essential for male fertility. *Sci China Life Sci*, 2023, 66: 1459–81.
- [35] Wang N, Tan HY, Lu Y, et al. PIWIL1 governs the crosstalk of cancer cell metabolism and immunosuppressive microenvironment in hepatocellular carcinoma. *Signal Transduct Target Ther*, 2021, 6: 86.
- [36] Huang H, Yu X, Han X, et al. Piwil1 regulates glioma stem cell maintenance and glioblastoma progression. *Cell Rep*, 2021, 34: 108522.
- [37] Garcia-Silva MR, Montenegro S, Dacosta S, et al. PIWIL1 is recruited to centrosomes during mitosis in colorectal cancer cells and is linked to cell cycle progression. *Sci Rep*, 2024, 14: 23928.
- [38] Li F, Yuan P, Rao M, et al. piRNA-independent function of PIWIL1 as a co-activator for anaphase promoting complex/cyclosome to drive pancreatic cancer metastasis. *Nat Cell Biol*, 2020, 22: 425–38.
- [39] Shi S, Yang ZZ, Liu S, et al. PIWIL1 promotes gastric cancer via a piRNA-independent mechanism. *Proc Natl Acad Sci U S A*, 2020, 117: 22390–401.
- [40] Feng D, Yan K, Zhou Y, et al. Piwil2 is reactivated by HPV oncoproteins and initiates cell reprogramming via epigenetic regulation during cervical cancer tumorigenesis. *Oncotarget*, 2016, 7: 64575–88.
- [41] Zeng G, Zhang D, Liu X, et al. Co-expression of Piwil2/Piwil4 in nucleus indicates poor prognosis of hepatocellular carcinoma. *Oncotarget*, 2017, 8: 4607–17.
- [42] Li W, Martinez-Useros J, Garcia-Carbonero N, et al. The

- clinical significance of PIWIL3 and PIWIL4 expression in pancreatic cancer. *J Clin Med*, 2020, 9: 1252.
- [43] Hammad G, Magdy M, Aboushousha T, et al. Decreased expression levels of PIWIL2, PIWIL3 and PIWIL4 are associated with poor prognosis and worse survival in bladder cancer patients. *Asian Pac J Cancer Prev*, 2025, 26: 2467–77.
- [44] Kim H, Barua A, Huang L, et al. The cancer testis antigen TDRD1 regulates prostate cancer proliferation by associating with the snRNP biogenesis machinery. *Oncogene*, 2023, 42: 1821–31.
- [45] Yoon H, Lee H, Kim HJ, et al. Tudor domain-containing protein 4 as a potential cancer/testis antigen in liver cancer. *Tohoku J Exp Med*, 2011, 224: 41–6.
- [46] Mo HY, Choi EJ, Yoo NJ, et al. Mutational alterations of TDRD 1, 4 and 9 genes in colorectal cancers. *Pathol Oncol Res*, 2020, 26: 2007–8.
- [47] Cai Y, Li N, Li H. YBX2 modulates mRNA stability via interaction with YTHDF2 in endometrial cancer cells. *Exp Cell Res*, 2023, 427: 113586.
- [48] Suzuki I, Yoshida S, Tabu K, et al. YBX2 and cancer testis antigen 45 contribute to stemness, chemoresistance and a high degree of malignancy in human endometrial cancer. *Sci Rep*, 2021, 11: 4220.
- [49] Yuan Z, Li B, Liao W, et al. Comprehensive pan-cancer analysis of YBX family reveals YBX2 as a potential biomarker in liver cancer. *Front Immunol*, 2024, 15: 1382520.
- [50] Chen YT, Venditti CA, Theiler G, et al. Identification of CT46/HORMAD1, an immunogenic cancer/testis antigen encoding a putative meiosis-related protein. *Cancer Immun*, 2005, 5: 9.
- [51] Liu K, Cheng L, Zhu K, et al. The cancer/testis antigen HORMAD1 mediates epithelial-mesenchymal transition to promote tumor growth and metastasis by activating the Wnt/ β -catenin signaling pathway in lung cancer. *Cell Death Discov*, 2022, 8: 136.
- [52] Wang C, Gu Y, Zhang K, et al. Systematic identification of genes with a cancer-testis expression pattern in 19 cancer types. *Nat Commun*, 2016, 7: 10499.
- [53] Laduron S, Deplus R, Zhou S, et al. MAGE-A1 interacts with adaptor SKIP and the deacetylase HDAC1 to repress transcription. *Nucleic Acids Res*, 2004, 32: 4340–50.
- [54] Cilensek ZM, Yehiely F, Kular RK, et al. A member of the GAGE family of tumor antigens is an anti-apoptotic gene that confers resistance to Fas/CD95/APO-1, interferon-gamma, taxol and gamma-irradiation. *Cancer Biol Ther*, 2002, 1: 380–7.
- [55] Zhang P, Cheng J, Liu Z, et al. NY-ESO-1 facilitates anoikis resistance and tumor metastasis by hijacking deubiquitinase OTUB1 to stabilize PP1 α . *Cell Death Dis*, 2025, 16: 682.
- [56] Chen L, Wu Q, Xu X, et al. Cancer/testis antigen LDHC promotes proliferation and metastasis by activating the PI3K/Akt/GSK-3 β -signaling pathway and the in lung adenocarcinoma. *Exp Cell Res*, 2021, 398: 112414.
- [57] Bhatia N, Xiao TZ, Rosenthal KA, et al. MAGE-C2 promotes growth and tumorigenicity of melanoma cells, phosphorylation of KAP1, and DNA damage repair. *J Invest Dermatol*, 2013, 133: 759–67.
- [58] Song X, Hao J, Wang J, et al. The cancer/testis antigen MAGEC2 promotes amoeboid invasion of tumor cells by enhancing STAT3 signaling. *Oncogene*, 2017, 36: 1476–86.
- [59] Yang SW, Li L, Connelly JP, et al. A cancer-specific ubiquitin ligase drives mRNA alternative polyadenylation by ubiquitinating the mRNA 3' end processing complex. *Mol Cell*, 2020, 77: 1206–21.e7.
- [60] Kim J, Woo AJ, Chu J, et al. A Myc network accounts for similarities between embryonic stem and cancer cell transcription programs. *Cell*, 2010, 143: 313–24.
- [61] Yin B, Zeng Y, Liu G, et al. MAGE-A3 is highly expressed in a cancer stem cell-like side population of bladder cancer cells. *Int J Clin Exp Pathol*, 2014, 7: 2934–41.
- [62] Kulkarni P, Shiraishi T, Rajagopalan K, et al. Cancer/testis antigens and urological malignancies. *Nat Rev Urol*, 2012, 9: 386–96.
- [63] Atanackovic D, Luetkens T, Hildebrandt Y, et al. Longitudinal analysis and prognostic effect of cancer-testis antigen expression in multiple myeloma. *Clin Cancer Res*, 2009, 15: 1343–52.
- [64] Shang B, Gao A, Pan Y, et al. CT45A1 acts as a new proto-oncogene to trigger tumorigenesis and cancer metastasis. *Cell Death Dis*, 2014, 5: e1285.
- [65] Epping MT, Wang L, Edel MJ, et al. The human tumor antigen PRAME is a dominant repressor of retinoic acid receptor signaling. *Cell*, 2005, 122: 835–47.
- [66] Planells-Palop V, Hazazi A, Feichtinger J, et al. Human germ/stem cell-specific gene TEX19 influences cancer cell proliferation and cancer prognosis. *Mol Cancer*, 2017, 16: 84.
- [67] Chen YT, Panarelli NC, Piotti KC, et al. Cancer-testis antigen expression in digestive tract carcinomas: frequent expression in esophageal squamous cell carcinoma and its precursor lesions. *Cancer Immunol Res*, 2014, 2: 480–6.
- [68] Caballero OL, Shousha S, Zhao Q, et al. Expression of

- cancer/testis genes in ductal carcinoma in situ and benign lesions of the breast. *Oncoscience*, 2014, 1: 14–20.
- [69] Futawatari N, Fukuyama T, Yamamura R, et al. Early gastric cancer frequently has high expression of KK-LC-1, a cancer-testis antigen. *World J Gastroenterol*, 2017, 23: 8200–6.
- [70] Tsang YH, Wang Y, Kong K, et al. Differential expression of MAGEA6 toggles autophagy to promote pancreatic cancer progression. *Elife*, 2020, 9: e48963.
- [71] Pineda CT, Potts PR. Oncogenic MAGEA-TRIM28 ubiquitin ligase downregulates autophagy by ubiquitinating and degrading AMPK in cancer. *Autophagy*, 2015, 11: 844–6.
- [72] Shukla SA, Bachireddy P, Schilling B, et al. Cancer-germline antigen expression discriminates clinical outcome to CTLA-4 blockade. *Cell*, 2018, 173: 624–33.e8.
- [73] Armstrong D, Chang CY, Hong MJ, et al. MAGE-A4 induces non-small cell lung cancer and tumor-promoting plasma cell accumulation. *Sci Adv*, 2025, 11: eads4227.
- [74] Coscia F, Lengyel E, Duraiswamy J, et al. Multi-level proteomics identifies CT45 as a chemosensitivity mediator and immunotherapy target in ovarian cancer. *Cell*, 2018, 175: 159–70.e16.
- [75] Zhang Y, Song Y, Li C, et al. Brother of regulator of imprinted sites inhibits cisplatin-induced DNA damage in non-small cell lung cancer. *Oncol Lett*, 2020, 20: 251.
- [76] Wang D, Chen Z, Lin F, et al. OIP5 promotes growth, metastasis and chemoresistance to cisplatin in bladder cancer cells. *J Cancer*, 2018, 9: 4684–95.
- [77] Yeon M, Kim Y, Pathak D, et al. The CAGE-MiR-181b-5p-S1PR1 axis regulates anticancer drug resistance and autophagy in gastric cancer cells. *Front Cell Dev Biol*, 2021, 9: 666387.
- [78] Hosoya N, Okajima M, Kinomura A, et al. Synaptonemal complex protein SYCP3 impairs mitotic recombination by interfering with BRCA2. *EMBO Rep*, 2011, 13: 44–51.
- [79] Wade PA. Methyl CpG binding proteins: coupling chromatin architecture to gene regulation. *Oncogene*, 2001, 20: 3166–73.
- [80] Akers SN, Odunsi K, Karpf AR. Regulation of cancer germline antigen gene expression: implications for cancer immunotherapy. *Future Oncol*, 2010, 6: 717–32.
- [81] Lian Y, Meng L, Ding P, et al. Epigenetic regulation of MAGE family in human cancer progression-DNA methylation, histone modification, and non-coding RNAs. *Clin Epigenetics*, 2018, 10: 115.
- [82] Chüeh AC, Liew MS, Russell PA, et al. Promoter hypomethylation of NY-ESO-1, association with clinicopathological features and PD-L1 expression in non-small cell lung cancer. *Oncotarget*, 2017, 8: 74036–48.
- [83] Woloszynska-Read A, Mhawech-Fauceglia P, Yu J, et al. Intertumor and intratumor NY-ESO-1 expression heterogeneity is associated with promoter-specific and global DNA methylation status in ovarian cancer. *Clin Cancer Res*, 2008, 14: 3283–90.
- [84] Lim JH, Kim SP, Gabrielson E, et al. Activation of human cancer/testis antigen gene, XAGE-1, in tumor cells is correlated with CpG island hypomethylation. *Int J Cancer*, 2005, 116: 200–6.
- [85] Lai TJ, Sun L, Li K, et al. Epigenetic induction of cancer-testis antigens and endogenous retroviruses at single-cell level enhances immune recognition and response in glioma. *Cancer Res Commun*, 2024, 4: 1834–49.
- [86] Ma R, Rei M, Woodhouse I, et al. Decitabine increases neoantigen and cancer testis antigen expression to enhance T-cell-mediated toxicity against glioblastoma. *Neuro Oncol*, 2022, 24: 2093–106.
- [87] Rao M, Chinnasamy N, Hong JA, et al. Inhibition of histone lysine methylation enhances cancer-testis antigen expression in lung cancer cells: implications for adoptive immunotherapy of cancer. *Cancer Res*, 2011, 71: 4192–204.
- [88] Wischnewski F, Pantel K, Schwarzenbach H. Promoter demethylation and histone acetylation mediate gene expression of MAGE-A1, -A2, -A3, and -A12 in human cancer cells. *Mol Cancer Res*, 2006, 4: 33949.
- [89] Alonso-Curbelo D, Ho YJ, Burdziak C, et al. A gene-environment-induced epigenetic program initiates tumorigenesis. *Nature*, 2021, 590: 6428.
- [90] Kiri S, Ryba T. Cancer, metastasis, and the epigenome. *Mol Cancer*, 2024, 23: 154.
- [91] Johnstone SE, Gladyshev VN, Aryee MJ, et al. Epigenetic clocks, aging, and cancer. *Science*, 2022, 378: 1276–7.
- [92] Lee YK, Park UH, Kim EJ, et al. Tumor antigen PRAME is up-regulated by MZF1 in cooperation with DNA hypomethylation in melanoma cells. *Cancer Lett*, 2017, 403: 144–51.
- [93] He J, Zhao Y, Zhao E, et al. Cancer-testis specific gene OIP5: a downstream gene of E2F1 that promotes tumorigenesis and metastasis in glioblastoma by stabilizing E2F1 signaling. *Neuro Oncol*, 2018, 20: 1173–84.
- [94] Kim Y, Park D, Kim H, et al. miR-200b and cancer/testis

- antigen CAGE form a feedback loop to regulate the invasion and tumorigenic and angiogenic responses of a cancer cell line to microtubule-targeting drugs. *J Biol Chem*, 2013, 288: 36502–18.
- [95] Song X, Song W, Wang Y, et al. MicroRNA-874 functions as a tumor suppressor by targeting cancer/testis antigen HCA587/MAGE-C2. *J Cancer*, 2016, 7: 656–63.
- [96] Hong JA, Kang Y, Abdullaev Z, et al. Reciprocal binding of CTCF and BORIS to the NY-ESO-1 promoter coincides with derepression of this cancer-testis gene in lung cancer cells. *Cancer Res*, 2005, 65: 7763–74.
- [97] Zhao J, Wang Y, Liang Q, et al. MAGEA1 inhibits the expression of BORIS via increased promoter methylation. *J Cell Sci*, 2019, 132: jcs218628.
- [98] Song X, Guo C, Zheng Y, et al. Post-transcriptional regulation of cancer/testis antigen MAGEC2 expression by TRIM28 in tumor cells. *BMC Cancer*, 2018, 18: 971.
- [99] Minges JT, Grossman G, Zhang P, et al. Post-translational down-regulation of melanoma antigen-A11 (MAGE-A11) by human p14-ARF tumor suppressor. *J Biol Chem*, 2015, 290: 25174–87.