·综　述·

临床常见药物导致药疹与人类白细胞抗原基因多态性研究进展

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摘要：药疹是最常见的药物不良反应，除引起皮肤黏膜损害，还可引起肝、肾、骨髓多系统损害，严重者可导致患者死亡。近年来特定药物导致的药疹与人类白细胞抗原基因(human leukocyte antigen，HLA)基因间的关联性研究取得了重大进展，部分研究成果已用于临床用药前筛查以预测和避免药疹的发生。本文从临床常见药物导致药疹与 HLA 基因多态性的关系及人种差异、基因筛查的临床价值及经济效益、HLA 基因介导药疹的免疫机制几个方面阐述，以期为个性化精准医疗及药物安全评价提供理论参考依据。

关键词：药疹；人类白细胞抗原；精准用药；经济效益

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Research Progress of Cutaneous Adverse Drug Reaction Caused by Common Clinical Drugs and Human Leukocyte Antigen Gene Polymorphism

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ABSTRACT: Cutaneous adverse drug reaction(CADR) is the most common adverse drug reaction. In addition to causing skin and mucosal damage, it can also cause damage to multiple systems such as the liver, kidney, and bone marrow. In severe cases, it can lead to death. In recent years, significant progress has been made in the study of the association between CADR and human leukocyte antigen(HLA) genes, and some research results have been used in pre-clinical drug screening to predict and avoid CADR. This article explained the relationship between CADR and HLA gene polymorphism, the clinical value and economic benefits of gene screening, and the immune mechanism of HLA gene-mediated CADR, in order to provide a theoretical reference for personalized precision medicine and drug safety evaluation.

KEYWORDS: cutaneous adverse drug reaction; human leukocyte antigen; precise medication; economic benefits

药物不良反应(adverse drug reactions，ADRs)是指正常剂量的药物用于预防、诊断、治疗疾病或调节生理机能时出现的和用药目的无关的有害反应。ADRs 累及皮肤则称之为“药物性皮炎”，即“药疹”(cutaneous adverse drug reaction，CADR)，是最常见的药物不良反应之一，可根据症状分为轻型药疹和重症药疹。轻型药疹包括斑丘疹、多形红斑型药疹、荨麻疹型药疹、固定性药疹等，一般停药后症状即能好转，重型药疹如重症多形红斑(Stevens-Johnson syndrome，SJS)、中毒性表皮坏死松解症(toxic epidermal necrolysis，TEN)、药物超敏反应综合征(drug-induced hypersensitivity syndrome，DIHS)[又称伴嗜酸性粒细胞增多和系统症状的药物反应(drug reaction with eosinophilia and systemic symptoms，DRESS)]、急性泛发型发疹性脓疱病(acute generalized exanthematous pustulosis，AGEP)等，因累及多器官系统，严重时可导致患者死亡[1]。近年来，人类基因组学迅猛发展，促进了个体化治疗与精准治疗的发展[2]。人类白细胞抗原(human leukocyte antigen，HLA)基因多态性与 CADR 的关联性研究有大量研究报道，用药前进行 HLA 风险基因筛查可显著降低相关药物 CADR 的发病率。但由于不同种族、地区 *HLA* 基因多态性差异较大，本文综述近年来临床常见

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药物导致 CADR 与 *HLA* 基因相关性研究进展，并对 *HLA* 基因筛查的潜在临床价值进行分析，为精准用药提供依据。

1 *HLA* 基因的结构与功能

HLA 基因位于人类第 6 号染色体 6p21.3 短臂区，是目前已知的人类最复杂基因系统。根据其在染色体上的排列可分为 3 个区域：Ⅰ类基因区包含 HLA-A、B、C，编码的经典 HLA Ⅰ类分子表达于所有有核细胞表面，识别和提呈内源性抗原肽，激发 $CD8^+$T 细胞应答。Ⅱ类基因区包含 HLA-DR、DP、DQ，编码的经典 HLA Ⅱ类分子主要分布于抗原提呈细胞及活化 T 细胞表面，识别和提呈外源性抗原肽，激发 $CD4^+$T 细胞应答。Ⅲ类基因区位于上述两类基因区域之间，包括补体基因 C2、B、C4 及参与炎症反应的 TNF、LTA、LTB 和 HSP 等位基因座。由于 HLA 分子呈现多种“自身”和“非自身”肽，因此 HLA 基因具有显著的多态性。

2 特定药物导致药疹与 *HLA* 基因多态性的关联性

2.1 卡马西平及其他抗癫痫药

抗癫痫药如卡马西平、苯妥英、奥卡西平和拉莫三嗪被广泛用于治疗癫痫、双相情感障碍和三叉神经痛。卡马西平是临床常用的芳香族抗癫痫药。2004 年 Chung 等[3]首次在中国台湾汉族人群中发现 *HLA-B*15:02* 与卡马西平诱导的 SJS 显著相关，具有 100%的敏感性和 97%的特异性。随后，这一结论在中国大陆[4-9]、中国香港[10]、泰国[11]、马来西亚[12]、印度[13]等人群中得到进一步验证，用药前 *HLA-B*15:02* 基因筛查可有效降低卡马西平诱导的 SJS-TEN 的发生率[14-15]。在欧洲、日本和韩国人群中，并未发现卡马西平诱导的 SJS/TEN 与 *HLA-B*15:02* 有关，在这些人群中 *HLA-A*31:01* 与卡马西平诱导的 DRESS 显著相关，与 SJS/TEN 相关，但关联性较弱[16-17]。Zhou 等[18]模拟了基因检测在特定国家/地区的成本效益，结果显示卡马西平用药前 *HLA-B*15:02* 的基因筛查仅在整个东亚和南亚地区具有成本效益，而 *HLA-A*31:01* 的检测在全球范围内可能具有成本效益。FDA 建议在卡马西平治疗前对中国、泰国、马来西亚和韩国患者进行 *HLA-B*15:02* 基因筛查，以减少卡马西平相关的 SJS/TEN。

另外，有研究显示 *HLA-B*15:11*(日本和韩国)[19-20]、*HLA-B*59：01*(日本)[21]、*HLA-B*57:01*(欧洲)[22]与卡马西平诱导的 SJS/TEN 密切相关。1 项病例对照研究表明在菲律宾开具卡马西平处方前筛查 HLA-B75 血清型、*HLA-B*15:21* 或 *HLA-A*24:07* 可预防卡马西平诱导的 SJS/TEN[23]。

芳香族抗癫痫药物具有相似的化学结构，在选择替代抗惊厥药时必须考虑交叉反应的可能性。苯妥英(中国台湾、泰国)[10-11,24]、奥卡西平(中国台湾)[25]、拉莫三嗪[24]引起 SJS/TEN 与 *HLA-B*15:02* 存在相关性，在汉族(中国台湾)及泰国人群中与 *HLA-B*13:01*、*HLA-Cw*08:01* 及 *HLA-DRB1*16:02* 与苯妥英引起 SJS/TEN 具有一定的相关性[24]。在马来西亚人群中，与耐苯妥英的对照(9.4%，3/32 例)相比，*HLA-B*15:13* 与苯妥因诱导的 SJS/TEN(53.8%，7/13 例)和 DRESS (100%，3/3 例)显著相关[26]。在澳大利亚原住民中，苯妥英诱导的 DRESS 与 *HLA-B*56:02* 明显相关(4.8%，95%CI(2.4%~7.8%)[27]。拉莫三嗪引起 SJS/TEN 与 *HLAB*38* 相关[28]。王伟等[29]学者研究发现，*HLA-DRB1*15:01* 也可能是中国汉族人群中抗癫痫药诱导 SJS/TEN 的危险因素，而 *HLA-A*24:02* 基因可能是芳香族抗癫痫药物之间交叉过敏反应的保护因素[27]，见表 1。很多研究由于样本量较小，未来仍然需要进行大样本的研究来进一步确证。

2.2 艾滋病抗病毒药物

阿巴卡韦为一种核苷类逆转录酶抑制剂，用于艾滋病抗病毒治疗。大约有 5%~8%的白人服用阿巴卡韦后可出现超敏反应[30]。2002 年，Mallal 等[31]和 Hetherington 等[32]的 2 项研究提出白人中阿巴卡韦超敏反应和 *HLA-B*57:01* 具有强关联性。Saag 等[33]研究表明美国白人、黑人阿巴卡韦超敏反应者 100%携带 *HLA-B*57:01* 基因。2008 年，Mallal 等[34]进行了 1 项多民族的前瞻性随机双盲试验，证实了 *HLA-B*57:01* 基因筛查能有效预防超敏反应发生。同时，*HLA-B*57:01* 对阿巴卡韦斑贴试验阳性反应的敏感性为 100%[35]。2008 年 FDA 将阿巴卡韦用药前 *HLA-B*57:01* 基因筛查写入用药指南中。但是，据报道在中国 HIV 感染者中 *HLA-B*57:01* 基因的携带率<1%[36-37]，所以有学者认为在中国常规检测 *HLA-B*57:01* 不具有成本效益[37]。Kapoor 等[38]成本效益分析结果也显示中国汉族、东南亚马来人和东南亚印第安人阿巴卡韦用药前基因筛查不具有成本效益。

奈韦拉平为非核苷逆转录酶抑制剂，其药疹

表 1 抗癫痫药物所致 CADR 与 HLA 基因多态性的关系

Tab. 1 Relationship between CADR induced by antiepileptic drugs and HLA gene polymorphism

药物	*HLA* 等位基因	最先发表年份	人群所在地区	药疹类型	是否纳入指南推荐[39]
卡马西平	*HLA-B*15:02*	2004	中国台湾[3]、中国香港[10]、中国大陆[4-9]、泰国[11]、马来西亚[12]和印度[13]	SJS/TEN	FDA[a]
	*HLA-A*31:01*	2006	欧洲[16]、日本[17]、韩国[19]	SJS/TEN、DRESS	FDA[b]
	*HLA-B*15:11*	2010	日本[20]、韩国[19]	SJS/TEN	否
	*HLA-B*59:01*	2011	日本[21]	SJS/TEN	否
	*HLA-B*57:01*	2019	欧洲[22]	SJS/TEN	否
苯妥英钠	*HLA-B*15:02*	2007	中国台湾[10,24]、泰国[11]	CADR	FDA[C]
	*HLA-B*13:01 HLA-Cw*08:01 DRB1*16:02*	2010	中国台湾[24]	SJS/TEN	否
	*HLA-B*15:13*	2017	马来西亚[26]	SJS/TEN、DRESS	否
	*HLA-B*56:02*	2019	澳大利亚[27]	DRESS	否
拉莫三嗪	*HLA-B*15:02*	2007	中国台湾[24]	CADR	否
	*HLA-B*38*	2008	欧洲[28]	SJS/TEN	否
奥卡西平	*HLA-B*15:02*	2010	中国台湾[24]	SJS/TEN	FDA[d]

注：a–该相关性广泛用于具有亚洲血统的患者，*HLA-B*15:02* 在非亚洲血统的个体(例如，高加索人、非洲裔美国人、西班牙裔和美洲原住民)中基本不存在。b–*HLA-A*31:01* 等位基因在中国汉族、韩国、日本、欧洲、泰国、拉丁美洲和其他印度血统的患者中的表达 5%~10%。c–*HLA-B*15:02* 是亚洲血统患者服用与苯妥英发生 SJS/TEN 的危险因素。d–应在具有遗传风险人群血统的患者中用药前检测 *HLA-B*15:02* 等位基因。

Note: a–This association is widely used in patients of Asian ancestry, and *HLA-B*15:02* was largely absent in individuals of non-Asian ancestry(e.g. Caucasianic, African-American, Hispanic, and Native American). b–*HLA-A*31:01* allele expression was 5%–10% in patients of Han Chinese, Korean, Japanese, European, Thai, Latin American and other Indian ancestry. c–*HLA-B*15:02* was a risk factor for SJS/TEN in patients of Asian ancestry taking phenytoin. d–*HLA-B*15:02* allele should be tested prior to administration in patients with a genetic risk population ancestry.

发生率为 13%~28%。撒丁岛 1 项研究发现 *HLA-Cw*08-B*14* 单倍型在奈韦拉平超敏反应组中显著过度表达[40]，日本人中 *HLA-Cw*08* 与奈韦拉平诱发的 CADR 相关[41]。在泰国，奈韦拉平相关 CADR 与 *HLA-Cw*04*[42] 和 *HLA-B*35:05*[43] 相关，且 *HLA-B*35:05* 斑贴试验阳性敏感性为 100%[35]，中国人中 *HLA-Cw*04* 与奈韦拉平诱发的 CADR 相关[44]，*HLA-C*04:01* 与马拉维人中奈韦拉平诱导的 SJS/TEN 有关[45]。Martin 等[46]在法国的 1 项研究显示奈韦拉平和依非韦伦过敏患者中 *HLA-DRB1*01* 的频率显著更高。近期 1 项来自印度东北部的研究得出 *HLA-B*35:05* 与奈韦拉平相关的重型药疹相关，新报告 *HLA-DRB1*03:01* 与依非韦伦相关重型 CADR 相关[47]。另外，非 HLA 基因可能在特定 CADR 表型的发展中发挥作用[48]，目前奈韦拉平相关的基因筛查尚未用于临床。非洲的 1 项研究认为拉替拉韦钾相关的 DRESS 与 *HLA-B*53:01* 相关，但标准化筛查是否可能有助于预防拉替拉韦钾相关的 DRESS 仍然不清楚[49]，见表 2。

表 2 艾滋病抗病毒药物所致 CADR 与 HLA 基因多态性的关系

Tab. 2 Relationship between CADR caused by HIV antiviral drugs and HLA gene polymorphism

药物	*HLA* 等位基因	最先发表年份	人群所在地区	药疹类型	是否纳入指南推荐
阿巴卡韦	*HLA-B*57:01*	2002	欧洲[31]、非洲[33]	DIHS	FDA[a]
奈韦拉平	*HLA-Cw*08-HLA-B*14*	2006	意大利[40]	DIHS	否
	*HLA-Cw*08*	2006	日本[41]	DIHS	否
	*HLA-DRB1*01*	2004	法国[50]	CADR	否
	*HLA-Cw*04*	2009	中国[44]、泰国[42]	CADR	否
	*HLA-B*35:05*	2009	泰国[42]、印度东北部[47]	CADR	否
	*HLA-B*35*	2011	印度[51]	DIHS	否
依非韦伦	*HLA-DRB1*01*	2004	法国[46]	CADR	否
	*HLA-DRB1*03:01*	2020	印度东北部[47]	SCAR	否
拉替拉韦钾	*HLA-B*53:01*	2020	非洲[49]	DRESS	否

注：a–所有患者使用阿巴卡韦前进行筛查，阿巴卡韦禁止用于 *HLA-B*57:01* 阳性患者。

Note: a–All patients were screened before using abacavir, and abacavir was prohibited for *HLA-B*57:01* positive patients.

2.3 抗菌药

氨苯砜为砜类抑菌药，用于各种感染性疾病及炎症性疾病的预防和治疗。氨苯砜引起 DIHS 发生率约为 0.5%~3.6%[52]，张福仁等[53]首次证实了氨苯砜所致 DIHS 与 *HLA-B*13:01* 具有强相关性(OR=20.53，P=6.84×10^{-25})。*HLA-B*13:01* 存在的敏感性和特异性分别为 85.5%和 85.7%，阴性预测值为 99.8%，这意味着几乎所有 *HLA-B*13:01* 阴性个体暴露于氨苯砜的都不会发生 DIHS，阳性预测值为 7.8%，表明 7.8%的 *HLA-B*13:01* 携带者在服用氨苯砜后会发展为 DIHS[53]。该结论在中国台湾和马来西亚人麻风患者[54]、印度尼西亚巴布亚麻风患者[55]、泰国非麻风患者[56]得到验证。刘红等[57] 1 项前瞻性研究表明，*HLA-B*13:01* 筛选是降低中国人群麻风患者 DIHS 发病率的有效策略。*HLA-B*13:01* 较低的阳性预测值表明该疾病的发展可能涉及其他遗传变异，张福仁团队进一步研究确定了 HLA-DRB1 中的 5 种氨基酸(位置 133，142，–17，11 和 13)变异，它们处于高度连锁不平衡状态，由这些赋予风险的氨基酸残基标记的 *DRB1*16:02* 和 *DRB1*15:01* 与中国人群的氨苯砜超敏反应综合征显著相关[58]。

复方新诺明为磺胺类抗菌药，HIV/AIDS 患者对其发生药物反应的风险比一般人群高 10 倍，日本患者中 *HLA-A*11:01* 与磺胺相关的 CADR 关联[59]。泰国患者中 *HLA-B*13:01* 等位基因与复方新诺明诱导的 DRESS 显著相关，而 *HLA-B*15:02* 和 *HLA-C*08:01* 等位基因与复方新诺明诱导的 SJS/TEN 显著相关[60]。韩国的 1 项研究表明抗结核药诱发的 DRESS 与 *HLA-Cw*04:01* 有关[61]。在中国汉族人群中，*HLA-B*51:01* 在克林霉素引起 CADR 患者中的频率显著高于对照组(P=0.000 6，OR=9.731，95%CI：2.927~32.353)[62]，*HLA-B*13:01* 与柳氮磺胺吡啶诱导的 DRESS 相关[63]。欧洲人中，*HLA-A*32:01* 与万古霉素诱导的 DRESS 密切相关[64]，见表 3。

2.4 其他药物常见引起药疹

别嘌呤醇是一种黄嘌呤氧化酶抑制剂，是痛风和高尿酸血症的常用处方药。Hung 等[65]研究表明中国汉族人群中 *HLA-B*58:01* 与别嘌呤醇诱导的 SJS/TEN 和 DRESS 密切相关。针对其他亚洲人群如泰国人[66]、日本人[67]和韩国人[68]的研究也获得了类似结果。欧洲研究发现 *HLA-B*58:01* 在 55%~64%的别嘌呤醇诱导的 SJS/TEN 患者中表达[28,69]。Kang 等[68]在韩国的 1 项研究发现别嘌呤醇诱导的 SCAR 与 *HLA-B*58:01* 正相关，与 *HLA-A*02:01* 负相关。与欧洲、澳大利亚和日本人群相比，中国汉族人、泰国人和韩国人中 *HLA-B*58:01* 与别嘌呤醇诱导的 CADR 之间的关联性更强[65]。在别嘌呤醇给药前对 *HLA-B*58:01* 进行基因检测被认为是泰国极具潜在成本效益的干预措施[70]。Zhou 等[18]研究显示与欧洲和美洲相比，在亚洲进行 *HLA-B*58:01* 的测试更可能具有成本效益。Chong 等[71]认为在使用别嘌呤醇前进行 *HLA-B* 58:01* 基因检测在马来西亚可能不具有成本效益。

在韩国和日本患者中观察到 *HLA-B*5901* 与醋甲唑胺诱导的 SJS/TEN 之间存在很强的相关性(P<0.001，OR=249.8，95%CI=13.4~4 813.5)[72]。在中国的研究中得到一致结论[73]。中国的 1 项研究表明丹参酮诱导的药疹患者较耐受者携带 *HLA-A*02:01* 的频率显著更高，分子对接分析证实丹参酮成分对 *HLA-A*02:01*(≤–31.38 kJ·mol^{-1})具有高亲和力[74]。中国汉族人群中雷奈酸锶诱发的 SJS/TEN 与 *HLA-A*33:03* 和 *HLA-B*58:01* 与 SJS/TEN 显著相关[75]。非甾体类抗炎药在内的感冒药导致的 SJS/TEN 在日本与 *HLA-B*44:03* 和 *HLA-A* 02:06* 相关，印度和巴西仅与 *HLA-B*44:03* 相关[76]，见表 4。

表 3 抗菌药物所致 CADR 与 HLA 基因多态性的关系

Tab. 3 Relationship between CADR and HLA gene polymorphisms caused by antimicrobials

药物	HLA 等位基因	最先发表年份	人群所在地区	药疹类型	是否纳入指南推荐
氨苯砜	*HLA-B*13:01*	2013	中国大陆[53]、中国台湾[54]、马来西亚[54]、泰国[56]、印度尼西亚巴布亚[55]	DIHS	否
复方新诺明	*HLA-B*13:01*	2020	泰国[60]	DRESS	否
	*HLA-B*15:02 HLA-C*08:01*	2020	泰国[60]	SJS/TEN	否
	*HLA-A*11:01*	2020	日本[59]	CADR	否
抗结核药	*HLA-Cw*04:01*	2013	韩国[61]	DRESS	否
柳氮磺胺吡啶	*HLA-B*13:01*	2014	中国[63]	DRESS	否
克林霉素	*HLA-B*51:01*	2017	中国[62]	CADR	否
万古霉素	*HLA-A*32:01*	2019	欧洲[64]	DRESS	否

表 4 其他药物所致 CADR 与 HLA 基因多态性的关系

Tab. 4 Relationship between other drug-induced CADR and HLA gene polymorphisms

药物	HLA 等位基因	最先发表年份	人群所在地区	药疹类型	是否纳入指南推荐
别嘌呤醇	*HLA-B*58:01*	2005	中国[65]、泰国[66]、日本[67]、韩国[68]和欧洲[28,69]	SJS/TEN、DRESS	FDA[a]
	*HLA-A*33:03 HLA-C*03:02*	2005	中国台湾[65]、韩国[68]、白种人[77]	SCAR	否
醋甲唑胺	*HLA-B*59:01*	2010	韩国[72]、日本[72]、中国[73]	SJS/TEN	否
丹参酮	*HLA-A*02:01*	2020	中国[74]	CADR	否
雷奈酸锶	*HLA-A*33:03 HLA-B*58:01*	2016	中国[75]	SJS/TEN	否
感冒药(NSAIDs)	*HLA-B*44:03 HLA-A*02:06*	2015	日本[76]	SJS/TEN	否
	*HLA-B*44:03*	2015	印度和巴西[76]	SJS/TEN	否

注：a–*HLA-B*58:01* 等位基因在亚洲(例如中国汉族、韩国、泰国)、非洲和夏威夷原住民/太平洋岛民血统的个体中的频率更高，考虑在遗传风险人群中检测 *HLA-B*58:01* 等位基因[39]。

Note: a–*HLA-B*58:01* alleles were more frequent in individuals of Asian(e.g., Han Chinese, Korean, Thai), African and Native Hawaiian/Pacific Islander descent, considering detection of *HLA-B*58:01* alleles in genetically-risk populations[39].

3 *HLA* 基因介导药疹的免疫机制

目前有 4 种机制假说来解释 T 细胞如何以 HLA 依赖性方式识别小化合物。

3.1 半抗原理论

半抗原理论认为致敏药物或药物活性代谢产物相对分子量太小不能引起免疫原性，而它们却充当半抗原与内源肽/蛋白质共价结合，从而在体内形成药物/半抗原肽复合物。药物、自身肽和 HLA 分子通过共价键形成复合物，进一步诱导药物特异性免疫反应。例如，青霉素与内源性肽结合，HLA 通过经典的加工所需途径将其呈递，从而触发 T 细胞活化，从而导致青霉素过敏[78]。

3.2 p-i 模型

在 p-i 模型(药理和免疫受体相互作用模型)中，药物或代谢产物通过不稳定的非共价方式直接结合到 HLA 和(或)TCR，不依赖于 APC 的传统抗原加工途径。例如，*HLA-B*15:02* 将卡马西平呈递给细胞毒性 T 淋巴细胞不需要细胞内代谢或加工，需要内源性肽结合以稳定细胞表面上的 HLAI 类复合物。*HLA-B*15:02* 的肽结合槽中的 3 个残基(Asn63、Ile95 和 Leu156)与卡马西平呈递和细胞毒性 T 淋巴细胞活化有关[79]。别嘌呤醇的主要活性代谢产物羟嘌呤醇与 *HLA-B*58:01* 非共价的、直接的在细胞表面结合，*HLA B*58:01* 的存在和高剂量的羟嘌呤醇协同作用增加细胞表面潜在免疫原性肽-羟嘌呤醇-*HLA B*58:01* 复合物的数量，从而导致更高的 T 细胞致敏风险[80]

3.3 改变肽库模型

在改变肽库模型中，致敏药物占据了 HLA 蛋白的肽结合槽中的位置，从而改变了结合裂隙和 HLA 结合的肽特异性。如阿巴卡韦过敏是唯一存在结构、生化和功能证据来支持改变的肽库模型得综合征，阿巴卡韦与 F 型口袋 *HLA-B*57：01* 相互作用，改变了抗原结合裂隙的形状和化学结构。内源肽的改变导致多克隆 T 细胞活化和自身免疫样系统反应表现[79]。

3.4 改变 TCR 库模型

在改变 TCR 库模型中，药物与 TCR 结合，导致 TCR 的构象变化，然后与 HLA/自身肽复合物结合以引发免疫反应。如磺胺甲恶唑改变了 TCR 的构象，提供了与 HLA/肽的潜在结合力[81]。

4 结语

药物导致的严重皮肤不良反应如 SJS/TEN 等尽管发生率低，但往往致命，*HLA* 基因多态性在 CADR 中发挥重要作用，通过易感基因筛查以个体化治疗是未来的研究目标。但是，只有基于不同种族的大样本的研究来进一步确证遗传关联的准确性，并进行成本效益分析，才能实施用药前筛查。此外，许多 HLA 等位基因与 CADR 的关联仅通过流行病学研究确定，其潜在的免疫机制仍不清楚，且 *HLA* 基因与药物相互作用并不能完全解释 CADR 的发生，可能是多个基因和环境因素的相互作用结果。尽管皮肤药物不良反应与 *HLA* 基因相关性研究为预测个体潜在 CADR 遗传易感性提供了基础，未来仍然需要进行大样本的研究来进一步确证。

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