

## Recent advances of pharmacogenomics in severe cutaneous adverse reactions: immune and nonimmune mechanisms

Ro-Lan Dao<sup>1,2</sup>, Shih-Chi Su<sup>1,2</sup>, and Wen-Hung Chung<sup>1,2,\*</sup>

<sup>1</sup>Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospitals, Taipei, Linkou, and Keelung, Taiwan

<sup>2</sup>College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are severe cutaneous adverse reactions (SCAR) which are majorly caused by drugs. Though the incidence rate is low, SCAR sometimes can be life-threatening and leads to lifelong sequelae. Many pharmacogenomic associations in immune and nonimmune related genes with the development of SCAR have been discovered recently and the pharmacogenetic tests have been applied to prevent specific drug-induced SCAR. In this review, we discuss the recent advances of pharmacogenomics in SCAR.

**Key words:** Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms

### INTRODUCTION

Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are known to have potential lethality and lifelong sequelae. SJS and TEN are delayed type mucocutaneous immune reactions with the involvement of widespread keratinocyte apoptosis. The clinical difference of SJS and TEN depends on their extent of epidermal detachment [1]. SJS, SJS/TEN over-

lap, and TEN can be classified as the degree of skin detachment involving less than 10%, 10–30%, and greater than 30% of body surface area, respectively [2, 3]. The manifestations of SJS/TEN range from mild exanthematous skin rashes to a large amount of bullae and extensive mucocutaneous sloughing [4-7]. Unlike SJS/TEN, DRESS usually involves less skin manifestations but more internal organ presentation and hematological abnormalities [2, 8]. In addition to typical eosinophilia, atypical lymphocytes, and hepatitis, recent clinical histopathological findings have showed that the dyskeratosis, epidermal spongiosis, and

**Correspondence:** Wen-Hung Chung  
Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospitals, Taipei, Linkou, and Keelung, Taiwan  
Tel: +886-3-328-1200-2216  
Fax: +886-2-2719-1623.  
E-mail: wenhungchung@yahoo.com; chung1@cgmh.org.tw

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**Received:** March 3, 2015  
**Accepted:** March 22, 2015

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severe interface vacuolization are significant in DRESS cases [9].

SCAR accounts for about 2% of hospital admissions [10] with varying incidence between 2 and 7 cases/million/yr in SJS/TEN [11-15] and 1/1,000 to 1/10,000 offending agent exposures in DRESS [16]. In spite of the low incidence, the mortality rate is 5–10% for SJS, about 30% for SJS/TEN overlap, nearly 50% for TEN [17-21], and 10% for DRESS [22]. Unfortunately, a consensus treatment guideline remains unavailable. Intravenous immunoglobulin (IVIg) [23, 24], cyclosporine [25-27] and systemic corticosteroids [28, 29] have been used to treat patients with SJS/TEN, yet a lack of consensus on the outcome is observed. Supportive care remains the most frequent monotherapy with proven benefit on mortality [30], although patients with SJS/TEN usually receive the combination treatment of IVIG, corticosteroids [31] or cyclosporine [27]. Recently, studies on the immunological mechanism of SJS/TEN have suggested that immunosuppressive agents, such as anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [23], anti-Fas ligand (FasL) monoclonal antibody, or perforin/ granzyme B inhibitors [32] might be useful for treating SJS/TEN; however, the real beneficial effects are not known due to lack of controlled clinical trial.

Previously, we found that the secretory granulysin acts as a primary cytotoxic molecule that leads to the disseminate keratinocyte apoptosis in SJS/TEN [33]. Granulysin is produced by cytotoxic T lymphocytes (CTLs), natural killer, and natural killer T cells, and released into the extracellular space along with other immune mediators (e.g., soluble FasL, granzymeB, and perforin) [33-35]. We found that depletion of granulysin by antigranulysin antibodies markedly decreased apoptosis of keratinocytes induced by blister fluids from patients with SJS or TEN [33], suggesting a potential of antigranulysin for therapeutic purposes in the future.

In this article, we primarily review the current advances in exploring the genetic predisposing factors and pathogenic mechanism of SCAR induced by drugs.

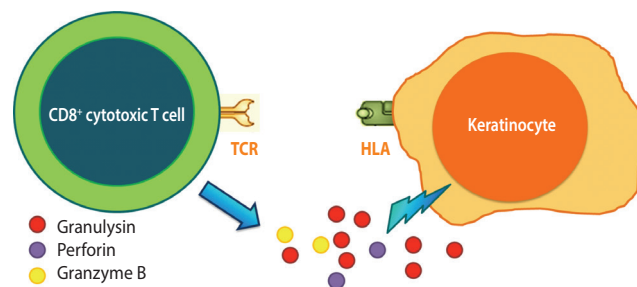
## IMMUNE MECHANISMS AND SCAR

Although several proposed hypotheses have been reported to explain how small molecule synthetic compounds are recognized by T cells in a major histocompatibility complex-dependent fashion, the pharmaco-immune concept remains the one that has been widely recognized. It illustrates a direct pharmacological interaction of a drug with immune receptors. Upon the non-covalent binding of an offending drug presented by a human

leukocyte antigen (HLA) molecule to the CD8+ T-cell receptor (TCR), the HLA-drug-TCR may initiate a series of reactions, resulting in an expansion of CTLs [36, 37], the releases of cytotoxic proteins [24, 33, 38], and induction of keratinocyte apoptosis in SJS/TEN. Recently, we also identified shared and restricted TCR usage in carbamazepine (CBZ)-induced SJS/TEN patients [39] and demonstrated that the endogenous peptide-loaded HLA-B\*15:02 molecule presented CBZ to CTLs without the involvement of intracellular drug metabolism or antigen processing [40]. More importantly, we found that granulysin acts as a major “killer” and is responsible for keratinocyte death [33] (Fig. 1).

## PHARMACOGENOMICS IN IMMUNE-MEDIATED MECHANISMS

In the ensuing decade, a number of important pharmacogenomic associations with SCAR have been found in different populations. In 1987, the genetic susceptibility was first being connected by the finding of HLA B12 and oxim- and sulfonamide-related TEN [41]. Since then, many of the genetic associations have been discovered, such as HLA-B\*57:01 and abacavir-induced hypersensitivity in European [42], and Thai and Cambodian children [43], HLA-B\*58:01 and allopurinol-induced SJS/TEN in Han Chinese [44], Thai [45], Japanese [46], Korean [47], and European [48], HLA-B\*15:02 and CBZ-SJS/TEN in Han Chinese [49, 50], Thai [51],



**Fig. 1.** Mechanisms of keratinocyte apoptosis in Stevens-Johnson syndrome/toxic epidermal necrolysis. The complex of drug antigen/metabolite-human leukocyte antigen (HLA)-T cell receptor (TCR) initiates immune reactions. Specific HLA allele predisposition and interaction with culprit drug allow the presentation of drug-bound HLA to the TCR which further triggers the activation of CD8+ cytotoxic lymphocytes and a series of specific immune reactions.

Indian [52], and Malaysian [53], HLA-B\*15:11 and CBZ-SJS/TEN in Japanese [54], Korean [55], and Han Chinese [56, 57], HLA-B\*59:01 and CBZ-SJS/TEN in Japanese [58], HLA-A\*31:01 and CBZ-SJS/TEN/drug-induced hypersensitivity syndrome in Japanese [59, 60], and CBZ-maculopapular exanthema (MPE)/DRESS in Han Chinese [61, 62], European [62, 63], HLA-B\*13:01 and dapson induced hypersensitivity in Han Chinese [64], HLA-B\*15:02 and lamotrigine-SJS/TEN in Han Chinese [65, 66], HLA-B\*15:02 and phenytoin (PHT)-SJS/TEN in Thai [51], HLA-B\*59:01 and methazolamide-SJS/TEN in Korean and Japanese [67], HLA-DRB1\*01:01 and nevirapine hypersensitivity in Australian [68] and French [69], HLA-B\*14:02 (or HLA-B\*14:02-Cw\*08:02 haplotype)-nevirapine hypersensitivity in Sardinian [70], HLA-B\*35:05 and nevirapine-MPE/DRESS in Thai [71], HLA-Cw\*08:01 or 08:02 and navirapine hypersensitivity in Sardinian [70] and Japanese [72], HLA-B\*73 and oxcam-SJS/TEN [48], HLA-A2 and B12 and oxcam-TEN [41], HLA-A29, B12, and DR7 and oxcam-TEN sulfonamide-TEN [41], HLA-B\*15:02 and oxcarbazepine-SJS/TEN [66].

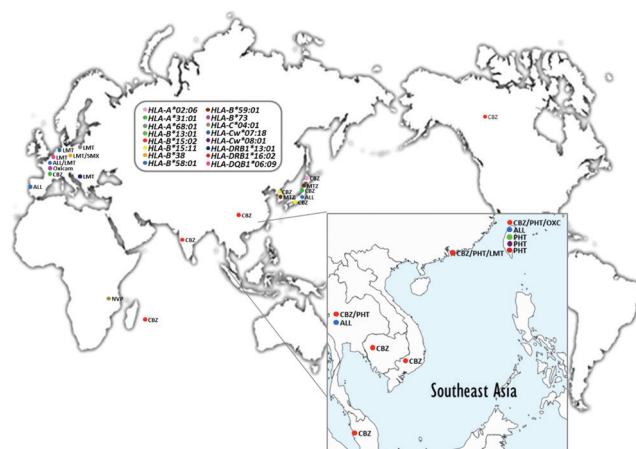
The genomic associations in HLA with drug hypersensitivity can be restricted to specific phenotypes. Our recent studies demonstrated a variable strength of association between the HLA genotypes and a wide spectrum of phenotypes of the CBZ hypersensitivity in Han Chinese. The most powerful CBZ-HLA association was the B\*15:02 in SJS/TEN, and the A\*31:01 and B\*51:01 in MPE/DRESS [57]. In addition, we also found a correlation between the strength of HLA-B\*15:02 association and degree of skin detachment in CBZ-SJS/TEN [57]. With international collaboration with RegiSCAR consortium containing European and Chinese populations, we further clarified that the HLA-A\*31:01 is a genetic predictor for CBZ-DRESS only, but not for CBZ-SJS/TEN [62].

Moreover, the associations of HLA and drugs-induced SCAR can be also different significantly in different ethnic populations. For example, studies did not show that patients with CBZ-SJS/TEN significantly associated with HLA-B\*15:02 in Europeans; however, this connection was still present in Han Chinese ancestry of Europeans. The ethnic difference can be tracked by the historical evolution and we did find an interesting fact in Asia. Although a general and historical cognition interprets that the Korean and Japanese ancestors originated from China, the HLA-B\*15:02 appears to be present at a low frequency (<1%) there [46, 55, 73]. U.S. Food and Drug Administration as well as many Asian health administrations have recommended HLA-B\*15:02 screening for CBZ new users of Asian ancestry since 2007 [74].

Different from the specificity of HLA-B\*15:02 in Han Chinese,

B\*15:11 and A\*31:01 had been reported to be predominantly associated with CBZ-SJS and HSS/SCAR respectively in Korean population [55]. Various HLA allele frequencies in worldwide populations decide the specificity of the ethnicity-related association. The frequency of HLA-B\*15:02 allele is about 1–8% in the countries of Southeast Asia, whereas it is rare or absent in Northeast Asian countries [55] or Caucasian [75]. The worldwide distribution of the associations between the causative drugs and HLA is illustrated in Fig. 2.

Other than the genetic association of SCAR with HLA, recent evidence also showed that the death of keratinocytes in SCAR may be contributed by the annexin A1-formyl peptide receptor 1 (FPR1). This study demonstrated that conditioned media from peripheral blood mononuclear cells (PBMCs) that had been exposed to the causative drug from patients with SJS/TEN induced the death of SJS/TEN keratinocytes, whereas that from PBMCs of patients with ordinary drug skin reactions (ODSRs) exposed to the same drug did not. Keratinocytes from ODSR patients or from healthy controls were unaffected by the conditioned media from SJS/TEN or ODSR PBMCs. Further investigations identified that the annexin A1 was associated with the cytotoxic level via the binding with its receptor FPR1 in keratinocytes, leading to the keratinocyte necroptosis in SJS/TEN [76].



**Fig. 2.** Worldwide distribution of causative drugs and human leukocyte antigen (HLA) association in Stevens-Johnson syndrome/toxic epidermal necrolysis. ALL, allopurinol; CBZ, carbamazepine; LMT, lamotrigine; MTZ, methazolamide; NVP, nevirapine; OXC, oxcarbazepine; PHT, phenytoin; SMX, sulfamethoxazole.

## PHARMACOGENOMICS IN NONIMMUNE MEDIATED MECHANISMS

Though the HLA predisposition plays a critical role in drug-induced SCAR, other factors like individual differences in drug clearance or metabolism may also contribute to SCAR development, recovery or prognosis. As knowing that the drug clearance is important for preventing further damage from the retention of drug toxicity in the body, drug metabolism becomes another dependent key for the SCAR development.

Recent evidences show that impaired drug metabolism may also involve in the pathogenesis of SCAR. Our recent study identified that a variant of CYP2C locus is related to PHT induced

SCAR. From a genome-wide association study encompassing 105 cases with PHT-related SCAR, we identified 16 significant single-nucleotide polymorphisms in CYP2C genes at 10q23.33. Further direct sequencing showed that CYP2C9\*3 which reduce CYP2C9 enzymatic activity was significantly associated with PHT-induced SCAR. PHT-induced SCAR and patients who carried CYP2C9\*3 showed a delayed clearance of plasma PHT [77]. CYP2C9\*3 has been known to be related to the drug metabolism, and it can attenuate the clearance of PHT [78, 79]. Previous study also showed an association of CYP2C9\*3 with PHT-induced MPE in Korean [80]. Another evidence showing genetic variability in a metabolizing enzyme can also contribute to SCAR was nevirapine-induced SJS/TEN that CYP2B6 G516T and T983C single nucleotide polymor-

**Table 1.** Genetic associations of drug-induced severe cutaneous adverse reactions (SCAR) in various populations

Drug classification	Offending drug	HLA allele	SCAR	Ethnicity
Antiretrovirals	Abacavir	B*57:01	Hypersensitivity	Caucasian [42], Thai and Combidian [43]
		DRB1*01:01	MPE/DRESS	Australian [68], French [69]
	Nevirapine	B*14:02 (or B*14:02-Cw*08:02)	Hypersensitivity	Sardinian [70]
		B*35:05	DRESS/MPE	Thai [71]
		Cw*08:01 or Cw*08:02	Hypersensitivity	Sardinians [70], Japanese [72]
Xanthine oxidase inhibitors	Allopurinol	CYP2B6	SJS/TEN	African in Mozambique [81]
		B*58:01	SJS/TEN/ DRESS	Han Chinese [44], Thai [45], Japanese [46], Korean [47], European [48]
Anticonvulsants	Carbamazepine	B*15:02	SJS/TEN	Han Chinese [49, 50], Thai [51], Indian [52], Malaysian [53]
		B*15:11	SJS/TEN	Japanese [54], Korean [55], Han Chinese [56, 57]
		B*59:01	SJS/TEN	Japanese [58]
		A*31:01	SJS/TEN/DIHS	Japanese [59, 60]
		A*31:01	MPE/DRESS	Han Chinese [61, 62], European [62, 63], Korean [55]
	Lamotrigine	B*15:02	SJS/TEN	Han Chinese [65]
	Phenytoin	B*15:02	SJS/TEN	Han Chinese [65, 66], Thai [51]
		CYP2C9*3	SJS/TEN/ DRESS	Han Chinese in Taiwan, Japanese, Malaysian [77]
NSAIDs	Oxcarbazepine	B*15:02	SJS/TEN	Han Chinese [66]
NSAIDs	Oxicam	B*73, A*2, B*12	TEN	European [41, 48]
Leprostatics	Dapsone	B*13:01	DRESS	Han Chinese [64]
Antibiotics	Sulfonamide	A29, B12, DR7	TEN	European [41]
	Sulfamethoxazole	B*38	SJS/TEN	European [48]
Antiglaucoma drugs	Methazolamide	B*59:01, CW*01:02	SJS/TEN	Korean and Japanese [67]

NSAID, nonsteroidal anti-inflammatory drug; MPE, maculopapular exanthema; DRESS, drug reaction with eosinophilia and systemic symptom; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DIHS, drug-induced hypersensitivity syndrome .

phisms were found to be associated with SJS/TEN susceptibility [81] (Table 1).

Allopurinol is a widely used drug for treating gout and hyperuricaemia and is notorious for its potential risk to induce SCAR. Although HLA-B\*5801 is strongly associated with allopurinol-induced SCAR, but the low positive predictive value of *HLA-B\*5801* suggesting that other factors are also involved in the pathogenesis of allopurinol-induced SCAR [44, 82, 83]. We recently revealed that the renal insufficiency directly affected the excretion of plasma oxypurinol, an active metabolite of allopurinol that is majorly eliminated through the kidney, and sustained high levels of oxypurinol in the plasma of patients with allopurinol-induced SCAR. An analysis between the allopurinol-SCAR cases and the tolerant controls showed that the impaired renal function was also significantly associated with allopurinol-SCAR. In addition, we also found that the high plasma levels of granulysin and oxypurinol after allopurinol discontinuation correlated with the high mortality in allopurinol-SJS/TEN and prolonged cutaneous reactions in allopurinol-DRESS [84]. We interpreted that the sustained and high levels of plasma oxypurinol may provoke CTLs and subsequently induce stronger immune reactions, therefore causing the prolonged disease remission, poor outcomes, and higher mortality in SCAR patients.

## CONCLUSIONS

Recent advance in pharmacogenomic researches has improved our understanding of SCAR in recent years and provides physicians and scientists a direction to deepen the mechanisms from aspects of pathology, immunology, and genetics. The findings of pharmacogenomic markers for SCAR have successfully implicated for clinical practice in many countries and prevented high-risk patients from SCAR-induced by some risk medicines, such as CBZ and allopurinol.

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