The Significance of HLA-Antigens in Dermatology

Santoso Cornain

Abstrak

"Human leukocyte antigens group A" (HLA) telah diketahui mempunyai hubungan pada derajat tertentu dengan berbagai penyakit kulit. Risiko relatif derajat rendah sampai sedang yang dihasilkan pada penelitian-penelitian terdahulu perlu dijelaskan dengan penelitian-penelitian serupa pada populasi-populasi lain. Upaya semacam itu telah diselenggarakan pada "International Histocompatibility Workshop and Conference". Makalah ini membahas kemaknaan HLA dalam dermatologi, baik hubungan antara HLA dengan berbagai penyakit kulit maupun beberapa aspek lain dari ekspresi HLA pada komponen-komponen kulit. Penelitian pendahuluan kami pada psoriasis dengan analisa "linkage disequilibrium", memberikan kesan hubungan antara HLA-B51 dan HLA-Cw7 dengan psoriasis. Telah dilaporkan bahwa ekspresi HLA-DR pada keratinosit telah ditemukan pada berbagai dermatosis. Ekspresi antigen tersebut pada sel dendritik dan limfosit T telah dikaitkan dengan perilaku biologiknya, aktivasinya dan patogenesis pada penyakit kulit tertentu. HLA-DR diekspresikan pada limfoma jenis sel T, yaitu Mycosis fungoides dan sindroma Sezary. Pada sebagian tumor kulit antigen HLA berkurang atau nihil dan antigen HLA tertentu mungkin bersifat protektif. Walaupun demikian, hubungan semacam itu masih kontroversial.

Abstract

Human leukocyte antigens group A (HLA) have been indicated to have some degree of association with various skin diseases. Low to moderate relative risk revealed in previous studies needs to be clarified by similar studies in other populations. Such an attempt has been organized in the International Histocompatibility Workshop and Conference. The paper discussed the significance of HLA in dermatology, both the association of HLA and various skin diseases and several other aspects of HLA expression on skin components. Our preliminary study in psoriasis with linkage disequilibrium analysis, suggested the association between HLA-B51 and HLA-Cw7 with psoriasis. It has been reported that HLA-DR expression on keratinocytes has been observed in various dermatoses. This particular antigenic expression on dendritic cells and T lymphocytes has been related to their biological behavior, activation and pathogenesis in certain skin diseases. HLA-DR was expressed in T cell lymphomas, namely Mycosis fungoides and Sezary's syndrome. Some skin tumors showed reduction or absence of HLA antigens and certain HLA antigen might be protective. However, such relationship was still controversial.

Keywords: *HLA antigens, psoriasis, dermatoses, T lymphomas, mycosis fungoides, Sezary's syndrome.*

INTRODUCTION

Human leucocyte antigens group A (HLA) have been studied to have certain relationship with the risk or susceptibility to various diseases.[1,2] During the last two decades the studies in skin diseases or systemic diseases with certain cutaneous manifestations have revealed some degrees of association between HLA and various skin diseases. Some have shown sufficient evidence with low to moderate relative risks, while some remain to be studied further. Such an attempt has been consistently carried out both globally until the last eleventh. International Histocompatibility Workshop and Conference and regionally until the last fourth Asia-Oceania Histocompatibility Workshop and Conference. Since participation by most of the countries would help to complete the analysis, we therefore started to join the regional workshop with the Indonesian population.[3] In addition to the population study we also initiated the disease study. For the latter,

Laboratory of Immunology, Department of Anatomic Pathology / Research Center for Medical Science and Technology, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

inter alia we have made a preliminary study on the association between HLA and psoriasis.

So far, reports on both the extension of studies of the association between HLA and various skin diseases and other related aspects have been accumulating.[4-24]

In this paper, we would like to discuss briefly about the significance of HLA in dermatology, concerning both the association between HLA and various skin diseases and several other aspects of HLA expression on skin components.

HLA AND ITS SIGNIFICANCE AND ASSOCIATION WITH SKIN DISEASES

Since the discovery of the first histocompatibility antigen in man by Dausset in 1958, a number of investigations have been consistently performed to collect sufficient evidence and to make better definition of the major histocompatibility system of man, which was further designated as HLA (human leukocyte antigen group A). The HLA complex is located in the short arm of human chromosome number 6, and contains genes encoding the HLA antigenic specificities of the HLA-A, HLA-B, HLA-C (Class I) and HLA-D, -DRR, -DP, -DQ (Class II). Besides that there are complement (C2, C4, C3d receptor) encoding genes (Class III), effector stimulating genes for lympholysis, genes of the Rogers and Chido red cell groups, Immune response (Ir) and immune associated ('Ia-'like) genes encoding B cell alloantigens, gene of phosphoglucomutase-3 (PGM 3) and PG5, etc.

The purpose of the HLA antigen determination (HLA typing) in organ transplantation has been well documented. The investigations have been carried out to extend the knowledge of the genetic predisposition in various diseases through studying the association of the HLA antigen and its gene, both in the population and in the family, with various diseases.[1,2]

The association between HLA and skin diseases has been shown by calculating the relative risks.

The current status of the association[1,2,4-22] are indicated in Table 1.

Both the principal skin diseases and the systemic diseases with some cutaneous manifestations are included. While the association appeared to be still varied for certain diseases, further confirming or clarifying investigations are encouraged. Our preliminary study on 19 Indonesian psoriasis patients, using linkage disequilibrium analysis, suggested the association between the HLA-B51 and HLA-Cw7 with psoriasis.

OTHER ASPECTS OF HLA EXPRESSION ON SKIN COMPONENTS

The HLA studies could also help in understanding the pathogenesis, histogenesis (determination of the cell origin) of certain skin diseases, biological behaviors of skin components and lymphocytic infiltrates.[23-36] See Table 2.

Table 1. The association between HLA and skin diseases

Disease	Antigen	Relative risk
Psoriasis vulgaris	HLA-B13	4.3
	HLA-Bw17	4.8
Cw6	HLA-Bw37	8.4
	HLA-Bw13, Aw30	16.1
	HLA-C26	13.3-24
	HLA-D	8-12
Pemphigus	HLA-A10	Jewish >
	HLA-D/DR	14.4
Dermatitis herpetiformis	HLA-B8	4.3
	HLA-D/DR	14.4
Leprosy-tuberculoid	HLA-B17	4.1
Systemic lupus erythematosus	HLA-B13,B17	3.7
	HLA-DR2,DR3	5.8
Cutaneous lupus	HLA-B8	4.6
	HLA-DRR3	4.3
Reiters' disease	HLA-B27	48.1
	HLA-B35	37.0
Behcet's disease	HLA-B5,B12	4.6
Erythema multiforme	HLA-DQB1*0301	4.1
Hemochromatosis/ porphyria cutanea tarda	HLA-A3	8.2
Skin cancer : in renal transplant	HLA-A3	2.6
Multiple basal cell carcinoma	HLA-DR1	2.1
Granuloma annulare	HLA-B31,B35	?
Genodermatosis	HLA-A2,A28,Cw2	?
Lichen sclerosus et atrophicus	HLA-Aw31	?
	HLA-B40	?

Table 2. HLA and pathogenesis

Situation	HLA expression related to pathological changes
1.	HLA-DR expression on keratinocytes in skin diseases (dermatosis): lichen planus, mycosis fungoides, cutaneous B-lymphoma, peudolymphoma, lupus erythematosus, para-psoriasis en plaque, bullous pemphigoid, drug reaction, contact dermatitis, actinic keratosis, pityriasis rosea, vitiligo, verrucous carcinoma, etc.
2.	HLA-DR expression on dendritic cells Ä deposition of immune complexes at dermo-epidermal junction : inflammatory skin diseases
3.	HLA-DR expression on activated T cells : sarcoidosis, granuloma, lichen planus, discoid lupus erythematosus
4.	HLA-A11, HLA-DR4 expression were reduced or absence : Skin cancers (factors: immunosuppression/ renal transplant, lack of cytotoxic T cells, human papilloma virus)

It is of interest that the expression of HLA-DR in normal state only occur in Langerhans' cells and syringeal epithelium. HLA-DR is normally undetected in keratinocytes. However, the expression of HLA-DR on keratinocytes have been observed in various skin diseases (dermatosis),[23-27] including: lichen planus, mycosis fungoides, cutaneous B lymphoma, pseudolymphoma, lupus erythematosus, parapsoriasis en plaque, bullous pemphigoid, drug reaction, contact dermatitis, actinic keratosis, pityriasis rosea, vitiligo, verrucous carcinoma, etc.

In regard with the significance in pathogenesis, the expression of HLA-DR has been encountered on dendritic cells[28,29] and T lymphocytes[30-32] found in relation with certain pathologic changes. The former was related to the deposition of immune complexes in the dermo-epidermal junction. The latter might indicate that the T lymphocytes were activated and might be consistent to the biological behaviours of the skin components and the pathogenesis of certain skin diseases, such as sarcoidosis granuloma, psoriasis, lichen planus, discoid lupus erythematosus.[33]

It is of interest, that mycosis fungoides and Sezary's syndrome are cutaneous T cell lymphomas, expressing HLA-DR or Ia-like antigen.[34,35] Reduction or absence of the HLA antigens have been observed in some skin tumors.[22,36,37] HLA-A11 has been considered to have protective effect against skin cancer,[21] which together with cytotoxic T cells might be interactive with extraneous factor such as human papilloma virus. However, such relationship might be still controversial as it was not observed in other studies.[20]

SUMMARY AND CONCLUSION

HLA complex has been studied extensively, both globally and regionally. The association of HLA and skin diseases has indicated a well define association with certain degree of relative risks in some and remains to be studied further in others. Our preliminary result in psoriasis suggested the association of the HLA-B51 and HLA-Cw7 with the disease.

The HLA-DR expression on keratinocytes has been observed in various dermatosis. Such an expression on dendritic cells and T lymphocytes has been related to their biological behavior, activation and pathogenesis in certain skin diseases. Mycosis fungoides and Sezary's syndrorme are T cell lymphoma which express HLA-DR. Some skin tumors showed reduction or absence of HLA antigens and certain HLA antigen might be protective. However, such relationship was still controversial.

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