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Remembrance of things past: HLA genes come back on the allergy stage

Donata Vercelli, MD

Arizona Respiratory Center, Arizona Center for the Biology of Complex Diseases (ABCD), and Department of Cellular and Molecular Medicine, University of Arizona, Tucson, AZ, USA

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Like most other research fields, immunology has witnessed the rise and fall of many paradigms. In the Seventies and early Eighties, the emphasis was on antigen-specific responses and the molecules underpinning them. The leading laboratories focused on the structure of T and B cell antigen receptors and the mechanisms underlying their seemingly inexhaustible ability to generate diverse repertoires. In parallel, others dissected the mechanisms restricting antigen-specific responses, thereby placing major histocompatibility (MHC) class I and class II HLA molecules center stage. Allergy was particularly keen on the study of HLA-dependent restriction of immune responsiveness. Allergen by allergen, then epitope by epitope, human and murine models were devised to identify the HLA alleles responsible for presentation to T cells. This intense interest in the role of HLA molecules was motivated by a fundamental (and still largely unanswered) question in our field: why is an antigen an allergen, or better, why do some, but not all, antigens evoke an IgE response, and why do they do this only in some individuals, even though virtually everyone in the population is exposed?

The focus on antigen/HLA interactions resulted in much work and much new knowledge. As the structure/function analyses of the T and B cell receptors made stunning progress, so did the understanding of HLA-dependent restriction of allergen responsiveness. By the early Nineties, papers addressing these issues were still making their way into major immunological journals, but the tide was rapidly turning, particularly thanks to the explosion of research on pattern recognition receptors and more generally, innate immunity. In many ways, allergy is still in the innate immunity era, even if the spotlight is currently on epithelial danger signals and innate type-2 helper cells¹⁻³.

But paradigms may soon shift back again, because allergy genetics is telling us the demise of allergen-specific responses might have been too hasty. After several years of hypothesis-

Telephone: 520-626-6387 Fax: 520-626-6970 donata@arc.arizona.edu

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driven candidate gene association studies, which predictably highlighted cytokines and “classical” genes of innate and adaptive immunity⁴, the field has been transformed by the advent of genome-wide association studies (GWAS)⁵. The indisputable strength of this approach resides in its unbiased nature and consequent ability to generate hypotheses, rather than just confirm them. The current interest in the epithelium as an innate mucosal barrier, and IL13/IL4R interactions as a key innate and adaptive pathway to asthma, eloquently illustrates how insightful an intense cross-talk between immunology and genetics can be⁶. Now, to the surprise of many, allergy and asthma GWAS are focusing attention on HLA genes once again, with a force and consistency we have to reckon with. The meta-analysis performed by the GABRIEL consortium⁷, the largest asthma GWAS to date, identified MHC class II HLA-DQ as the most significant asthma association signal and reported a distinct, even stronger HLA-DRB1 association for serum IgE levels. Comparable findings emerged from the TENOR asthma study in the US⁸ and two large studies from Japan^{9, 10} (Table 1). The analysis of plasma total IgE levels, performed in the large Framingham Heart Study and published in this issue of our journal¹¹, confirms the central role of class II HLA genes as determinants of susceptibility to allergy-related phenotypes, and raises the interesting possibility class I HLA molecules might be involved as well.

Because of the unbiased nature of GWAS, it is difficult to argue with their results, especially when they replicate – and in the case of HLA, they do. Rather, we need to understand what these results may mean. An intriguing scenario is one in which the differential ability to respond to allergenic antigens reveals a gene-environment interaction, that is, a situation in which the outcome of the exposure depends on the genetic background of the exposed. For several years we have known that quantitative events control the differentiation and function of helper T cells¹²: antigen/HLA/T cell receptor interactions determine the strength of T cell activating signals, which in turn play a major role in T cell fate decisions. In the case of HLA and allergens, exposure of individuals who express the “right” type and level of HLA molecules (a result of their genetic make-up) to the “right” common allergenic molecules (a result of still elusive biochemical properties) may generate signals that prompt a Th2 cell fate choice and IgE production. Through such a process, a qualitative event (expressing the HLA alleles restricting responses to a given environmental allergen) would lead to a quantitative one (achieving the signal strength that promotes Th2 cell differentiation). If this scenario is correct, it would be hard to imagine a more striking example of the threshold effects that are likely to provide a mechanistic underpinning for gene-environment interactions¹³.

Interestingly, allergy is not alone in facing a resurgence of the interest in HLA-mediated events. The list of complex diseases for which GWAS have shown powerful associations with HLA genes is growing steadily, and includes conditions as seemingly distinct as rheumatoid arthritis, Crohn's disease, multiple sclerosis, several types of lymphoma, Graves' and Parkinson's disease, schizophrenia and narcolepsy – just to mention a few (for a complete and constantly updated list, see www.genome.gov/gwastudies¹⁴). Given the complexity of linkage disequilibrium at the HLA locus and the relatively low resolution of GWAS, these studies cannot establish the extent to which distinct diseases share HLA determinants. The nature, source and identity of the antigens involved in HLA-mediated responses are also unclear. Regardless, genetics is reminding us that the quality and quantity

of T cell activation in response to specific antigens is likely to affect susceptibility to multiple complex diseases much more than we were ready to imagine. Our next challenge is to devise an integrated conceptual and experimental framework in which each piece of the puzzle -antigen-specific responses, innate events, and the interplay of both with environmental exposures – can find its appropriate mechanistic niche.

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Table 1

Author, Year Reference	Phenotype	Initial Sample Size	Replication Sample Size	Reported HLA Gene	P-value	OR
Hirota, 2011 Ref. 11	Asthma	1,532 Japanese cases, 3,304 Japanese controls	5,639 Japanese cases, 24,608 Japanese controls	<i>HLA-DQB1</i>	5×10^{-15}	1.17
				<i>HLA-DRA</i>	5×10^{-15}	1.15
				<i>HLA-DQA2</i>	5×10^{-12}	1.18
				<i>HLA-DOA</i>	4×10^{-9}	1.13
Noguchi, 2011 Ref. 10	Asthma	938 Japanese pediatric cases, 2,376 Japanese pediatric controls	818 Japanese pediatric cases, 1,032 Japanese pediatric controls, 835 Korean pediatric cases, 421 Korean pediatric controls	<i>HLA, DPB1</i>	2×10^{-10}	1.40
Li, 2010 Ref. 9	Asthma	607 cases, 3,294 white controls	NA	<i>HLA-DQB1</i>	9.5×10^{-6}	0.68
Moffatt, 2010 Ref. 8	Asthma	10,365 cases, 16,110 controls	NA	<i>HLA-DQ</i>	7×10^{-14}	1.18
	IgE	7087 asthmatics, 7667 controls	NA	<i>HLA-DRB1</i>	8×10^{-15}	NR

NA: not available

NR: not reported

Adapted from www.genome.gov/gwastudies (Ref. 17). Accessed December 2011