Article ID: WMC003091 ISSN 2046-1690

Relationship between the T-cell Diversity and the Defence Polymorphism among Classical Populational Morphs and their Interbreeding Town-village Hybrid Offspring

Corresponding Author:
Dr. Ilko Bakardzhiev,
MD, PhD, Medical College, Medical University of Varna, 9000 - Bulgaria

Submitting Author:
Dr. Ilko Bakardzhiev,
MD, PhD, Medical College, Medical University of Varna, 9000 - Bulgaria

Article ID: WMC003091

Article Type: Research articles

Submitted on:26-Feb-2012, 10:23:37 PM GMT **Published on:** 27-Feb-2012, 07:00:53 AM GMT

Article URL: http://www.webmedcentral.com/article_view/3091

Subject Categories:IMMUNOLOGY

Keywords:T-cell diversity, Phytohemagglutinin- histamin method, Harmonized and disharmonized populational gene pools

How to cite the article: Bakardzhiev I , Radev S , Panova D , Michev V , Pehlivanov G . Relationship between the T-cell Diversity and the Defence Polymorphism among Classical Populational Morphs and their Interbreeding Town-village Hybrid Offspring . WebmedCentral IMMUNOLOGY 2012;3(2):WMC003091

Source(s) of Funding:

Not applicable

Competing Interests:

Not applicable

Relationship between the T-cell Diversity and the Defence Polymorphism among Classical Populational Morphs and their Interbreeding Town-village Hybrid Offspring

Author(s): Bakardzhiev I , Radev S , Panova D , Michev V , Pehlivanov G

Abstract

The problem of creating an easy, quick, field, mass screening, in vivo discrimination test is still on the agenda. We believe that such potential has the phytohemagglutinin- histamin (PHA-H) intradermal method of Zhukov et al. (1984). This method reveals not only the normal immunomodulatotor (Th/Ts) index (NIMI) and Th2 activity, but also the identification of normally occuring T-regulatory cells (nTregs). This study aims to check this hypothesis among 672 young navy sailors, coming from classical populational morphs(CPMs): hereditary villagers and hereditary town dwellers.This is a randomized longitudinal populational follow- up study (RLPFS) with a 10-year duration (2000- 2009). This RLPFS has the highest known reliability compared to cross sectional studies and proves that thePHA-H in vivo test after Zhukov et al. (1984) is a quick, convenient and reliable mass screening T-cell discrimination method. From the position of a common denominator such as general outcome of health / disease (H/D) response ratio the CPMs are dramatically (H/D) dominated by NIMI(44,4% vs.29,2 %) and are epigenetically harmonized and coadapted PGPs (60 % vs. 40 %), compared to the reverse ratio (40,9% vs. 59,1 %) for the town-village hybrid, which actually is an abridged version of the Western hybrid societies. The latter are in much more difficult disadaptive position since they are in a phase of detrimental reflexive (hybrid?hybrid) mating.

Introduction

The interdependence between immune cell diversity and exogenous (invading pathogens or innocuous agents) have always been the object of vigorous discussion and detailed studies.

The fact that the same T-cells (Th1, Tcs, Tregs, Th 17) and their respective citokines protect us against infections as well as allregies. Rapidly growing investigations in this field are on the road to take down from the pedestal the Th1/T2 paradigm and the associated “hygienic hypothesis” with it. A new paradigm steps in instead, according to which the successful response against allergic or microbial agents is the result of a dynamic regulation and modulation of T-regulatory cells (T-regs), T-effector cells (Th1, Th2, Th17) and dendrocytes (Dcs) under the influence of microbial components in particular toll-like receptor (TLR) ligands.

Material and Methods

The present randomized longitudinal populational follow- up study (RLPFS) includes a total of 672 young 18- year-old navy sailors. Five hundred and forty individuals belong to the evolutionary classical inbreeding CPMs such as: hereditary villagers group, born and living in towns (HVsT) and hereditary town dwellers (HTDs). Because of their self- balancing inbreeding (HVsT) or unlocking of heterosis (HTDs) their populations function as harmonized populational gene pools (HPGP). The remaining 132 individuals, the so called TVHs due to already 300 years of urbanogenical chaotic and over-accelerated cross-breeding (panmixia) are epigenetically determinated disharmonicPGPs(DPGPs). The latter logically leads to an interlocus disequillibrium, the so called epistatic genetic suppression. The ratio between T-helper (Th) CD 4+ T-cells and T-supressors(Ts) CD8 + T-cells is marked as immuno-modulatory index (IMI). In our case this ratio was established in a system of mass screening testing by the phytohemagglutin-histamin method of Zhukov et al. (1984) (10).

The skin on the inner side of the right arm was cleaned with 70% ethyl alcohol and then strictly intradermally was injected 0.1 ml 0.04 % phytohemagglutinin (PHA) and candidin with needle 19. All antigenes have been produced in the Infectious and Parasitic Desease Centre inSofia(5). In the same way and at a symetric place on the left armpit was injected PHA and without pulling the needle out with another syringe was injected 0.1ml histamin (H).

The results of the testing were interpreted after 18 hours by measuring the diameter of of the erythematous halo in mm by a special mould after Bencart. The cases where the differences in the diameters of the left armpit and the control (right armpit) were less than 10 mm were established as normalIMI(NIMI, n=240). When the difference beween the two sides was 10-30 mm in favour of the left armpit (PHA+H), it was marked as an increased Th2 activity (n=162, >Th2). Conversely, when the difference was in favour of the rigt armpit (PHA) it was marked as an increased Ts activity (n=84, >Ts). The cases of zero reactions bilaterally after the skin testing were marked 0-IMI(n=54). According to some autors (Sagakushi 2000; Maloy, Powrie 2001) 0-IMIis a peripheral immune tolerance due to a high activity of naturally occurring T-regulatory cels (n T-regs) (4, 8). More recent immunologic data (Schimdt-Weber, Blacer 2004, Infante-Durante et al 2000, Happel et al 2005) requires a new understanding of the concept of NIMI.(1,2,3,6,7,9) The NIMI (n=240, 44,5%) should be viewed as a harmonic and dynamic balance of protective effector T-cells (Th 1, Th17 Tcs) by the leading role of the inducible T-regs (iT-regs): T-regulatory 1 cells (Tr1) and Th 3 cells. The importance of this rapid in vivo immunologic method has been confirmed by the Zhukov et al. 1984 by parallel testing of 10 healthy and 20 individuals with chronic skin disease aged 18-25 years with the help of monoclonal antibodies OKT4 and OKT8. Following Schwartz's 1993 thesis, the individuals with > Ts (n=84) were subdivided into cytotoxic Ts (Tcs, n=30, 5,56%) when they were carriers of multiple infections and allergic resistance (MIAR). This suggests that they are high IFN ? producers. The remaining Ts cells (n=54, 10%) are week IFN ? producers (8). The CPMs (n=540) was further subdivided into highly immune individuals (HII, n=324) and low immune individuals (LII, n=216). The figures of T-cell distribution among TVHs (n=132) is as follows: NIMI -24,2 %; Tcs 12,5 % ; nT-regs-25 %; Tss-8,33 % and Th2-25%. The validity of all ideas and hypotheses mentioned so far concerning the Th/Ts ratio and Tcell diversity have been tested in real conditions, in a system of highly reliable ten-year RLPFS (2000-2009). The present systematic survey includes standartized specific information and guidelines to the diagnosis of three most frequent human deseases: allergy, influenza and influenza- like conditions and tinea pedis. We have introduced complex phenotype traits (markers)- MIAPR and MIAPS, classified as triple and double trait. The latter have been classified as full (f) and midle (m) trait. In the first group are classified individuals who reject all the tree tested diseases and to a degree the discrete types. In the second group are the individuals susceptable to permanent (seasonal or throughout the year) chronic diseases or to seasonally abating types. Statistical analysis was performed with the Student-Fisher method.

Results and Discussion

The present 10-year randomized longitudinal monitoring reveals remarkable interconnections (Tabl. 1). The carriers of NIMI among CPMs strongly dominate (44,5 %) and among the associated with themHIIthis dominance is dramatic (74%). According to our still unpublished data this configuration among TVHs is with an impressive immunodeficient profile: 29,2 % and 66,7 % respectively.

TheHIIvsLIIare 8,5-13,4 times (80-100%, p< 0,001) more powerful generators of healthy adaptive responses in the general H/D outcome balance. Taken together this supports our basic hypothesis that CPMs (HVs and HTDs) are epigenetically (evolutionary) well harmonized populational gene-pools and due to it are higly immune societies. The leading position of > n Tregs, like generator of triple MIAPR phenotype, as well as of 100 % healthy adaptive responses is in harmony with new data showing that nTregs not only suppress but actively kill their target cells. Against this background (tabl. 1) a three times higher prevalence of Th2 versa >Tss amongLIIcan be observed but with regards to the heavy (f-and m-) MIAPS phenotypes >Tss is more than 1.32 times (78%) vs >Th2 (59%) respectively. Taken together with regards to the general outcome H/D responses balanceLIIvsHIIare more than 16 times higher generators of disease adaptive responses. A comparative analysis will show that TVHs in the end generates 1.3 times weaker f. MIAR compared to the 2.45 times more powerful f. MIAS vs CPMs. We can draw the inevitable conclusion that TVHs related epigenetically D.PGP (including its analogue WHSs) are intrisically a causative factor (causa sui) which determines their high susceptibility to chronically refractory diseases and carriers of highly pathogenic flora. The higher 1.47 MIAS of TVHs is an indicator of progredient chronic infections and allergic processes which are connected with a high proinflamatory citokine activity that can be normally seen not only from Tss and Th2 cells but nT-regs as well. This is not a paradox but the result from of an ambivalent very discrete and sophisticated function of nTregs which not only ensures a peripheral immune tolerance but also partcipation in the chronic inflamation, acting as a co-factor preventing from

collateral tissue damages (11).

Conclusion

This study proves that thePHA-H in vivo test after Zhukov et al (1984) is a convenient and reliable, mass screening, T- cell discrimination method. This was demonstrated in the dramatic direct corelation betweenHIIandLIIrelated T-cell diversity and the two poles of human adaptation: the MIAR and MIAS wich are reducible to the concrete PGP differentiation level, leaving its mark as a general outcome of H/D response balance. It is easy see that there is another missing supreme causative factor, which not only subordinates and predeterminates all aspects of patho and epidemiogenesis of H and D but also determines the final defense and immune capacity of the particluar major phenotype- race, ethnos, their demographic genetic lines and their interbreeding hybrid offsprings. This is an epigenetical start-given by means of the type mating (inbreeding or panmixia), harmonized or disharmonized PGP and hence a high or low genetic homeostasis. Its attribute functions are high or low complex defensive capacity and high or low immune homeostasis.

Abbreviations

IMI, immuno-modulatory index, NIMI, normal immunomodulatotor index, nTregs, normally occuring T-regulatory cells, CPMs, classical populational morphs, RLPFS, randomized longitudinal populational follow- up study, H/D, health / disease,PHA-H, phytohemagglutinin- histamin, iT-regs, inducible T-regs, Dcs, dendrocytes, TLR, toll-like receptor, HVsT, hereditary villagers group, born and living in towns, HTDs, hereditary town dwellers, HPGP, harmonized populational gene pools, MIAR, multiple infections and allergic resistance, HII, highly immune individuals,LII, low immune individuals, (f) full, (m) midle.

References

1. Happeel K.I., Rubin PJ, Zheng M. et al. Divergent roles of IL-23 and IL-12 in host defence against Klebsiella pneumonia. J. Exp. Med., 202; 2005: 761-769

2. Infante- Duarte C., Horton M., Birne C, Kamradi T. , Microbial lipopetides induce the production of IL-17 in Th cells. J. Immunol., 165; 2000: 6107-6115

3. Jutel M, Blaser K, Akdis C. Histamin in allergic inflammation and immune modulation.Inf. Arch. Allergy Immunol., 2005; 137:82-92

4. Maloy KJ, Powrie F. Regulatory T celss in the control of immune pathology. Nat. Immunol., 2; 2001; 816-822

5. Petrunov B Alergene fur die Diagnose und Behandlung. Sofia, Zentrum fur infectiose und Parasitenkrankheiten, 1980: 4-15, (in Bulgarian)

6. Sakagushi S. Regulatory T cells: key controllers of immune self tolerance. Cell, 101; 2000:455-458

7. Schmidt- Weber C. B, Blaser K. Immunological mechanisms in specific immunotherapy. Springer Semin. Immunopathol. 25 ; 2004: 377-390

8. Schwartz RH. Immunologic tolerance. In Fundamental immunology. W. F. Paul ed. 3,New York, Raven Press, 1993: 677-732

9. Verhagen J, Taylor A, Blaser K, et al. T regulatory cells in allergen-specific immunotherapy. Int. Rev. Immunol., 24; 2005: 833-848

10. Zhukov VI, Usenko R.S, Veksler HM, Determination of immune responsiveness in patients with chronic dermatosis by intradermal test with phytohemagglutinin and histamine. Vestn. Dermatol. Venerol. Moskva, 1984:12-14(in Russian)

11. Bopp T, Jonuleit H , Schmitt E. Regulatory T cells – the renaissance of the suppresor T cells. Annals of medicine, 2007; 39:322-334

Illustrations

Illustration 1

Table 1. Relationships between multiple infectious allergic polymorphism and t-cell diversity, among H.PGP and D.PGP

IMI (Th/Ts ratio		n	Defence polymorphism															PGP differ. level General outcome of H/D responses' ratio	
			MIAR						MIAS										
			triple		double		total		triple			double			total				
			f	m	f	m	f	m	f	m	l	f	m	l	f	m	l		
			n/%		n/%		n/%		n/%			n/%			n/%			n/%	
HII	H.PGPs NIMI*	240	17	91	48	72	65	163	0	0	0	0	5	7	0	5	7	228	12
			7,08/37,9		20/30		27,1/67,9		0/0/0			0/2,08/2,92			0/2,08/2,92			95/5	
	nTregs	54	18	24	0	12	18	36	0	0	0	0	0	0	0	0	0	54	0
			33,3/44,4		0/22,2		33,3/66,7		0/0/0			0/0/0			0/0/0			100/ 0	
	>Tcs	30	6	0	6	12	12	12	0	0	0	0	0	6	0	0	6	24	6
			20/0		20/40		40/40		0/0/0			0/0/20			0/0/20			80/20	

LII **>Tss**	54	0	0	0	6	0	6	0	25	0	6	11	6	6	36	6	6	48
		0/0		0/11,1		0/11,1		0/46,3/0			11,1/20,3/11,1			11,1/66,7/11,1			11,1/88,9	
>Th2	162	0	0	0	11	0	11	11	36	7	13	36	48	24	72	55	11	151
		0/0		0/6,79		0/6,79		6,79/22,2/4,32			8,02/22,2/29,6			14,8/44,4/33,9			6,79/93,21	
H.PGPs Total	540	41	115	54	108	95	228	11	61	7	19	52	67	30	113	74	323	217
		7,59/21,3		22,5/20,0		17,6/42,2		2,04/11,3/1,3			3,52/9,62/12,4			5,55/20,9/13,7			59,8/40,2	
TVHs D.PGPs Total	132	12	12	6	24	18	36	6	6	0	12	30	24	18	36	24	54	78
		9,01/9,01		4,54/18,2		14,6/27,3		4,54/4,54/0			9,01/22,7/18,2			13,6/27,3/18,2			40,9/59,1	

Disclaimer