Interaction between mucosal and cutaneous immune responses to Streptococcus pyogenes in psoriasis: a role for antigen specific IgA and CLA+ T cells

Carmen De Jesús-Gil[1], Marta Ferran[2], Anca Chiriac[3,4], Antonio Celada[5], Ramon M. Pujol[2] and Luis F. Santamaria-Babí[1]*

[1] Translational Immunology, Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Barcelona, Spain, [2] Department of Dermatology, Hospital del Mar, IMIM, Universitat Autònoma de Barcelona, Barcelona, Spain, [3] Department of Dermatophysiology, Apollonia University, Iasi, Romania, [4] Dermatology Department, Nicolina Medical Center, Iasi, Romania, [5] Macrophage Biology, Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Barcelona, Spain

Introduction

Although mucosal and cutaneous tissues are closely involved in psoriasis pathology, the interaction between their specific immune responses has not been deeply explored. *Streptococcus pyogenes* infection is well-known to trigger and exacerbate psoriasis lesions in both guttate and plaque forms of the disease. The purpose of this study is identifying humoral immune response to *S. pyogenes* in psoriasis patients and address any connection with in vitro response in cocultures of CLA+ T cells and epidermal cells after stimulation with *S. pyogenes* extract.

Material and methods

Blood and skin from untreated psoriasis patients (n=52) and controls (n=15) were collected under informed consent. Presence of IgG and IgA against *S. pyogenes* extract (SE) was analyzed through ELISA, using plasma as primary antibody source. Moreover, memory CLA+ and CLA- T cells were purified from blood samples through immunomagnetic separations, and epidermal cells (Epi) were obtained by chemical and mechanical treatment of skin punches. $5x10^4$ CLA+ or CLA- T cells were cocultured with $3x10^4$ autologous epidermal cells and activated by 1μg/ml Streptococcus pyogenes extract (SE). After 5 days of culture, IL-17A and IFN-γ were measured by fluorescent bead-based immunoassay in the supernatants. Data are represented by scatter or bar plots showing the median (red bar) and 95% confidence interval (CI), or as linear regression. Simple T-test was used to compare two different groups (*: p<0.05; **: p<0.01; ***: p<0.001).

Results

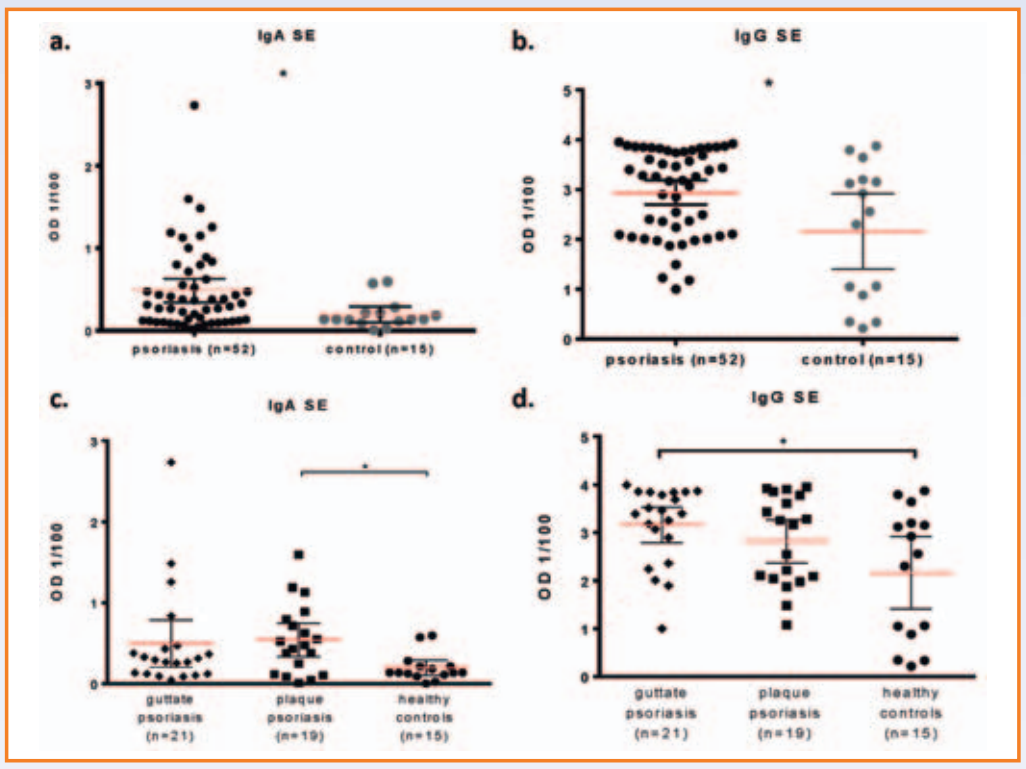

Figure 1. Psoriasis patients show increased Igs levels against *S. pyogenes* compared to controls. Optical density (OD) of plasma dilution 1/100, after background subtraction, is shown in vertical axis. In general, psoriasis patients showed increased levels of plasma anti-SE IgA (**a**) and IgG (**b**). Interestingly, according to their diagnosis, plaque psoriasis individuals had higher anti-SE IgA (**c**) whereas guttate psoriasis showed higher anti-SE IgG (**d**) when compared to controls.

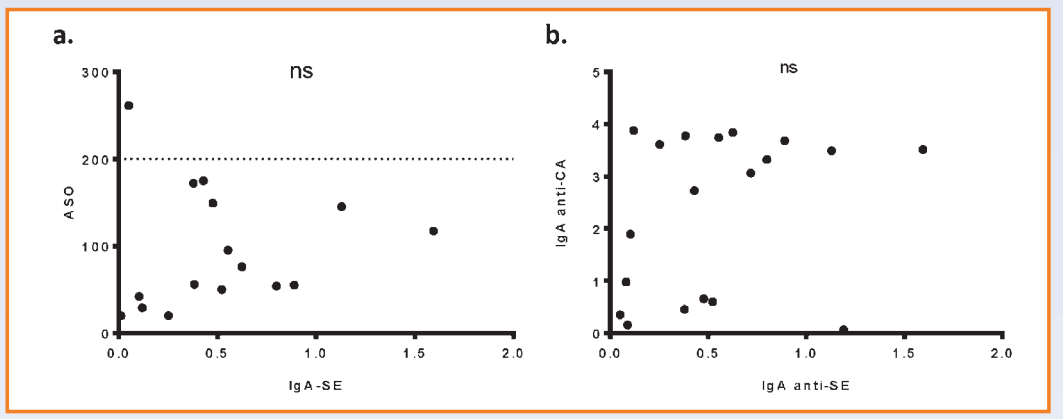

Figure 2. Mucosal immune response against *S. pyogenes* in plaque psoriasis patients is independent to ASO titter and Igs response to other microbial triggers of psoriasis. Within plaque psoriasis patients, we analyzed whether anti-SE IgA levels were related to their Anti-Streptolysin O titer (ASO), which is the general test that checks for a S. pyogenes infection. We observed that (**a**) anti-SE IgA levels do not correlate to ASO titer and, even more interestingly, that 18 out of 19 plaque psoriasis patients have a negative ASO titer (<200UI/ml); so it could point out IgA levels as a new disease related biomarker. Moreover, in order to study the relevance of this mucosal immune response to SE, we also determined plasma IgA levels against *Candida albicans* (CA), which is another microbe well-known to trigger and exacerbate the disease. ELISAs were performed using CA extract as a substrate, as explained before. Of important note, we observed (**b**) no significant correlation between anti-SE and anti-CA IgA plasma levels in plaque psoriasis patients, indicating that both microbe-specific immune responses are independent from each other.

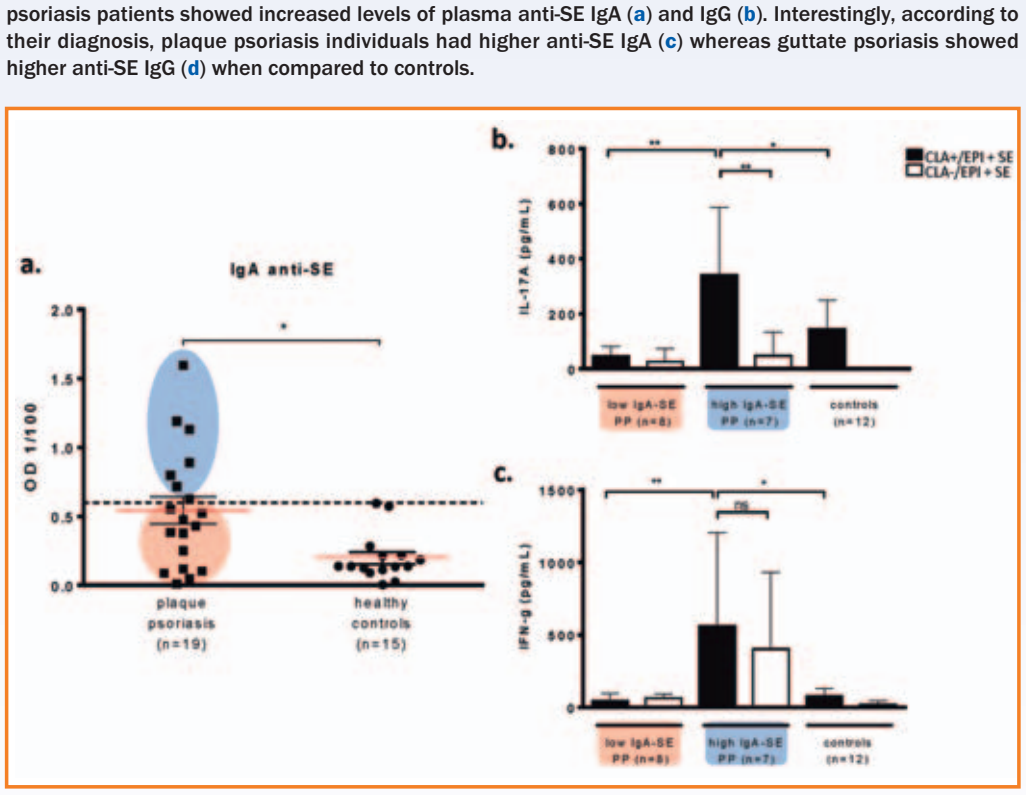

Figure 3. Plaque psoriasis patients with higher anti-SE IgA levels have stronger SE-dependent IL17 response *in vitro*. According to their specific IgA anti-SE plasma levels, PPP patients were classified in two groups: low (n=8) or high (n=7). Importantly, PPP with high plasma IgA anti-SE levels have stronger SE dependent *in vitro* induction of IL17A (**a**) by CLA+T cells, but not CLA-T cells, when compared to PP patients with low IgA anti-SE or controls. Withal, SE-induced IFN-γ response (**b**) does not follow this distinction.

		Guttate psoriasis (n=21)	Plaque psoriasis (n=19)	P value
ASO		435,52	94,75	< 0,0001
PASI		7,02	15,79	< 0,0001
Length of disease (months)		5,36	45	< 0,001
Age of onset		25,36	34,92	< 0,0001
HLA Cw6	Positive	90,5%	36,8%	NA
	Negative	9,5%	47,4%	NA
	Unknown	-	15,8%	NA
Flare associated to Streptococcal infection	Yes	76,1%	-	NA
	No	4,7%	100%	NA
	Unknown	19,2%	-	NA

Table 1. Clinical features of guttate and plaque psoriasis patients. NA: not assigned, ASO: Anti-streptolysin O antibody titer, PASI: Psoriasis Area Severity Index, UK: unknown.

Remarks and Conclusions

The combined analysis of IgA and CLA+ T cell response to the same antigen in psoriasis constitute a relevant tool to understand how microbial exposure in mucosa influence psoriasis trigger and development. Microbe specific IgA could be considered a potential new biomarker for better understanding patients' heterogeneity and their response to different therapeutical approaches.

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