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Blood to skin recirculation of CD4$^+$ memory T cells associates with cutaneous and systemic manifestations of psoriatic disease

Marco Diani [a,1], Marco Galasso [b,1], Chiara Cozzi [a,c], Francesco Sgambelluri [c], Andrea Altomare [a], Clara Cigni [d], Elena Frigerio [a], Lorenzo Drago [e], Stefano Volinia [b], Francesca Granucci [d], Gianfranco Altomare [a], Eva Reali [c,*]

[a] I.R.C.C.S Istituto Ortopedico Galeazzi, Department of Dermatology and Venereology, University of Milan, Milan, Italy
[b] Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy
[c] I.R.C.C.S Istituto Ortopedico Galeazzi, Laboratory of Translational Immunology, Milan, Italy
[d] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy
[e] I.R.C.C.S. Istituto Ortopedico Galeazzi, Laboratory of Clinical Chemistry and Microbiology, University of Milan, Milan, Italy

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ABSTRACT

Blood to skin recirculation could play a role in the pathogenesis of psoriasis. To investigate this possibility we dissected the phenotype of circulating T cells in psoriasis patients, calculated the correlation the clinical parameters of the disease and performed a parallel bioinformatics analysis of gene expression data in psoriatic skin.
We found that circulating CCR6$^+$ CD4$^+$ T_{EM} and T_{EFF} cells significantly correlated with systemic inflammation. Conversely, the percentage of CXCR3$^+$ CD4$^+$ T_{EM} cells negatively correlated with the severity of the cutaneous disease.
Importantly CLA$^+$ CD4$^+$ T_{CM} cells expressing CCR6$^+$ or CCR4$^+$CXCR3$^+$ negatively correlated with psoriasis severity suggesting recruitment to the skin compartment. This assumption was reinforced by gene expression data showing marked increase of *CCR7* and CLA-encoding gene *SELPLG* expression in psoriatic skin and strong association of their expression. The data enlightens a role for CD4$^+$ T cells trafficking between blood and skin in cutaneous and systemic manifestations of psoriasis.

1. Introduction

Psoriasis is a chronically relapsing hyperproliferative skin disease, affecting about 2% of the population worldwide, which is associated with systemic inflammation and comorbidities, such as psoriatic arthritis and cardiovascular diseases.

Much progress has been made in understanding the etiology of psoriasis revealing the involvement, at cutaneous level of a complex interplay between epidermal keratinocytes, T cells and dendritic cells.

In psoriatic plaques, CD4$^+$ T cells with Th1 and Th17 phenotype have been considered for long time as the main pathogenic T-cell subpopulations [1–3]. In the last years, however, the role of CD8$^+$ T cells has been revived by the discovery of autoreactive T cells specific for cathelicidin (LL-37), keratinocyte-derived antimicrobial peptide and for ADAMTS-like protein 5 (ADAMTSL5) produced by melanocytes [4, 5]. CD8$^+$ T cells with tissue resident memory (T_{RM}) phenotype are abundantly present in psoriatic epidermis, and have been described in non lesional skin, at sites of recurrent psoriasis, indicating a role in site-specific disease memory [6–9]. In this new context, the fraction of dermal CD4$^+$ T cells secreting IL-17 and possibly γδ T cells can play a pivotal role in the amplification phase of inflammation by generating a self-sustaining inflammatory loop [10–12]. Th17 cells, indeed, have been shown to have a central role in sustaining inflammation in psoriatic plaques, by enhancing the inflammatory response of keratinocytes and creating a positive feedback loop around the IL-23/IL-17 axis [13, 14]. Despite the progresses in this field, very little is known about the role of T cell recirculation in the pathogenesis of cutaneous psoriasis and its systemic manifestations.

Skin to blood recirculation of memory T cells is an emerging mechanism that in physiological conditions can distribute antigen-specific T cells both to the lymph nodes and to the peripheral tissues [15–19]. We hypothesized that a similar dynamic balance between tissue

Abbreviations: PBMC, peripheral blood mononuclear cells; T_{CM}, central memory T cells; T_{EM}, effector memory T cells; T_{EFF}, effector T cells; PASI, Psoriasis Area and Severity Index; CRP, C-reactive protein; CLA, cutaneous lymphocyte-associated antigen; Th1, T helper 1 cells; Tc1, cytotoxic T cells; Th17, IL-17-producing T helper cells; Tc17, IL-17-producing cytotoxic T cells.

* Corresponding author at: I.R.C.C.S Istituto Ortopedico Galeazzi, Laboratory of Translational Immunology, via Riccardo Galeazzi 4, 20161 Milan, Italy.
E-mail address: eva.reali@grupposandonato.it (E. Reali).

[1] The authors equally contributed to this work.

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Table 1
Clinical and demographic characteristics of patients and healthy subjects included in the study.[a]

No	Sex	Age	Disease	PASI	Type of Psoriasis	CRP	Familiarity for psoriasis	Comorbidities
PS02	M	40	PSO	10.5	Vulgaris/Eruptive	0.98	Mother	Allergic asthma
PS03	M	37	PSO	6.5	Vulgaris	0.05	No	None
PS04	M	24	PSO	7.0	Vulgaris	0.14	Father	None
PS05	F	58	PSO	7.5	Vulgaris	0.05	No	Hypercholesterolaemia, familial polyposis
PS07	M	56	PSO	12.5	Vulgaris	0.71	No	Hypercholesterolaemia, arterial hypertension, dilated cardiomyopathy
PS08	F	55	PSO	8.8	Vulgaris	0.02	Mother/Grandfather	None
PS11	F	43	PSO	8.2	Vulgaris	0.51	No	None
PS12	F	61	PSO	5.1	Vulgaris/Eruptive	0.38	Mother	None
PS13	M	46	PSO	7.5	Vulgaris	0.08	No	None
PS14	M	38	PSO	5	Vulgaris	0.93	No	None
PS15	F	50	PSO	8.5	Vulgaris	0.04	No	None
PS16	F	63	PSO	12.9	Vulgaris	0.07	Mother/Aunts	Rhizarthrosis
PS20	M	30	PSO	9.5	Vulgaris	0.70	No	None
PS23	M	50	PSO	12.0	Vulgaris	0.71	No	Hypercholesterolaemia
PS24	F	25	PSO	9.0	Vulgaris	0.03	No	None
PS26	F	41	PSO	11.4	Vulgaris/Eruptive	0.17	Father	Hypothyroidism
PS31	M	52	PSO	13.5	Vulgaris	0.16	Mother	Hypercholesterolaemia
PS34	M	20	PSO	19.6	Vulgaris	0.19	Mother	None
PS44	M	60	PSO	19.7	Vulgaris	0.95	No	None
PS46	M	52	PSO	18.0	Vulgaris/Eruptive	0.75	No	Diabetes
PS52	M	31	PSO	4.2	Vulgaris	0.18	No	Depressive disorder
PS53	M	61	PSO	10.5	Vulgaris	0.44	Grandmother	Hypercholesterolaemia, diabetes
PS54	M	53	PSO	20.2	Vulgaris	0.16	No	Hypercholesterolaemia
PS63	M	37	PSO	19.2	Vulgaris	0.28	Cousin	allergic rhinitis
PS76	M	25	PSO	18.4	Vulgaris	0.60	Mother	None
PS80	M	39	PSO	14	Vulgaris	0.32	Sister/Grandmother	None
PS81	M	45	PSO	8	Vulgaris	0.06	No	Ischemic heart disease, arterial hypertension, hypercholesterolaemia
PS82	M	59	PSO	15	Vulgaris	0.26	No	None
C17	F	43	None	0.0	–	–	No	None
C18	M	42	None	0.0	–	–	No	None
C19	F	38	None	0.0	–	–	No	None
C21	F	29	None	0.0	–	–	No	None
C25	M	56	None	0.0	–	–	No	None
C28	F	51	None	0.0	–	–	No	None
C33	F	40	None	0.0	–	–	No	None
C36	F	45	None	0.0	–	–	No	None
C40	M	55	None	0.0	–	–	No	None
C41	M	22	None	0.0	–	–	No	None
C42	M	45	None	0.0	–	–	No	None
C43	M	41	None	0.0	–	–	No	None
C45	F	55	None	0.0	–	–	No	None
C48	F	34	None	0.0	–	–	No	None
C57	F	37	None	0.0	–	–	No	None
C58	F	56	None	0.0	–	–	No	None
C89	F	24	None	0.0	–	–	No	None
C90	F	23	None	0.0	–	–	No	None
C91	M	29	None	0.0	–	–	No	None
C72	M	57	None	0.0	–	–	No	None
C73	F	37	None	0.0	–	–	No	None
C74	M	55	None	0.0	–	–	No	None
C77	M	49	None	0.0	–	–	No	None
C92	M	38	None	0.0	–	–	No	None
C93	F	34	None	0.0	–	–	No	None

Abbreviations: F, female; M, male; PSO, psoriasis.
[a] In total 28 patients with psoriasis, 25 healthy control subjects were recruited into the study.

resident memory T cells and the recirculating pool could play a role also in the pathogenesis of psoriasis. In psoriasis patients we have recently found that circulating $CCR4^+$ $CD4^+$ memory T cells significantly correlated with disease severity, whereas a strong negative correlation was found between $CCR5^+$ $CD4^+$ memory T cells and the Psoriasis Area and Severity Index (PASI) score [20]. A subset of $CCR4^+$ $CD8^+$ $CD103^+$ T_{EFF} cells was also identified that positively correlated with both systemic inflammation and the severity of the cutaneous disease, suggesting that they could represent a link between cutaneous and systemic disease manifestations. To investigate further this aspect, we dissected the phenotype of the circulating memory T cell compartment in patients and control subjects by analyzing the T_{CM}, T_{EM} and T_{EFF} phenotype, the pattern of CCR6, CCR4, CXCR3 chemokine receptor expression and the expression of the skin homing molecule CLA and the T cell activation marker CD69. For each specific subset we calculated the correlation with PASI score and with the extent of systemic inflammation measured as serum level of C reactive protein (CRP) in individual patients.

In order to investigate whether blood to skin trafficking events that could emerge from the analysis of the circulating compartment can find correspondence in a parallel variation of trafficking receptor and memory T cell marker genes in psoriatic skin, we analyzed gene expression in a large cohort of patient and control subjects.

2. Materials and methods

2.1. Patients

53 patients from the Department of Dermatology, Istituto di Ricovero e Cura a Carattere Scientifico Istituto Ortopedico Galeazzi (Milan, Italy), 28 with a diagnosis of cutaneous psoriasis and 25 healthy