9 Schallreuter KU, Bahadoran P, Picardo M *et al.* Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? *Exp Dermatol* 2008; **17**:141–60.

Mesenchymal stem cells participate to inflammatory skin process of atopic dermatitis

DOI: 10.1111/bjd.15412

Linked Article: Orciani *et al.* Br J Dermatol 2017; **176**:1569–1576.

An important new involvement of mesenchymal stem cells (MSCs) in the complex scenario of atopic dermatitis (AD) is addressed by Orciani *et al.* in the current issue of the *BJD*.[1] In the last decade, researchers have investigated deeply on possible MSC involvement in the onset of different diseases.[2,3] Among different types of adult stem cells, MSCs have been studied extensively and applied in several scientific and clinical fields, including dermatology. MSCs are undifferentiated, multipotent and self-renewing cells that reside in many adult tissues.[4] They have several major characteristics including (i) the ability of homing to areas of inflammation and tissue damage, such as wounds or tumours;[3] and (ii) the capacity to modulate innate and acquired immune responses.[5] Interestingly, Orciani *et al.*[1] have previously hypothesized that the psoriatic microenvironment may induce resident skin MSCs to produce angiogenic and proinflammatory mediators, contributing to the development of skin lesions.[6,7] Moreover, it has been shown by Liu *et al.* that MSCs obtained from psoriatic skin lesions decreased the inhibitory effects on T-cell proliferation.[8] An aberrant immune response, particularly by T cells, is also typical of AD, which is characterized by a marked imbalance of T-helper (Th)2 vs. Th1/Th17, especially in the early phase whereas a mixed Th1/Th2 pattern is found at the chronic stage.[9] Phenotypic analysis of peripheral blood mononuclear cells derived from patients with AD demonstrated a marked increase in the interleukin (IL)-17^{+}CD4^{+} T-cell population compared with healthy controls. The highest percentage of IL-17-producing cells was found in severe AD, suggesting a direct correlation between the presence of Th17 cells and severity of the disease.[10,11] In their original article in the current issue of the *BJD*, Orciani *et al.*[1] convey their valuable experience with MSCs, evaluating whether a Th1/Th2 imbalance could already be detected in undifferentiated cells of AD. They have analysed the expression profile of 22 genes and proteins related to Th1, Th2 and Th17 cytokines/chemokines in MSCs from patients with AD (AD-MSCs) compared with healthy controls (C-MSCs). They have shown that 14 of 22 genes related to the Th1/Th17 pathway were upregulated whereas three of 22 genes related to the Th2 pathway were downregulated in AD-MSCs compared with C-MSCs. Moreover, they showed in this paper that the profile of AD-MSCs retraces the Th1/Th17 cell environment observed in differentiated cells of chronic AD. Overall, the data from this manuscript provide novel insights into AD pathogenesis, suggesting that the inflammatory process detected in the MSCs has a determining role in the typical Th1/Th2 imbalance. In summary, the findings reported by Orciani *et al.*[1] in the current issue of the *BJD* have highlighted the current understanding of the interaction between MSCs and the inflammatory response. Finally, we would like to emphasize that although there is much evidence supporting the effectiveness of MSCs in clinical dermatological therapy, such as wound healing, it is important to underline that the inflammatory microenvironment might also induce transplanted MSCs to behave abnormally, modulating any possible beneficial effects. Future studies will need to elucidate the role of stem cells in the control of inflammatory skin diseases.

Acknowledgments

The authors would like to acknowledge with gratitude Dr Serena Lembo, Department of Medicine, Surgery and Dentistry, University of Salerno, Italy.

Conflicts of interest

None to declare.

A. Balato[1]
G. Caiazzo[2]
Departments of [1]Advanced Biomedical Sciences, and [2]Clinical Medicine and Surgery, University of Naples Federico II, Via S. Pansini, 5, 80131 Naples, Italy
E-mail: annabalato@yahoo.it

References

1 Orciani M, Campanati A, Caffarini M *et al.* T helper (Th)1, Th17 and Th2 imbalance in mesenchymal stem cells of adult patients with atopic dermatitis: at the origin of the problem. *Br J Dermatol* 2017; **176**:1569–76.
2 Salvolini E, Orciani M, Lucarini G *et al.* VEGF and nitric oxide synthase immunoexpression in Down's syndrome amniotic fluid stem cells. *Eur J Clin Invest* 2011; **41**:23–9.
3 Wen S, Niu Y, Yeh S, Chang C. BM-MSCs promote prostate cancer progression via the conversion of normal fibroblasts to cancer-associated fibroblasts. *Int J Oncol* 2015; **47**:719–27.
4 Klimczak A, Kozlowska U. Mesenchymal stromal cells and tissue-specific progenitor cells: their role in tissue homeostasis. *Stem Cells Int* 2016; **2016**:4285215.
5 Kidd S, Spaeth E, Dembinski JL *et al.* Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using *in vivo* bioluminescent imaging. *Stem Cells* 2009; **27**:2614–23.
6 Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008; **8**:726–36.
7 Campanati A, Orciani M, Consales V *et al.* Characterization and profiling of immunomodulatory genes in resident mesenchymal stem cells reflect the Th1-Th17/Th2 imbalance of psoriasis. *Arch Dermatol Res* 2014; **306**:915–20.
8 Liu R, Wang Y, Zhao X *et al.* Lymphocyte inhibition is compromised in mesenchymal stem cells from psoriatic skin. *Eur J Dermatol* 2014; **24**:560–7.

9 Napolitano M, Megna M, Patruno C *et al.* Adult atopic dermatitis: a review. *G Ital Dermatol Venereol* 2016; **151**:403–11.
10 Di Cesare A, Di Meglio P, Nestle FO. A role for Th17 cells in the immunopathogenesis of atopic dermatitis? *J Invest Dermatol* 2008; **128**:2569–71.
11 Koga C, Kabashima K, Shiraishi N *et al.* Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol* 2008; **128**:2625–30.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Audio S1. Author audio.

Psoriasis and the interleukin-10 family: evidence for a protective genetic effect, but not an easy target as a drug

DOI: 10.1111/bjd.15158

Linked Article: Galimova *et al.* Br J Dermatol 2017; **176**:1577–1587.

Interleukin (IL)-10 is an anti-inflammatory cytokine that suppresses production of cytokines in macrophages and modulates antigen presentation by dendritic cells and suppresses costimulatory reactions by acting on T cells.[1] IL-10 also plays an important role in B-cell activation and in autoantibody production and acts as an inhibitory factor during the production of T helper cytokines.[2] Recently, a specific subset of IL-10-producing regulatory B cells was identified as so-called B-10 cells and has been shown to ameliorate imiquimod-induced, psoriasis-like skin inflammation in a mouse model.[3] Interestingly, the absolute number of IL-10-producing regulatory B cells has been found to be decreased in patients with psoriasis, while the number of B-10 progenitor cells happened to be increased, implying that there are abnormalities in the process of B-10 cell development from B-10 progenitor cells in psoriasis.[4] Moreover, it is well known that psoriasis is characterized by a cutaneous IL-10 deficiency.[5] Therefore, we may conclude that IL-10 is intricately involved in the pathogenesis of psoriasis.

Interestingly, genome-wide association studies have failed so far to identify IL-10 as a major genetic risk factor in contrast to genes in the IL-23/T17 axis.[6] Therefore, it is timely that Galimova and her coworkers, in this issue of the *BJD*, report on their extensive analysis of genetic polymorphisms in the IL-10 gene cluster on chromosome 1q31 with regard to psoriasis.[7] They actually analysed 48 single-nucleotide polymorphisms of the IL-10 gene cluster covering IL-10, IL-19, IL-20 and IL-24 in a fairly large sample of 377 patients with psoriasis and 403 control individuals and identified a haplotype in the IL-10 gene that conferred a protective effect. This effect even 'survived' a Bonferroni correction for multiple testing and remained significant ($P_c = 0{\cdot}004$). Even more interesting are their results of a two-locus interaction between a marker in the IL-10 gene and a marker in the IL-20 gene. Although their study lacks a replication cohort, which would have given further validation, their findings are in line with a much earlier family-based association study showing a protective effect of an allele in the IL-10 promoter.[8] Taken together, these two studies implicate members of the IL-10 gene family as acting in a protective way against psoriasis. The question therefore arises: could IL-10 be a further target to treat psoriasis in the future? In German, my answer would be 'Jein' – meaning 'yes and no' at the same time. As a matter of fact, recombinant IL-10 was tried already, 18 years ago, as one of the first biologic agents in psoriasis[9] and in the meantime seven clinical trials have been conducted including several phase II studies,[5,10] but recombinant IL-10 as a biologic has so far not found its way into clinical practice, probably because other biologic agents are superior.

One limitation of biologic agents is that they do not reach inside the cell to target intracellular signalling pathways, but bind with receptors on extracellular membranes or extracellular milieu.[11] This approach apparently failed for IL-10. In contrast, small drugs like the phosphodiesterase 4 inhibitor apremilast can reach within the cell and by decreasing intracellular cAMP increase, among others, the anti-inflammatory cytokine IL-10.[11] It is conceivable that similar small drugs may be developed in the future and that they may perhaps overcome the blockade of IL-10-producing regulatory B cells from their B-10 progenitor cells. Thus, it is my feeling that IL-10 remains an attractive, but certainly not easy, target in expanding our future therapeutic armamentarium for the treatment of psoriasis.

Acknowledgments

I want to thank Prof. Stefan Beissert, Dresden, for advising me on immunological aspects.

Conflicts of interest

None to declare.

Department of Dermatology, University Hospital of Münster, Von-Esmarch-Str. 58, 48149 Münster, Germany
H. Traupe
E-mail: traupeh@ukmuenster.de

References

1 Jacob SE, Nassiri M, Kerdel FA, Vincek V. Simultaneous measurement of multiple Th1 and Th2 serum cytokines in psoriasis and correlation with disease severity. *Mediators Inflamm* 2003; **12**:309–13.
2 Taga K, Tosato G. IL-10 inhibits human T cell proliferation and IL-2 production. *J Immunol* 1992; **148**:1143–8.
3 Yanaba K, Kamata M, Ishiura N *et al.* Regulatory B cells suppress imiquimod-induced, psoriasis-like skin inflammation. *J Leukoc Biol* 2013; **94**:563–73.