CPD • Noteworthy paper

CED
Clinical and Experimental Dermatology

CPD

Understanding psoriasis: the development of the immune pathogenesis

Molly Papadopoullos[1] and Paul Devakar Yesudian[2]

[1]*School of Medicine, Cardiff University, Cardiff, UK; and* [2]*Department of Dermatology, Wrexham Maelor Hospital, Wrexham, UK*

doi:10.1111/ced.15360

From its early descriptions, psoriasis was considered a disorder of keratinocytic proliferation. Research has provided more detailed understanding of the immunopathogenesis in chronic plaque psoriasis. In turn, the treatments have evolved from bran baths and injections of sterilized milk in ancient times, to modern-day systemic immunosuppressants and biologics.[1] Specifically, a change in the aetiopathogenesis from keratinocyte proliferation to immunological hyperactivity can be attributed to the seminal publication in *Immunology Today* by Valdimarsson *et al.* in 1986.[2] This was the first article to propose that the disease was associated with significant immunological dysfunction, and emphasized the interaction between epidermal T lymphocytes and antigen-presenting cells in initiating and maintaining psoriatic lesions. The authors proposed the immune dysfunction theory based on a previous observation that epidermal T lymphocytes and dendritic cells were depleted with psoralen ultraviolet A treatment, mirroring the clinical improvement in psoriasis seen with this therapy.[3]

In their publication,[2] Valdimarsson *et al.* established that psoriatic plaques were associated with infiltrations of epidermal T helper (Th) lymphocyte cells. Activation of these Th cells occurred within the dermis, and in turn gave rise to the release of epidermal proliferation factor (EPF), which then stimulated Th cells to generate more EPF. They proposed that this vicious circle was responsible for the persistence and enlargement of psoriatic lesions.

In the longitudinal study by Baker *et al.*,[3] an equal quantity of Th cells and T suppressor (Ts) cells were seen within the epidermis of persistent chronic plaques. Resolving psoriatic lesions showed prominence of Ts cells, in contrast to the higher level of Th cells seen in the erupting lesions. Thus, the formation and persistence of psoriatic lesions was associated with an influx of Th cells, whereas resolution was preceded by a reduction in Th cells. The influx of activated Th cells from disruption of epidermal cells and epidermal/dermal junction injury explained the Koebner phenomenon of trauma-induced lesions in uninvolved psoriatic skin.

This immunological model led to the use of ciclosporin, a selective immunosuppressant known to inhibit Th cell function via calcineurin inhibition, in the management of plaque psoriasis.[4] In 1986, Griffiths *et al.*[5] successfully treated 10 patients with severe psoriasis that was unresponsive to conventional treatments, using low doses of ciclosporin over a period of 12 weeks. The dose started from 2 mg/kg and was increased by 1 mg/kg if no improvement was noted by Day 14. The clearance of psoriasis with ciclosporin after 12 weeks of treatment lent further evidence to the hypothesis that psoriasis was a disorder induced by T lymphocytes, which in turn resulted in abnormal keratinocyte proliferation. Treatment of severe plaque psoriasis using ciclosporin was later approved by the US Food and Drug Administration in 1997.[6]

The early work by Valdimarrson *et al.*[2] was therefore foundational in the development of an immune-mediated pathogenesis of psoriasis. It shifted the emphasis of treatment and research from inhibition of keratinocyte proliferation to immune modulation. Modern research has now established that environmental factors, such as stress, trigger the expression and signalling of interleukin (IL)-23/IL-17, resulting in the development of psoriasis.[7] The revolutionary hypothesis by Valdimarrson *et al.*[2] changed the way we manage psoriasis, leading to the modern cytotoxic and biologic era, and demonstrating the direct impact that laboratory-based research can have on clinical medicine.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None.

Correspondence: Dr. Molly Papadopoullos, School of Medicine, UHW Main Building, Heath Park, Cardiff CF14 4XN, UK
E-mail: mollyp08@hotmail.co.uk

Accepted for publication 1 August 2022

Ethics statement

Ethics approval not applicable. The patient provided informed consent for publication of their case details and images.

Data availability

Data are available on request from the corresponding author.

References

1 Reid C, Griffiths C. Psoriasis and treatment: past, present and future aspects. *Acta Derm Venereol* 2020; **100**: 69–79.
2 Valdimarsson H, Bake B, Jónsdótdr I *et al*. Psoriasis: a disease of abnormal keratinocyte proliferation induced by T lymphocytes. *Immunol Today* 1986; **7**: 256–9.
3 Baker B, Swain AF, Griffiths CEM *et al*. Epidermal T lymphocytes and dendritic cells in chronic plaque psoriasis: the effects of PUVA treatment. *Clin Exp Immunol* 1985; **61**: 526–34.
4 Bendtzen K, Tvede N, Svensen H. Ciclosporin (cyclosporin A): molecular biology and clinical use. *Int J Med Sci Res* 1984; **12**: 874–6.
5 Griffiths CEM, Powles AV, Leonard JN *et al*. Clearance of psoriasis with low dose cyclosporin. *Br Med J* 1986; **293**: 713–32.
6 Soleymani T, Vassantachart J, Wu J. Comparison of guidelines for the use of cyclosporine for psoriasis: a critical appraisal and comprehensive review. *J Drugs Dermatol* 2016; **15**: 293–301.
7 Yan D, Gudjonsson J, Le S *et al*. New frontiers in psoriatic disease research, Part I: genetics, environmental triggers, immunology, pathophysiology, and precision medicine. *J Invest Dermatol* 2021; **141**: 2112–22.

CPD questions

Learning objective

To demonstrate up-to-date knowledge of the recognition and management options for psoriasis.

Question 1

Which of the following is the correct mechanism of action of ciclosporin in the treatment of psoriasis?

(a) Binding to nuclear vitamin D3.
(b) Disruption of keratinocyte-keratinocyte binding and softening of the stratum corneum.
(c) Inhibition of calcineurin.
(d) Inhibition of dihydrofolate reductase.
(e) Inhibition of tumour necrosis factor (TNF)-α.

Question 2

With reference to the study by Barker *et al*., which of the following statements is correct?

(a) Higher proportion of T helper (Th) cells are seen in the epidermis in persistent psoriatic plaques.
(b) Formation of psoriatic plaques is associated with an influx of T suppressor (Ts) cells.
(c) An influx of Ts cells explains the Koebner phenomenon.
(d) Resolving psoriatic plaques have a predominance of Ts cells.
(e) Ts cells are seen in new erupting psoriatic plaques.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures.
- Reflect on the article.
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions.
- Complete the required evaluation component of the activity.

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.