Understanding psoriasis: the development of the immune pathogenesis

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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 Valdimarsson *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 Valdimarsson *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.

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Noteworthy paper

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

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.