Psoriasis is a chronic, relapsing, inflammatory skin disorder associated with significant comorbidity that confers a disease burden that is often more than ‘skin deep’. The most common type, chronic plaque psoriasis (psoriasis vulgaris), which accounts for up to 90% of all cases, is characterised by plaques that feature redness (erythema), thickening (induration) and scaling (desquamation). Our understanding of psoriasis, while still incomplete, has rapidly advanced in recent decades, from being a dysregulation of epidermal keratinocytes to being an immune-mediated inflammatory disease. Indeed, psoriasis has served as a model for elucidating the mechanisms of chronic inflammation.1,2 Owing to this, an understanding of the immune system is crucial to an understanding of psoriasis pathogenesis and therapy.

Effective immunity depends on the ability to discriminate between self and non-self at a molecular level. Self molecules are those to which self-tolerance has been established, such as molecules located on the surface of normal body cells. Non-self molecules are those that are foreign to the body, such as those located on the surface of pathogens or cells transplanted between genetically non-identical individuals. Fragments of abnormal proteins made by tumour cells within the body and advertised on the surface of those cells can also be recognised as non-self. Any non-self molecule that can induce an immune response in the body is called an antigen. Occasionally, self molecules can aberrantly elicit an immune response, such as in autoimmune disease, and such antigens are called autoantigens. Several psoriasis autoantigens have been described recently,3-5 but their contribution to disease pathogenesis remains an open question.

Immunology

There are two fundamentally different types of immune response:6,7

- Innate (natural) immune responses are rapid upon exposure, but have no antigenic specificity and provide immunity that is unaltered on repeated exposure
- Adaptive (acquired) immune responses are slow upon initial exposure, but have antigenic specificity and provide immunity that is improved on repeated exposure.

Innate immunity

Innate immunity comprises barriers that prevent pathogens, such as viruses, bacteria and parasites, from entering the body (e.g. skin, hair and bodily secretions like sweat and sebum) or cellular responses that limit their ability to move throughout the body. Innate immune system responses are mediated by many types of white blood cells (leukocytes):

- Cells that ingest pathogens (phagocytes), including monocytes, macrophages, neutrophils, mast cells and dendritic cells (DCs)
- Cells that contain cytoplasmic granules (granulocytes), including neutrophils, basophils, mast cells and eosinophils
- Natural killer cells that destroy infected host cells.

DCs are key sentinels of the immune system (Langerhans cells are DCs of the skin and mucosa), and they are activated directly by molecular patterns on the surface of pathogens and indirectly by cytokines produced by other cell types (Box 1).8,9 Receptors on phagocytes like DCs recognise protein markers on the surface of the pathogen without knowing what type of pathogen it is or whether they have seen it before. The pathogen then becomes surrounded and engulfed (phagocytosed) by the phagocyte. The membrane of the phagocyte pinches in and forms a vesicle around the pathogen within the phagocyte called a phagosome. The pathogen is broken up (lysed) by fusing of the phagosome with another vesicle called a lysosome. After the phagosome and the lysosome fuse to create a phagolysosome, enzymes from within the lysosome degrade the pathogen. Antigens derived from protein fragments in the pathogen debris are then transported to the phagocyte cell surface as part of the antigen.
B cells and can occur in two forms: a soluble form that is secreted by B cells and a membrane-bound form that is attached to the B cell surface to function as an antigen receptor (referred to as the B cell receptor). In terms of antigen specificity, each mature B cell expresses only one type of antibody that is unique to that cell. Only B cells that produce working antibodies that do not bind to self-antigens exit the bone marrow. In this way, the immune system is able to generate a diverse range of B cells against all potential antigens prior to exposure. This ensures that we have protection against most pathogens that we may come into contact with and that our immune system does not attack our own body cells in an autoreactive fashion. Binding of an antigen that is specific to a particular B cell receptor activates that B cell, inducing it to proliferate rapidly (thereby making multiple clones of itself) and differentiate into memory B cells or antibody-secreting effector cells called plasma B cells.

**Effective immunity depends on the ability to discriminate between self and non-self at a molecular level**

B cell-mediated immunity is sometimes called humoral immunity because it is mediated outside of cells in the humors (medieval term for body fluids). Humoral immunity targets pathogens as they spread by moving from cell to cell through body fluids, as well as those pathogens that multiply outside of cells. Activated B cells function to mediate humoral immunity by secreting antibodies that recognise and bind pathogens outside of cells, thereby neutralising pathogens and/or marking them for elimination.

The specificity of antibodies has been exploited for therapeutic purposes. Biologics (UK), also known as biologics (US), are medical products produced by living cells. With the exception of etanercept, current biological therapies used to treat psoriasis are monoclonal antibodies (mAb), meaning that in the case of each therapeutic agent the antibodies are identical to each other as they are produced by many identical cells (a single clone of cells). In each case, therapeutic mAb production employs recombinant DNA technology to express a gene that encodes an antibody that has the ability to bind to a specific target, which could be a protein on the cell surface (e.g. a cytokine receptor) or a protein that is secreted by the cell (e.g. a cytokine) (Box 1).

**T cells**

T cells originate in the bone marrow but mature in the thymus. T cell receptors (TCRs) are the antigen receptor on the T cell surface, and as per B cells, each mature T cell expresses only one type of TCR that is specific to that cell. Only T cells that produce functional TCRs that do not bind to self-antigens exit the thymus. Of these T cells, approximately 95% produce a TCR that is type αβ (known as αβ T cells) and 5% produce a TCR that is type γδ (known as γδ T cells). In addition to TCRs, T cells exiting the thymus express one of two types of cell surface marker called cluster of differentiation (CD) which act as a co-receptor: either CD4 or CD8.

The TCR molecules on a T cell can only recognise antigens displayed on the surface of antigen-presenting cells in the context of an antigen-presenting molecule called a major histocompatibility complex (MHC). MHC-restricted antigen recognition by T cells facilitates immune surveillance of not only ‘non-self’ antigens (e.g. foreign proteins produced by pathogens), but also ‘altered-self’ antigens (e.g. aberrant proteins produced by tumour cells owing to malfunction). Importantly, MHC molecules also determine compatibility for organ transplantation. There are two types of MHC molecules: MHC class I (MHC-I) – which present antigens derived from proteins that originate inside the cell (intracellular antigens), and MHC class II (MHC-II) – which present antigens derived from proteins that originate outside the cell (extracellular antigens). Specific recognition of an MHC/antigen complex by a TCR that a particular T cell expresses will activate that T cell and induce it to proliferate (thereby making multiple clones of itself) and differentiate into memory T cells or effector T cells.
Cellular immunity targets pathogens that survive in phagocytes and pathogens that infect non-phagocytic cells (cellular immunity can also target tumour cells, transplanted cells and damaged cells). Naïve CD4+ T cells, also known as naïve T helper (T\textsubscript{H}) cells or T\textsubscript{H}0 cells, upon activation, function to provide molecular signals (cytokines) that coordinate innate/adaptive effector cell activity and thereby direct efficient immune reactions. Activated CD8\textsuperscript{+} T cells, known as T cytotoxic (T\textsubscript{Cyt}) cells, function to destroy target cells that advertise themselves as altered (e.g. through infection or tumourigenesis).

### Antigen presentation to T helper cells

To reiterate, TCRs on T cells can only recognise antigens that are presented in the context of MHC on the surface of cells. Macrophages and DCs are particular cases of phagocytes that present antigen in the context of MHC-II proteins. A similar process happens with B cells, even though B cells are part of the adaptive (specific) immune system, whereas phagocytes are part of the innate (non-specific) immune system. B cells that recognise a pathogen (through antibody on their surface binding to antigens on the pathogen’s surface) then engulf and degrade the pathogen and display antigenic pieces in the context of MHC-II proteins on their cell surface.

Macrophages, DCs and B cells are called professional antigen-presenting cells (APCs). The significance of MHC-II presentation of extracellular antigens by professional APCs is that it is required for recognition by CD4\textsuperscript{+} T cells (that is, of those T cells that are able to recognise an antigen, only those that are CD4\textsuperscript{+} are able to bind to it in the context of MHC-II). Naïve CD4\textsuperscript{+} T cells (i.e. T\textsubscript{H}0 cells) that recognise an antigen in the context of MHC-II become activated T\textsubscript{H} cells and provide signals to coordinate innate/adaptive effector cell activity (Figure 1).

### T helper cell differentiation

Activated T\textsubscript{H}0 cells differentiate into functionally unique cell subsets depending mainly on the cytokine milieu to which they are exposed (Table 1).\textsuperscript{15-21} Activated DCs, in addition to presenting antigens, secrete cytokines in response to the specific molecular patterns that they detect during pathogen encounter (via pattern recognition receptors on the DC surface). Depending on the specific molecular patterns that the activated DC detects, it releases a specific range of cytokines that directs the activated T\textsubscript{H}0 cell to differentiate into a T\textsubscript{H}1 cell type that can drive an efficient immune response to the pathogen encountered (Figure 2).

Currently, the three most characterised T\textsubscript{H}1 cell subsets derived from activated T\textsubscript{H}0 cells are T\textsubscript{H}1, T\textsubscript{H}2 and T\textsubscript{H}17. For intracellular pathogens such as viruses, bacteria such as \textit{mycobacterium tuberculosis} or tumours, a T\textsubscript{H}1 cell-mediated immune response is generated. For extracellular pathogens such as bacteria and helminths, a T\textsubscript{H}2 cell-mediated humoral (antibody) response is generated. The T\textsubscript{H}17 subset is specific for extracellular pathogens such as \textit{candida} and bacteria such as \textit{staphylococci} (Figure 2).

### Antigen presentation to T cytotoxic cells

All cells that have a nucleus (including professional APCs) possess MHC-I on their surface (note that one of the few cell types that does not have a nucleus and so does not possess MHC-I on the surface is red blood cells). Antigens that are derived from proteins that originate inside cells (intracellular antigens) bind to MHC-I proteins and are transported to the cell surface to be presented. Examples of intracellular antigens include fragments of viral proteins that are made inside infected cells and fragments of abnormal proteins that are made inside tumour cells owing to malfunction.

MHC-I presentation of intracellular antigens by nucleated cells is required for antigen recognition by CD8\textsuperscript{+} T cells (that is, of those T cells that are able to recognise an antigen, only those that are CD8\textsuperscript{+} are able to bind to it in the context of MHC-I). CD8\textsuperscript{+} T cells that recognise an antigen in the context of MHC-I become activated T\textsubscript{Cyt} cells and kill the target cell that has advertised itself as infected or malignant (Figure 1).

### Pathophysiology of psoriasis

As reviewed elsewhere,\textsuperscript{22} inflammation has physiological purposes, but can also...
Dendritic cells (DCs) are crucial in initiating immune responses to pathogens. They are equipped to present antigens to T cells, activating them to become effector T cells. There are different subsets of T cells, each with distinct functions:

- **T<sub>H1</sub> cells** secrete cytokines like IL-2, IFN-γ, and TNF-α, promoting cellular immunity and acting against intracellular pathogens.
- **T<sub>H2</sub> cells** secrete IL-4, IL-5, IL-6, and IL-13, which are involved in inducing humoral immunity and host defense against extracellular pathogens.
- **T<sub>H17</sub> cells** produce IL-17, IL-21, and IL-22, driving tissue inflammation and immune responses against parasitic and fungal infections.

### Physiologic inflammation

Physiologic inflammation requires that the response is downregulated appropriately (resolved), otherwise lymphocyte infiltration and continued release of cytokines can drive chronic inflammation and tissue destruction. Psoriasis is now considered to be a chronic systemic inflammatory condition mediated by innate and adaptive immune cells in the absence of known infectious agents or antigens. Disease initiation in psoriasis is thought to involve an interplay between environmental and genetic factors. Increased insights into the immunopathogenesis of psoriasis have formed the basis for targeted biological approaches to treat the disease.

Psoriasis was initially considered to be the result of a very simple pathogenic process of keratinocyte dysregulation involving accelerated cell division. Later, however, during a pilot study to investigate the effect of ciclosporin A in psoriasis, it was found that the disease is not caused by a simple process of keratinocyte dysregulation but rather involves a complex interplay between environmental and genetic factors.
Dendritic cells

Proximal regulators

Naïve T helper cells

Activated T helper cells

Cytokines

Keratinocyte

Figure 3.
Targeting the IL-23–Th17–IL-17 pathway: Activated DCs in the skin and mucosa present antigens and secrete cytokines that lead to the differentiation of Th1 and Th17 cells (IL-12, IL-6, and TGF-β stimulate Th17 development and the expression of IL-23R on the Th17 cell surface). IL-23-secreted by activated DCs stimulates Th17 cells to secrete a range of cytokines including IL-17A, IL-17E, IL-17F, and TNF-α, which drives keratinocyte hyperproliferation and inflammation. Keratinocyte-derived pro-inflammatory cytokines amplify the immune response in psoriatic plaques and create a positive feedback loop of inflammation. Ustekinumab (Stelara®) binds to the p40 subunit of IL-12 and IL-23 to prevent IL-12 and IL-23 binding to IL-12R and IL-23R, respectively. Guselkumab (Tremfya®) binds to the p19 subunit of IL-12 to prevent IL-12 binding to IL-12R. Targeting the p19 subunit of IL-12 instead of its p40 subunit provides blockade of IL-23 but not IL-12 (thereby leaving IL-12 signaling and Th1 type immunity unaffected). Infliximab (Remicade®), Adalimumab (Humira®), Etanercept (Enbrel®), Brodalumab (Kyntheum®, Leo Laboratories), and adalimumab (Humira®) bind to TNF-α to prevent TNF-α binding to TNFR. Secukinumab (Cosentyx®, Novartis) and ixekizumab (Taltz®, Eli Lilly and Company) bind to IL-17A to prevent IL-17A (i.e. IL-17AA and IL-17AF) binding to IL-17RA-IL-17RC. Brodalumab (Kyntheum®, Leo Laboratories) binds to IL-17RA to prevent IL-17A, IL-17AF, IL-17FF, and IL-25 (not shown) binding to IL-17RA-IL-17RC. Secukinumab (Cosentyx®, Novartis) and ixekizumab (Taltz®, Eli Lilly and Company) bind to IL-17A to prevent IL-17A (i.e. IL-17AA and IL-17AF) binding to IL-17RA-IL-17RC. Brodalumab (Kyntheum®, Leo Laboratories) binds to IL-17RA to prevent IL-17A, IL-17AF, IL-17FF, and IL-25 (not shown) binding to IL-17RA-IL-17RC.

animal experimental evidence challenged the importance of T<sub>H1</sub> cells in the induction and maintenance of chronic inflammatory disease and suggested a critical role for IL-23 in autoimmunity. Research has since shown that the development of ustekinumab to target the p40 subunit of IL-12 was rather fortunate, in that ustekinumab actually blocks both IL-12 and IL-23.37 In fact, IL-23 blockade alone has been shown to be sufficient to achieve both clinical and molecular responses in patients with moderate-to-severe psoriasis.38 Furthermore, preclinical evidence that IL-12 exerts an anti-psoriatic effect by limiting skin inflammation suggests that collateral targeting of IL-12 by anti-p40 monoclonal antibodies is counterproductive in the therapy of psoriasis.39 The recently developed therapeutic mAbs that target the p19 subunit instead of its p40 subunit provide blockade of IL-23 but not IL-12 (thereby leaving IL-12 signaling and T<sub>H1</sub> type immunity unaffected) (Figure 3).38 The knowledge gained with respect to the clinical utility of blocking IL-23 via its p40 subunit was a step-change in our understanding of the pathophysiological basis of psoriasis.40-42 and led to the discoveries that IL-23 interaction with IL-23 receptors on CD4<sup>+</sup> T cells drives differentiation to the T<sub>H17</sub> subset (Figure 2 and Table 1).43 IL-23 promotes and stabilises T<sub>H17</sub> cells to produce IL-17A, IL-17F and TNF-α.44 Physiologically, T<sub>H17</sub> cells and their associated cytokines form a part of the adaptive cell-mediated immune response that provides host defence against fungi (such as candida) and extracellular bacteria (such as staphylococcus aureus).45,46 Pathologically, the cytokines produced by activated T<sub>H17</sub> cells, IL-17A in particular, appear to have a pivotal role in inducing keratinocytes to produce cytokines that amplify the immune response in psoriatic plaques and create a positive feedback loop of inflammation.47

Today, the IL-23–T<sub>H17</sub>–IL-17 axis (summarised in Box 2) is the focus of considerable research with respect to the development of molecules that have therapeutic effect not only in psoriasis, but also in PsA. IL-23 blockade inhibits stimulation of T<sub>H17</sub> cells and in turn results in reduced T<sub>H17</sub> cell secretion of a repertoire of cytokines that are important for immunity at mucocutaneous surfaces, one of which (i.e. IL-17A) has proved to be clinically critical in psoriasis pathogenesis.47 Therapeutic mAbs that target IL-17A have proved more efficacious than an anti-IL-12/IL-23 agent (i.e. ustekinumab) in clinical practice.48,49 It is worthwhile noting, however, that CD8<sup>+</sup> T cells and γδ T cells can also contribute IL-17F, IL-22 and tumour necrosis factor (TNF)-α.50,51 Moreover, cells of the innate immune system can be stimulated to produce IL-17A via IL-23-dependent as well as possibly IL-23-independent pathways.52 In this context, direct blockade of IL-17A or its receptors on target cells (such as keratinocytes) inhibits the pro-inflammatory impact of this cytokine, regardless of source.

### BOX 2.

**Current model of psoriasis initiation and maintenance.**

1. **Initial triggers**, such as physical trauma or bacterial products, lead to activation of Langerhans cells (dendritic cells of the skin and mucosa).
2. Activated Langerhans cells present antigens to CD4<sup>+</sup> T cells and secrete cytokines such as interleukin (IL)-12 and IL-23.
3. IL-1β, IL-6 and transforming growth factor (TGF)-β stimulate activated CD4<sup>+</sup> T cells (i.e. T<sub>H0</sub> cells) to differentiate into T<sub>H17</sub> cells; IL-23 stimulates T<sub>H17</sub> cells to secrete cytokines such as IL-17A, IL-17F, IL-22 and tumour necrosis factor (TNF)-α.
4. IL-17A, IL-22 and TNF-α activate keratinocytes to proliferate and induce them to secrete antimicrobial peptides and pro-inflammatory cytokines (e.g. IL-1β, IL-6 and TNF-α and chemokines; IL-17A has proved to be clinically critical in psoriasis pathogenesis.
5. Keratinocyte-derived pro-inflammatory cytokines activate Langerhans cells and activate innate immune cells to produce pro-inflammatory cytokines such as interferon (IFN)-α, IFN-γ and TNF-α, thereby establishing a positive feedback loop of chronic disease.
Within approximately 10 years of developing psoriasis, an estimated 20–30% of individuals develop psoriatic arthritis.53 It is a chronic inflammatory spondyloarthropathy (affecting axial and/or peripheral skeleton) associated with psoriasis.53 It is noteworthy, however, that onset of joint symptoms precedes the appearance of skin lesions in approximately 20% of PsA patients.53,55-57 Psoriatic joints have inflamed entheses (the points at which ligaments or tendons attach to bones) and synovia (the soft tissues which line the non-cartilaginous surfaces within joints that have capsules), with focal erosions of bone and cartilage.53 As a result of these inflammatory changes, dactylitis (inflammation of digits) is a hallmark of peripheral PsA. With particular focus on the hand, the nail is a continuous structure with the enthesis at the distal interphalangeal joint (DIPJ), and nail involvement predicts enthesopathy in patients with psoriasis.58 It has been postulated that mechanical injury to the nail and/or DIPJ apparatus may traumatising the associated enthesis resulting in activation of the IL-23–TGF-β–IL-17 axis via prostaglandin release,59 with IL-17A released from IL-23-responsive cells resident at the traumatised enthesis leading to irreversible bone erosion.60-62

Conclusion

Our understanding of the pathophysiology of psoriasis has developed over time and currently focuses on the IL-23–TGF-β–IL-17 axis. This has led to a rapid increase in the development of biologicals that inhibit cell signaling mediated by either IL-23 or IL-17. Despite significant expansion in the therapeutic armamentarium for treating psoriasis, the existing ‘treat to phenotype’ approach neglects the individual patient’s underlying molecular pathology. The lack of a ‘treat to pathology’ approach may in part explain why some patients fail to respond to a therapy targeting one particular cytokine/cytokine receptor interaction, but may have an excellent response to one targeting another: We are now on the verge of an exciting new era, with international efforts established to develop a personalised medicine approach to treating psoriasis patients. In the UK, world-leading dermatologists have partnered with industry and the Psoriasis Association in the Medical Research Council-funded UK PSORT (Psoriasis Stratification to Optimise Relevant Therapy) consortium. By identifying the molecular and clinical features that predict which biological agent is likely to be more useful in a particular patient, the aim of future clinical practice will be to tailor treatment to the individual, thereby improving outcomes. In this, the first of a two-part review, we have explored key aspects of immunology and the basis for the immunopathology of psoriasis. In addition, we have highlighted the importance of the IL-23–TGF-β–IL-17 axis in psoriasis and PsA disease pathology and how this is the target of current and newly emerging therapies. In the second part of this review, we will discuss how the underlying immunopathology of psoriatic disease is intrinsically linked to many associated comorbidities, and we will conclude by surveying the future direction of drug development to treat psoriasis. 

Abbreviations

APC, antigen-presenting cell
CD, cluster of differentiation
CA, cyclosporin A
CSF, colony-stimulating factor
dC, dendritic cell
dIPJ, distal interphalangeal joint
IFN, interferon
IL, interleukin
mAb, monoclonal antibody
MHC-I, major histocompatibility complex class I
MHC-II, major histocompatibility complex class II
PsA, psoriatic arthritis
TCR, T cell receptor
TC, T cell, T helper cell
TGF, transforming growth factor
TNF, tumour necrosis factor

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