The development of psoriasis is thought to be precipitated by an inflammatory response in the skin triggered by injury, infection, allergy, chemicals or stress. Innate immune cells, such as Langerhans' cells become activated and produce proinflammatory cytokines such as IL-1, IL-6 and TNF-α. Activated Langerhans' cells migrate to skin lymph nodes and present antigens to CD4+ T cells. Production of TGF-β, IL-6 and IL-23 stimulates the differentiation of T cells into Th17 helper T cells that migrate into skin and secrete IL-17. Keratinocytes become activated by IL-17 stimulation and secrete additional cytokines that attract other immune cells to the skin resulting in self-perpetuating inflammatory processes in the skin.
It is thought that psoriasis is precipitated by an inflammatory response in the skin triggered by injury, infection, allergic reaction, chemical irritants or stress. An innate immune response begins with activation of local phagocytes such as Langerhans’ cells (a type of skin-resident dendritic cell) that engulf foreign antigens or pathogens and migrate to lymph nodes in the skin where processed peptide antigens are presented to T cells. In psoriasis, Th17 polarised CD4+ helper T cells play a central role in the development of the condition, although there is also involvement of Th1 and Th22 phenotypes. Naïve CD4+ T cells differentiate into Th17 phenotypes following cytokine stimulation with TGF-β and IL-6, with IL-23 as an additional growth factor. IL-23 appears to play an important role in the development of psoriasis as demonstrated by the clinical benefit of anti-IL-23 therapies as well as genetic linkage to defects in the IL-23 signalling pathway.
Naive CD4+ helper T cells (T<sub>N</sub>) are activated by dendritic cells, such as Langerhans’ cells in the skin, in the T cell zone of secondary lymphoid organs such as lymph nodes. The phenotype of the activated T cell is determined by cytokine stimulation. Naive CD4+ helper T cells differentiate into Th17 CD4+ helper T cells following stimulation by TGF-β and IL-6 with additional enhancement by IL-23 stimulation. The activated T cell undergoes clonal expansion and effector cells migrate from the lymph node to the site of infection using cell-surface homing receptors. The destination of effector T cells is also determined by the dendritic cell interaction. Langerhans’ cells originate from the skin and induce activated T cells to express the skin-homing receptors, CLA and CCR4.
Homing of effector T cells to the skin and extravasation into the dermis is a multi-step process that begins with initial binding of CLA and CCR4 receptors expressed on T cells to E-selectin and CCL17 chemokine ligands on skin post-capillary venule endothelial cells, respectively. Additional stabilisation then occurs by binding of T cell integrins LFA-1 and VLA-4 to endothelial cell adhesion molecules ICAM-1 and VCAM-1, respectively. The T cell then extravasates into the dermis by moving between endothelial cells (also known as diapedesis). Following activation by Langerhans’ cells, Th17 effector cells migrate from skin lymph nodes to the dermis by this mechanism.
Th17 CD4+ helper T cells are so called because they secrete IL-17, a pro-inflammatory cytokine that stimulates other cells to respond to an infection. There are variant isoforms of IL-17 designated IL-17A through F. Th17 polarised T cells secrete isoforms IL-17A and IL-17F that binds the heterodimeric IL-17 receptor composed of IL-17RA and IL-17RC polypeptide chains. This IL-17 receptor is expressed on epithelial cells such keratinocytes in the skin. Keratinocytes are activated upon stimulation of the IL-17 receptor. Genetic mutations in the CARD14 gene that encodes a protein involved in the activation of the transcription factor NFκB has been strongly linked to the development of psoriasis due to prolonged NFκB activity. NFκB is required for the transcription of keratinocyte-derived immune modulating cytokines.
Keratinocytes activated by IL-17, produce antimicrobial peptides such as β-defensins and cathelicidins that participate in the control of micro-organisms. In psoriasis the cathelicidin LL-37 is thought to play a role in modulation of the condition. In response to IL-17 stimulation, activated keratinocytes also secrete immunomodulatory cytokines.
Keratinocytes produce the IL-17C isoform of IL-17 which binds the alternative IL-17 receptor composed of the IL-17RA and IL-17RE polypeptide chains. IL-17C does not bind to the same receptor as IL-17A and IL-17F. The IL-17C receptor is also expressed by keratinocytes and IL-17C stimulation activates the cell. Similarly, keratinocytes produce IL-36 that also activates keratinocytes by binding to the IL-36 receptor. IL-36Ra is an IL-36 receptor antagonist molecule that competes with IL-36 for binding to the IL-36 receptor. Genetic mutations in the IL-36Ra gene has been shown to cause a distinct form of pustular psoriasis.
Activated keratinocytes produce CCL20, a chemokine that binds to the CCR6 chemokine receptor expressed by immune cells such as myeloid dendritic cells, Th17 CD4+ helper T cells and also gamma-delta CD4+ T cells. Recruitment of these CCR6+ immune cells into the dermis is facilitated by CCL20 chemokine gradients.
Activated keratinocytes produce chemokines that recruit neutrophils to the dermis. CXCL1, -2, and -3 bind to the CXCR2 receptor expressed by neutrophils, while CXCL8 can bind to both CXCR1 and -2 receptors. In psoriasis, large numbers of neutrophils are recruited to inflamed skin due to these chemokines.
Vascular endothelial cell growth factor (VEGF) is produced by activated keratinocytes and binds to the VEGFR2 receptor on skin capillary endothelial cells promoting angiogenesis. In psoriasis increased blood supply is evident below the epithelial cell layer of inflamed skin. The vessels are also dilated which gives psoriatic lesions a red colour.
An amplification of activation signals targeting keratinocytes occurs via cytokines produced by immune cells that have been recruited to the skin. Th17 CD4+ helper T cells, gamma-delta CD4+ T cells and neutrophils all produce IL-17A and IL-17F that can activate additional keratinocytes by binding to the IL-17 receptor (IL-17R, RA+RC polypeptide chain variant). Myeloid dendritic cells produce IL-1, IL-6 and TNF-α that are proinflammatory cytokines and enhance inflammatory responses in the skin.
The hallmark histological observations of psoriatic skin is a thickening of the epidermal cell layer, with defects in the normal development and maturation of keratinocytes and the formation of plaques. Accumulation of immune cells in the skin, particularly neutrophils occurs. Increased blood supply is also evident. Once this stage has been reached following the original trigger (injury, infection, allergic reaction, chemical, stress etc) the condition can become self-perpetuating due to the constant cytokine stimulation (particularly IL-17) of keratinocytes and influx of inflammatory cells into the skin.