Psoriasis – New Insights into an Old Disease

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With an estimated worldwide incidence of about 2%[1], psoriasis is the most common autoimmune disease in the world with about 80 million affected persons, 20 million of whom being affected in a moderate to severe way. Though psoriasis is common in people of all ages, it appears more frequently in early adulthood.

Environmental factors, immunology and genetics all play an important role in the onset of the disease[2,3]. Due to its chronic nature, physical appearance and high degree of morbidity, the disease can have significant effects on a person's physical and mental health as well as social life. Typically the condition is characterized by the presence of red scaly skin plaques[4]. The histopathological features of psoriasis include growth and dilation of the superficial blood vessels (redness) and hyperplasia of the epidermis (plaques and scales). The epidermic hyperplasia is the result of a rapid proliferation and maturation of keratinocytes resulting in incomplete granular keratinocytes and squamous corneocytes terminal differentiation. Thus, the squamous keratinocytes retain intact nuclei (parakeratosis) and reduce their release of extracellular lipids that normally are responsible for the adherence of the corneocytes. This lack of adherence results in the characteristic scale or flakes of the psoriatic lesions.

An understanding of the pathogenesis of psoriasis requires knowledge of the immunologic processes occurring in the skin. Together with the peripheral lymph nodes and circulating immunocompetent T lymphocytes, a number of immunological actions within the skin layers, effectively render the skin an important lymphoid organ. This collection of antigen-presenting cells (APCs), the epidermotropic T cells, the dermal capillary endothelial cells, cytokine-synthesizing keratinocytes, and the draining lymph nodes form what has become known as skin-associated lymphoid tissue (SALT). In addition, through the effect of different cytokines and chemical mediators, other cells such as mast cells, tissue macrophages, granulocytes, fibroblasts, and dendritic cells, interact with one another.

The cellular physiological picture of psoriasis can be split into the induction phase and the elicitation phase. During the induction phase, APCs in the epidermis process antigens (autoantigens or bacterial antigens) and once in the lymph nodes, present this information to the CD4 helper and CD8 T-cells. An immune reaction occurs with the proliferation and release of both effector and memory T cells (elicitation phase). Through the release of neutrophil, monocyte and keratinocytes chemotactic and activating cytokines, these cells increase the inflammatory reaction in the epidermis.

Drug	Molecular Action	Physiological Action
Methotrexate (most widely used systemic drug)	• competitive inhibitor of the enzyme dihydrofolate reductase - inhibits thymidylate synthesis	• inhibits the replication and function of T and B cells • suppresses the secretion of cytokines • suppresses epidermal cell
Cyclosporin	• binds cyclophilin, (immunosuppressant-binding protein). The complex binds to and inhibits the enzyme, calcineurin, resulting in blockage of signal transduction pathways that are dependent on the transcription factor, NF-AT (nuclear factor of activated T cells)	• inhibition of the cytokines IL-2 and IFN-γ (inhibits T-helper cell activation and proliferation)
Phototherapy (widely used treatment in moderate to severe psoriasis)	• formation of photoadducts with DNA	• direct effect on the proliferation of epidermal keratinocytes • reduces the dendritic (Langerhans) and cytotoxic T cells • reduces cytokine secretion
Mycophenolate mofetil (also used in prevention of organ transplant rejection and in the treatment of rheumatoid arthritis)	• inhibits the enzyme, inosine monophosphate dehyrogenase	• inhibits purine synthesis in lymphocytes and thus reduces lymphocyte proliferation, antibody production, and the formation of adhesion molecules in response to antigenic or mitogenic stimulation
Hydroxyurea (mainly used in haematological malignancies and in sickle cell disease)	• inhibits ribonucleotide diphosphate reductase, the enzyme that converts ribonucleotides to de oxyribonucleotide triphosphates	• depresses basal cell replication in the epidermis • reverses the abnormal keratin proliferation in psoriatic plaques • inhibits vascular proliferation in the dermis • lowers the neutrophil count in the skin with decreased formation of pustules and microabscesses in psoriatic plaques
Thioguanine	• chemical analogue of guanine and adenosine - incorporated into DNA in place of guanine, leading to DNA derangement	• suppresses lymphocyte and keratinocyte proliferation
Liarozole	• inhibitor of the cytochrome P450 pathway	• decreases the number of CD11+ cells • decreases ICAM-1 expression • decreases keratinocyte proliferation
Fumaric acid esters	• induction of preferential apoptosis in activated T cells through NF-B pathway	• inhibits T-cell activity and causes a shift from a Type 1 helper T cell response to a Type 2 helper T cell response
Pimecrolimus	• binds to FKBP-12 protein – inhibits the enzyme, calcineurin resulting in blockage of signal transduction pathways that are dependent on the transcription factor, NF-AT (nuclear factor of activated T cells)	• specific inhibitor of the production of proinflammatory cytokines from T cells and mast cells • reduces proliferation of T cells after antigen-specific or nonspecific stimulation

Figure 1: *Pharmacological action of drugs used in psoriasis*

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The trigger for the abnormally increased T-cell infiltration is thought to be either due to a dysregulatory response or due to the continuous activation of the APCs. Bacterial, viral (retrovirus) and keratinocyte proteins (autoreactivity) have been implicated as the causative antigens.

From the genetic point of view, psoriasis is a genetically heterogenous disorder with multiple genes involved as well as complex environmental interactions that can explain the heterogeneity of both the severity and location of the disease manifestation.

Two main genetic loci on chromosomes 6p and 17q have been reported in genome scans. The HLA-Cw6 phenotype has been found to increase the risk of psoriasis by about 10 fold. Similarly to other HLA-linked conditions (eg. Coeliac Disease), though the HLA locus is an important risk factor, the fact that around 10% of the population carry the phenotype and only 2% have the condition, indicates that other genetic/environmental factors are at play. In fact, the PSORS1 locus near the HLA-C has been estimated to account for 30% to 50% of the genetics contribution to psoriasis.

Two regions within chromosome 17q have been associated with psoriasis and being relatively distant from each other, seems to indicate that they have an independent effect on the disorder. The two genes within the first peak are SLC9A3R1 and NAT9 whilst RAPTOR has been identified within the second peak.

SLC9A3R1 is a scaffold protein, linking plasma membrane proteins to the actin cytoskeleton in epithelial cells. External signals can lead to changes in signal transduction and cell growth via this protein. Thus disruption of this scaffold, could prolong the time that the antigen is presented to the T cell receptor, leading to prolonged inflammation. The actual DNA change, seems to be the loss of a RUNX1 site lying between the two genes. This variant is quite common in the population, so the actual associated susceptibility risk is low (this is a running theme with other variants predisposing to complex disease, that is, they are common in the general population and thus require additional susceptibility factors). RUNX1 is a major transcription factor in the development of haematopoietic cells. Though the actual consequence of loss of this particular RUNX1 site is unknown, alterations in RUNX1 sites in other genes predispose to other autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis).

RAPTOR is a binding and regulatory factor of mTOR, a major regulator of T

cell function and growth, through the cytokine-triggered protein kinase cascade that leads to the phosphorylation of the eukaryotic initiation factor, PHAS-1, in activated T lymphocytes. Rapamycin binds to and blocks the function of mTOR, leading to immunosuppression.

Other susceptibility loci for psoriasis reside on chromosomes 1q21, 3q21, 4q, 7p, 8, 11, 16q and 20p. A recent study has identified over 1300 altered gene expression within lesional skin when compared to uninvolved skin.[5]

Similar to other disease, the study of the genetic pattern in psoriasis can lead to the identification of novel pathophsyiological biochemical pathways and thus help to identify targets for novel therapeutics. In addition, a deeper understanding of the genetic background can also assist in disease prediction, prognosis, as well as in the pharmacogenomics of psoriasis. The latter could even lead to the creation of personalised therapies.

Treatment aspects

As a chronic disease with exacerbations, remissions, and recurring lesions, the treatment options for Psoriasis depend on the extent and severity of the disease, safety aspects of systemic agents, economic issues, accessibility to phototherapy treatment centres and quality-of-life issues. Various treatments are available and are used either alone or in combination. The therapeutic mechanism of most traditional drugs can be explained through their action on T-cell function.

The Biologics

Biologic or 'Biologic response modifiers' is the generic term for a group of hormonal, neuroactive and immunoreactive compounds that act at the cellular level. Whilst derived from living material (human or non-

human), they are produced through recombinant DNA techniques and possess pharmacological activity. Biologics include monoclonal antibodies, fusion proteins, cytokines, lymphokines, and other antiproliferative agents.

The biologics currently approved for psoriasis (Figure 2) are either fusion proteins or monoclonal antibodies and can be divided into three main groups based upon their modes of action:
- Group 1: Reduce the number of pathogenic T cells
- Group 2: Inhibit T-cell activation and migration
- Group 3: Block the activity of inflammatory cytokines

The Future

Psoriasis is a disorder of chronic T-cell stimulation with a genetic predisposition in which environmental triggers play a major role. With a greater knowledge of the molecular pathways responsible for both general as well as cutaneous immunology, new, highly specific, immune-targeting biologic modifiers can be developed. These would ideally have an excellent long term safety profile as well as being an effective treatment to ease most if not all problems associated with the disease.

References

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Drug	Group	Type	Structure	Action
Infliximab	3	MA	Anti-TNF-α	Neutralizes serum and membrane bound TNF-α
Etanercept	3	FP	Human IgG1 Fc + TNF-α receptor	Combines with TNF-α in serum (acts as receptor)
Efalizumab	2	MA	Human IgG + murine variable against CD11a subunit of LFA-1	Blocks interaction of LFA-1 with ICAM-1
Alefacept	1	FP	IgG Fc + LFA-3	Blocks T-cell activation by interfering with CD2/LFA-3 interaction

Figure 2: *Currently approved biologics for psoriasis (MA: Monoclonal Antibody; FP: Fusion Protein).*