Translational Research in Psoriasis

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ABSTRACT. Translational research is a coordinated process that converts scientific knowledge about diseases from basic research into the development of therapeutic or diagnostic procedures in order to improve public health. Recent insights into the pathogenesis of psoriasis have greatly promoted the rational development of new therapeutic approaches. The integration of genetic predisposition and pathogenetic events defined the cytokine cascade as a target for therapeutic interventions. Applying various phases of translational research has enabled development of novel therapies that combine high efficacy with convincing safety profiles, with important implications for public health. (J Rheumatol Suppl. 2015 Nov;93:17–20; doi:10.3899/jrheum.150627)

Key Indexing Terms:
TRANSLATIONAL RESEARCH PSORIASIS THERAPY ETIOLOGY

The terms "translational research" or "translational medicine" emphasize a continuous, bidirectional flow between basic, clinical, and patient-oriented research. The principal goal of translational research is to translate scientific innovations that affect public health. Despite this clear objective, no unique understanding of translational research has been achieved, and the term means different things to different people depending on the respective point of view[1]. The recent scientific and therapeutic developments in psoriasis show the importance of a detailed analysis and definition of the meaning of translational research.

Defining Translational Research

From the scientist's perspective translational research means harnessing knowledge from basic research to develop applications such as drugs, devices, or treatment options for patients. This is the classical "from bench to bedside" concept. In contrast, public health agencies instead focus on building the evidence base for integration of applications into practice and demonstrating health effects at the population level with the clear goal of translating research into practice.

These goals are essentially no different from those of traditional academic clinical research. Yet from the perspective of public health agencies, translational research emphasizes concrete strategies to expedite successful implementation.

The importance of translational research for public health perspectives is best illustrated by the efforts of the US Centers for Disease Control to develop systematics and methodology for translational research. The result is a framework of 4 phases covering the process from identification of genetic or molecular causes of a disease to designing an effective diagnostic or treatment[2]: (T1) translates a basic genome-based research or cellular or molecular discoveries into a clinical application. This includes observational, Phase I and II clinical studies; (T2) assesses the value of a genomic, cellular, or molecular application for health practice leading to evidence-based guidelines, such as Phase III clinical studies; (T3) moves evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research; and (T4) evaluates the "real world" health outcomes of a clinical application in practice. Thus, translational research fosters a multidirectional and multidisciplinary integration of basic, patient-oriented, and population-based research, with the longterm aim of improving public health.

Psoriasis: from Serendipity to True Translational Research

Psoriasis is a prime example of how therapeutic development may change from serendipity to translational research. Initially, pathogenetic concepts in psoriasis were initiated by clinical observations, and the efficacy of particular treatments had a major effect on experimental approaches and pathogenic concepts. The clinical effects of the antiproliferative activities of aminopterin and methotrexate[3], for example, prompted the investigation of epidermal hyperproliferation[4]. The therapeutic efficacy of cyclosporine[5] or CD4 monoclonal antibodies[6] drew attention to the role of T cells in psoriasis, and the tremendous effects of tumor necrosis factor-α (TNF-α) antagonists[7] finally proved that cytokines of the innate and adaptive immune system mediate the inflammatory hyperproliferation of the epidermis.

Today, translational research in psoriasis meets both the perspectives of scientists and health authorities. This is based on pathogenetic understanding, which allows a bidirectional flow of information between bench and bedside for the

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rational development of new treatment approaches. It covers the entire spectrum, ranging from genetic predisposition (summarized in[8]) to the inflammatory mechanisms of skin lesions (Figure 1). Different gene variants related to proinflammatory signaling cascades [*CARD14*, caspase recruitment domain family member 14, etc.) and skin barrier function (*LCE3C_LCE3B-del*, etc.) may predispose to an increased inflammatory response to infections or otherwise trivial proinflammatory triggers. Upon activation of innate immunity, certain gene variants related to antigen processing (*ERAP-1*, *PSMA-6*) and antigen recognition (HLA-Cw6, HLA-B27 alleles) allow for an activation and clonal expansion of T cells against autologous proteins in the skin that are presented by the respective HLA molecules[9]. The presence of certain gene variants that influence the functional development of T-cell responses (*IL12B, IL23R, IL23A, TRAF3IP2*, etc.) then leads to the differentiation and expansion of activated T cells into the T helper (Th)17 cell type. These Th17 cells produce a particular pattern of cytokines, which is characterized by interleukin 17A (IL-17), IL-17F, IL-22, TNF-α, and, in a subset of Th17 cells, IFN-γ[10]. Together these cytokines induce epidermal hyperplasia, accumulation of neutrophilic granulocytes, and production of chemokines and antimicrobial peptides[10,11]. Clinically, this appears as the typical hyperproliferative, scaling inflammatory plaques, which are interspersed with subcorneal Munro microabscesses and spongiform pustules in the case of plaque psoriasis, or macroscopically visible pustules in the case of pustular psoriasis (Figure 1).

The 4 Phases of Translational Research in Psoriasis Drug Development

The knowledge of this sequence of events from genes to clinical manifestation has allowed the development of new therapeutic approaches that meet all phases of translational research. This is exemplified by the clinical development of the p40 monoclonal antibody (mAb) ustekinumab. The discovery of the role of Th17 cells in the psoriatic immune response identified the mechanisms of Th17 activation and differentiation as a potential therapeutic target[11]. T1, the translation of basic research into clinical application that first utilized these insights, was a Phase I clinical study, which in a small patient cohort proposed that a monoclonal antibody neutralizing IL-23 and IL-12 may be efficient in the treatment of chronic plaque psoriasis[12]. T2, two Phase III clinical trials, translated these insights into clinical application and evidence-based practice guidelines. They showed that blocking IL-23 and IL-12 was indeed highly efficient in the treatment of moderate to severe chronic plaque psoriasis, with efficacy and safety maintained with every 12-week dosing in the majority of patients[13,14]. T3, evaluation of interventions in practice, was a Phase IV clinical trial comparing the efficacy of ustekinumab to TNF-α antagonist etanercept[15]. T4, from practice to population health effects, was outcome research consisting of a longterm extension study of up to 5 years' duration. In addition to efficacy and safety[16], the population health effects were assessed regarding the risk for cardiovascular events and mortality, which are increased in psoriasis. This showed that the cardiovascular event rate

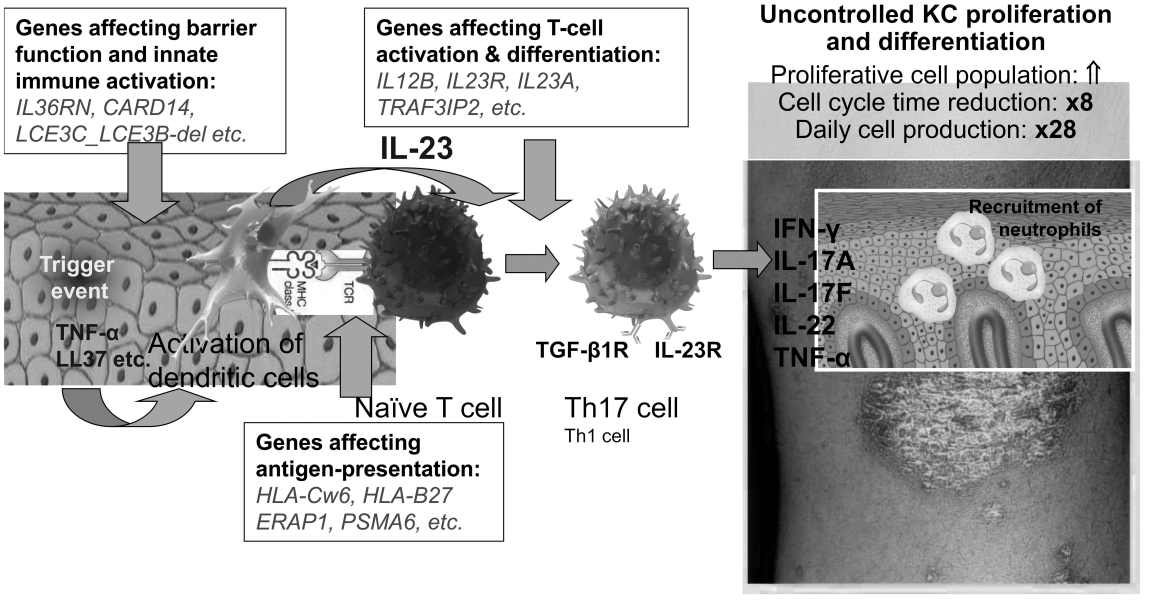

Figure 1. Translating genetic predisposition into a hierarchy of pathogenic events. Gene variants affecting skin barrier function and innate immune activation promote an increased response of innate immunity to trivial triggers. This activates dendritic cells. Certain gene variants affecting antigen-processing and presentation then facilitate the presentation of particular autoantigens that are being recognized by T cells. Upon activation of these T cells certain gene variants promote their differentiation into Th17 cells, which induce psoriatic inflammation by a particular pattern of cytokines. TNF-α: tumor necrosis factor-α; MHC: major histocompatibility complex; IL-23: interleukin 23; KC: keratinocytes.

with ustekinumab longterm treatment was lower than the expected incidence[17].

These insights have spurred development of other drugs that address Th17 pathways and are likely to soon find their way into the clinic[18]. Secukinumab, a monoclonal antibody (mAb) neutralizing IL-17A, the IL-17 receptor-specific mAb brodalumab, or the IL-23-specific antibody guselkumab, all show promising results in terms of efficacy and safety for the treatment of chronic plaque psoriasis.

Increasing Specificity and Efficacy of Treatment by Precise Interference with Psoriasis Pathogenesis

Each immunosuppressive therapy is a balancing act between the desired suppression of pathogenic immune responses and an undesirable inhibition of protective immunity. The advantages of a targeted interference with psoriasis pathogenesis are obvious. The more precisely the individual steps of the cascade are interrupted, the higher the therapeutic efficacy and the lower the risk of unwanted side effects of therapy (Figure 2).

The folic acid antagonist methotrexate has both antirheumatic and antiproliferative effects on many organs and is potentially hepatotoxic and nephrotoxic, with corresponding dropout rates[19]. The broad immunosuppressant cyclosporine, which may efficiently control psoriatic inflammation, has an increased risk for lymphoma and severe infections, impaired renal function, and elevated arterial blood pressure, at least with longterm use.

TNF antagonists are already showing a much more specific interference with the pathogenetic cascade. By blocking key signal and effector pathways of the innate and adaptive immune system, however, they are associated with an increased risk of serious viral and bacterial infections and, in particular, with reactivation of tuberculosis[20]. With IL-12/-23 blockade the risk of tuberculosis is not augmented[16], while the selective interference with T-cell activation and differentiation increased efficacy. Addressing IL-23 alone or IL-17 seems to be even more effective, balancing efficacy and risks in favor of therapeutic safety.

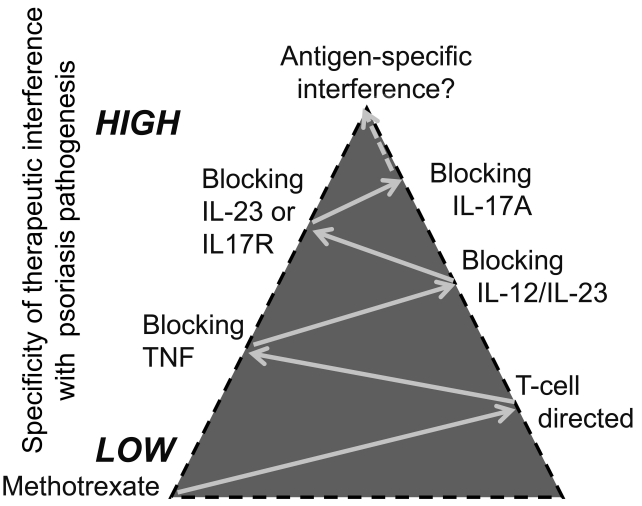

Figure 2. Translating pathogenetic events into an increased specificity of treatment approaches. The development of therapeutic approaches in psoriasis during translational research. With each new target, the therapeutic specificity of interference with the pathogenetic cascade increases. IL-23: interleukin 23.

Perspectives of Translational Research in Psoriasis

In summary, the shift to translational research in psoriasis has created new, more effective, and safer treatment options. In the interest of public health this implies a higher efficacy with lesser risks of side effects and, accordingly, a better utilization of available financial resources. The next step in the clarification of psoriasis pathogenesis is the identification of autoantigens of the psoriatic immune response. Once achieved, this should trigger new developments for a targeted elimination of pathogenic T cells and, as a result of translational research, facilitate not only suppression, but also a cure of psoriasis. These longterm goals may no longer be so far away.

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