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Impact of Environment and Genetics on the Pathogenesis of Non-Communicable Inflammatory Skin Diseases

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Dedicated to my family

Abstract

Chronic non-communicable inflammatory skin diseases (CNISDs), including psoriasis, hidradenitis suppurativa, and autoimmune blistering diseases, represent a major and increasing global health burden. These disorders arise from complex interactions between genetic susceptibility, environmental exposures, and dysregulated immune responses. Although targeted biologic therapies have transformed clinical management, the upstream mechanisms that initiate and sustain chronic cutaneous inflammation remain incompletely understood. This cumulative dissertation aimed to elucidate key determinants of CNISD pathogenesis by integrating epidemiological analysis, genetic discovery, and mechanistic immunological studies. First, a large-scale real-world data analysis using electronic health records from the TriNetX network examined the relationship between obesity and the risk of chronic inflammatory diseases. In a cohort comprising more than three million individuals, obesity was associated with a significantly increased risk for a broad spectrum of inflammatory conditions, including several dermatological diseases. These findings highlight obesity as a systemic and potentially modifiable driver of immune dysregulation and chronic inflammation. Second, a forward genetics approach in a murine model of Aldara-induced psoriasiform dermatitis identified Itga11, encoding integrin α11, as a previously unrecognized genetic modulator of inflammatory skin disease. Functional studies demonstrated that Itga11 deficiency attenuates skin inflammation, reduces immune cell infiltration, and alters extracellular matrix remodeling, implicating fibroblast-mediated tissue architecture as a critical regulator of immune responses in the skin. Third, the functional role of interferon-γ (IFN-γ) in epidermolysis bullosa acquisita (EBA) was investigated using an antibody-transfer mouse model. Pharmacological inhibition of IFN-γ significantly reduced disease severity and neutrophil recruitment, demonstrating that IFN-γ promotes autoantibody-mediated cutaneous inflammation. Together, these studies demonstrate that CNISDs are driven by the interplay of systemic metabolic factors, genetic modifiers, and local immune mechanisms. By combining population-scale analyses with experimental models, this work provides new insights into disease pathogenesis and identifies potential avenues for therapeutic intervention targeting metabolic, stromal, and immunological pathways.

Contents

1 Introduction

Chronic, non-communicable, inflammatory skin diseases (CNISDs) are a substantial and expanding burden to healthcare systems around the world. These diseases, such as psoriasis, atopic dermatitis, hidradenitis suppurativa, epidermolysis bullosa acquisita (EBA), and other rare autoimmune or autoinflammatory dermatoses (AD/AAIDs), are lifelong conditions and often first manifest during young adulthood. Beyond the cutaneous lesions, CNISDs are associated with several systemic diseases, including metabolic syndrome, depression, cardiovascular disease, and malignancy. Thus, the impact of CNISDs is enormous, including physical pain, psychological anguish, social disgrace, and enormous economic costs.

The increasing incidence of CNISDs necessitates an improved understanding of their pathogenesis, which is still ill-defined despite the availability of various therapies. In the past, inflammatory skin diseases were perceived as localized diseases. However, a change of paradigm has emerged over the past two decades with the growing awareness that CNISDs are of systemic nature involving the deranged interplay among the immune system, skin barrier, and, increasingly, metabolic and nervous systems. This integrated perception is consistent with the increasingly recognized comorbidity associated with CNSID.

Immune dysregulation, specifically of the adaptive immune system, is a major element in CNISDs. The cytokines that are necessary to initiate and amplify skin inflammation are produced by different subsets of T-helper (Th) cells, in particular the Th1, Th17 and Th22 subsets, by the release of interferon-gamma (IFN-γ), interleukin-17 (IL-17) and IL-22, respectively. Dendritic cells, macrophages, and neutrophils participate in this inflammatory response through antigen presentation, release of more proinflammatory mediators, and increased immune cell recruitment. Furthermore, the innate immune system and tissue resident cells including keratinocytes and fibroblasts participate in inducing chronicity by responding to external stimuli and reinforcing inflammatory response via feedback loops.

Simultaneously, environmental and systemic risk factors have been growingly implicated in the pathogenesis of CNISDs. Disease flares could be induced by environmental triggers, such as microbial dysbiosis, chemical stimuli, and UV exposome among others. Genetic components and epigenetic modifications also may be key factors on the individuals to be susceptible to the disease

and to develop severity. On the other hand, systemic risk factors, including obesity and psychological stress, might fuel immune derangement through neuroendocrine-immune crosstalk and systemic inflammation dysfunction. More recently, the concept of “metaflammation,” or metabolic inflammation, has emerged as a promoter of immune responses, connecting such lifestyle-dependent factors as diet and adiposity with components of cutaneous inflammation.

Fibroblasts and other mesenchymal cell types that were once considered passive structural components of the skin are now known to play a central role in immune regulation and disease pathogenesis. They secrete various chemokines, cytokines, and matrix-remodeling enzymes that affect immune cell behavior. The crosstalk between fibroblasts and immune cells becomes particularly significant in chronic diseases, where tissue remodeling and immune cell infiltration form a self-perpetuating inflammatory niche. Likewise, the last decades have shown that the extracellular matrix not only acts as the supporting structure for cells but can actively modulate the immune responses via the process of mechanotransduction and the various signaling molecules that reside within the extracellular matrix.

Therapeutically, CNISDs are managed by targeted biologics and small molecule inhibitors of major cytokine pathways (i.e., TNF-α, IL-17, IL-23 as well as the JAK/STAT pathway). These therapies have dramatically transformed clinical practice in psoriasis and atopic dermatitis. Unfortunately, not every patient responds to these treatments, and in most cases, continued treatment is necessary to maintain the therapeutic efficacy. Moreover, those treatments mainly regulate downstream immunity rather than targeting upstream agents that cause inflammation. Thus, there is a growing demand for modalities that can detect, interrupt, or reverse the systemic or structural elements that fuel the inflammatory circuits that lead to chronic inflammation of the skin.

This cumulative thesis aims to contribute to better understanding of the pathogenesis of CNISDs by combining epidemiological, genetic and immunological insights. At large, we aim to provide a comprehensive understanding of CNISDs and to elucidate their modifiable risk factors and propose potential therapeutic targets.

Study I

The first cohort study will be performed at a population level in order to assess the effect of obesity on the risk of CNISDs and other chronic inflammatory conditions. Using aggregate data from over six million patients within the TriNetX electronic health record network, this study provides a relatively broad perspective on the relationship between adiposity and inflammation. Notably, it further identifies specific cutaneous and systemic comorbidities that demonstrate relatively uniform risk elevations in overweight and obese patients. It further investigates demographic subpopulation (i.e., sex and race) modifiers to provide some understanding of the potential variation in CINSDs susceptibility.

Study II

The second study uses a forward genetics strategy in a mouse model of psoriasiform dermatitis to reveal underlying genetic factors of disease severity. By eliciting whole animal responses to Aldara®-induced skin inflammation in 13 inbred mouse strains, the study demonstrates marked strain dependent differences and utilizes genome wide association study approach to reveal *Itga11* as a putative gene. Subsequent experiments in *Itga11*-deficient mice demonstrate a suppressive effect in inflammation, indicating that integrin alpha 11 on fibroblasts contributes to extracellular matrix composition and immune cell infiltration. This discovery reveals a new node in the tissue-specific control of inflammation and underscores the potential of genetic discovery in the context of preclinical models.

Study III

The third proposed study applies a hypothesis-driven experimental strategy to analyze the function of IFN-γ in EBA, a well-characterized autoimmune blistering disorder. Based on previous results that identified the augmented IFN-γ production subsequent to Treg depletion, the study investigates whether pharmacological suppression of IFN-γ can improve disease *in-vivo*. These findings indicate that IFN-γ functions as a disease-promoting cytokine in experimental EBA, as reintroducing IFN-γ into IFN-γ-deficient mice was associated with increased disease severity and enhanced neutrophil infiltration. Although the therapeutic effect was modest, the work provides insight into cytokine networks in an autoantibody-mediated autoimmune disease; and the small numbers in this study do not preclude such disease as a possible target for IFN-γ therapy.

These three studies demonstrate the potential impact of integrative approaches that include real-world data, hypothesis-free genetic discovery, and targeted mechanistic exploration.

Furthermore, the present thesis is based on a translational approach, where one area feeds the hypotheses and treatment strategies of the other. The recognition of obesity as a modifiable risk factor calls attention to the need for lifestyle interventions and public health policies. The identification of *Itga11* as a functionally relevant risk gene in a mouse model of psoriasis expands the set of genes that can be specifically targeted in fibroblasts and highlights the relevance of mouse models in the discovery of new cellular players in inflammation. Lastly, the targeted blockade of IFN-γ in EBA not only confirms a cytokine that has already been implicated in other autoimmune diseases but also paves the way for an application of immunomodulatory therapies across different diseases.

2 Paper 1: Large-scale analysis highlights obesity as a risk factor for chronic, non-communicable inflammatory diseases

In the present study we investigated the implications of obesity as a systemic, modifiable risk factor in CNIDs, a category of diseases incorporating different dermatological pathologies. For this, we used the health record (EHR) database TriNetX encompassing data of more than 120 million from health care organizations around the globe (though mainly from the US). The study included more than 3.1 million individuals who were defined by the ICD-10-CM code E66 (overweight or obese) and propensity score matched cohort of non-overweight/obese controls. The purpose was to contrast the risk of a subsequent diagnosis with a total 46 chronic inflammatory diseases among the two groups.

At the start of the study, the current understanding was that obesity is associated with certain inflammatory diseases, e.g., psoriasis and hidradenitis suppurativa, but systematic evaluations across a broad spectrum of CNIDs remained overall scarce. Furthermore, for several of the investigated diseases, conflicting data had been published regarding the risk imposed by obesity for CNIDs manifestation. This knowledge gap was addressed in the current study, which used a retrospective cohort design with propensity score matching (PSM) to account for confounding factors, including those related to age, sex, race, smoking status, and mental health comorbidities. By including positive control, i.e., type 2 diabetes (T2D), for which obesity is a well-established risk factor, we also included an internal validation into the study design.

The results indicate a strong association between obesity and the risk of subsequent CNIDs diagnosis. The risk of any CNID diagnosis in the overweight/obese compared to controls in the primary analysis was 28.5% vs 17.6%, corresponding to a hazard ratio (HR) of 1.52. This was also consistent in all sensitivity analyses, whether considering BMI-based definitions and or restricting the period of follow-up to consider potential surveillance bias. Increase of risk was observed within multiple diseases represented in dermatology, rheumatology, endocrinology, gastroenterology, hematology, and neurology.

Of all skin diseases, hidradenitis suppurativa showed the highest association with obesity, with HRs close to 4.0 in all the analyses. Other dermatoses with substantial increases in risk were prurigo nodularis, urticaria, cutaneous lupus erythematosus, and vitiligo. Importantly, the study

also reported an increased risk for systemic inflammatory conditions considered less strongly associated with obesity such as systemic lupus erythematosus (SLE), ankylosing spondylitis, and autoimmune hepatitis, indicating a wider immunological influence of overweight and obesity.

Subgroup analyses delineated some, but not many, sex and racial disparities. Sex-stratified analyses showed higher propensity in women for some diseases; specifically for hidradenitis suppurativa, vitiligo, and type 1 diabetes (T1D). Race-stratified analyses found that several of the associations were stronger in White patients, by contrast associations in Black or African American patients were generally weaker or nonsignificant. These results suggest that demographic factors relevant for inflammatory disease pathogenesis should be included in investigations and indicate that personalized preventive strategies are warranted.

Mechanistically, it has been suggested that the association between obesity and CNIDs may be driven by chronic low-grade systemic inflammation from the adipose tissue. In obese subjects, especially in those with central obesity, adipocytes and infiltrating macrophages secrete high levels of proinflammatory cytokines including IL-6, TNF-α, and leptin, all of which can promote systemic innate and adaptive immune responses. This proinflammatory state might reduce the threshold for immune dysregulation and autoimmunity, especially in genetically susceptible individuals. In addition, obesity-associated metabolic alterations such as insulin resistance and dysregulated lipid metabolism can influence immune cell function and promote inflammatory mechanisms.

The major strengths of the study were the large sample size, wide disease range and the robustness of the analytical approach. However, there are some limitations to be addressed. Because of the use of ICD-10 codes, there is a possibility of misclassification, and the use of EHR data may be less sufficient for capturing disease onset and severity. Furthermore, not all patients had BMI measurements and severity, and duration of obesity could not be analyzed. Unmeasured confounding factors such as socioeconomic status, diet, and physical activity, that are generally not recorded in EHRs, also needed to be considered as potential limitation. Notwithstanding these limitations, the robustness of the results across different methods of analysis suggests the reliability of our conclusions.

This study adds importantly to our understanding of the manner in which obesity acts as central player in driving the systemic pro-inflammatory process that potentially led to the development of CNIDs. The results also dispute the traditional concept of obesity as a comorbidity on CNIDs , and rather establish it as a central pathogenic factor. The findings highlight the importance of integrated approaches to prevention and management of obesity. Clinically, this information supports heightened awareness of inflammatory conditions in overweight and obese patients, particularly in women and those with White ancestry for whom risk was increased and most pronounced.

In the setting of chronic inflammatory skin diseases (CISDs), our work offers epidemiologic validation of mechanistic associations that have been demonstrated in smaller clinical and experimental studies. Taken together, greater susceptibility of obese patients to suffer from hidradenitis suppurativa, prurigo nodularis, and cutaneous lupus erythematosus may parallel experimental findings indicating that obesity-induced inflammation influences cutaneous immune dysregulation. These observations provide robust indications for studying novel therapies, e.g. combining wight loss strategies to anti-inflammatory treatment to control systemic inflammation in obese patients with CNIDs.

In conclusion, this comprehensive EHR-based study shows that obesity independently increases the risk of multiple chronic inflammatory diseases (CIDs), including of the skin, at the population level. These findings have significant implications for public health, clinical practice and research to elucidate mechanistic pathways through which metabolic and immune dysregulation may be connected. They also paved the way for further studies within this thesis, that treat the genetic and immunological determinants of the CNIDs in a more mechanistic manner.

3 Paper 2: Forward Genetics Identifies *Itga11* as a Modulator of Psoriasiform Dermatitis

In this investigation, we used forward genetics in a murine model to study genetic basis of psoriasiform dermatitis. Psoriasis is a chronic, complicated, immune-mediated, inflammatory skin disorder with significant genetic and environmental components. The Aldara®-induced psoriasiform dermatitis (AIPD) model in mice reproduces several features of human psoriasis, i.e., epidermal hyperplasia, dermal immune cell infiltration, and role of cytokines, including IL-17 and TNF-α. Despite the findings from genome-wide association studies in humans that have defined a number of psoriasis susceptibility loci, relatively little is known about the genetic contributions that shape disease severity, especially regarding tissue-specific responses and stromal constituent cell types.

To address this, we applied Aldara® cream to 13 inbred strains of mice and scored skin inflammation with a modified Psoriasis Area and Severity Index (PASI). The clinical disease manifestations were quite different amongst the strains, with the CAST/EiJ mice showing the most severe inflammation and the NZO/HlLtJ and FVB/NJ mice showing only mild responses. These findings further indicate a major genetic effect in controlling susceptibility to disease and its severity.

Genome-wide association mapping/admixture mapping was done through Efficient Mixed-Model Association eXpedited (EMMAX) and haplotype block identification through Haploview using two single nucleotide polymorphisms (SNPs) within intronic regions of the *Itga11* gene which were associated with AIPD severity. *Itga11* is the gene encoding integrin alpha 11 (α11) subunit associated with the beta 1 subunit, to constitute the α11β1 collagen receptor. While α11β1 is known to be involved in the processes of wound healing and fibrosis, its contribution to inflammatory skin diseases has not been examined.

To elucidate the functional importance of *Itga11* in psoriasiform inflammation, we also assessed the susceptibility to AIPD in *Itga11*-deficient (*Itga11*$^{-/-}$) mice. Disease severity in these knockout mice was significantly lower compared to wild-type littermates, reflected by changes in PASI, epidermal thickness and immune cell infiltration. More specifically, histological examination demonstrated a reduction in hyperkeratosis and acanthosis, while immunohistochemistry revealed

a decreased level of the psoriasis-associated proliferation marker Ki-67. Flow cytometric analysis of enzymatically digested skin tissue (skin homogenates) revealed a decrease in dermal T cells, macrophages, and notably TRMs, believed involved in recurrences and chronicity of psoriatic lesions.

To further understand the molecular basis of these findings, we performed bulk RNA-sequencing of lesional skin from WT and *Itga11*$^{-/-}$ mice. Littermate wild-type and *Itga11*$^{-/-}$ mice had comparable expression profiles homeostatic condition. However, after Aldara® application, a clear separation could be observed. In total, 686 genes were differentially expressed between wildtype and *Itga11*$^{-/-}$ mice. Following the induction of psoriasiform dermatitis gen set enrichment analysis revealed pathways in extracellular matrix (ECM) organization, immune regulation, and lipid metabolism. Importantly, the expression of matrix metalloproteinases (e.g., *Mmp10*, *Mmp13*) and genes related to collagen were significantly reduced in knockout mice, indicating defective turnover. Deconvolution analysis with scRNA-seq reference data substantiated those fibroblasts were the predominantly *Itga11*-expressing cell type in the inflamed skin.

These results are consistent with the model that fibroblast-expressed *Itga11* regulates regulating the composition and architecture of the ECM, which in turn influences the ability of immune cells to traffic to and remain in the dermis. Impaired ECM remodeling in knockout mice could decrease the capacity of T cells and other immune cells to migrate and persist in inflamed tissues, thereby attenuating the inflammatory response. This stromal control of immunity illuminates the new concept of organ-specific immune modulation in which stromal cells are actively involved in programming the immune microenvironment.

Furthermore, the work highlights the benefit of unbiased methods to identify new pathogenic pathways. Forward genetics screens, unlike candidate gene studies, are unbiased and free from preconceptions, making it possible to discover unexpected modulators such as *Itga11*. The use of the AIPD model across various genetically diverse mouse strains enabled the investigators to capture natural variation of immune responses reflecting the diversity of human psoriasis.

The implications for this study extend beyond psoriasis. *Itga11* and the α11β1 integrin may also be relevant in other fibrotic or inflammatory diseases where fibroblasts and ECM remodeling play pivotal roles.

Furthermore, in cancer biology, fibroblast-integrins play a role in tumor invasion and escape from immune destruction. Insights into the functions of such integrins in inflammation responses could also lead to new therapeutics that regulate stromal-immune crosstalk.

From a translational standpoint, it suggests that *Itga11* may be a good candidate for pharmacological intervention. However, there are no known clinical drugs targeting α11β1, the interest in integrin-based therapy in various disciplines warrants further investigation in this area. Blockade of integrin signaling might lead to decreased fibroblast activation, impairment of immune cell infiltration, and in the end to diminished chronic inflammation. These therapies would be adjunctive to the currently available biologics targeting cytokines and could offer an option to patients who do not respond to standard treatments.

Collectively, our study highlights the importance of considering the tissue microenvironment in immune-mediated skin diseases. Fibroblasts as active regulators of the immune response rather than passive structural cells. They secrete chemokines, modulate the ECM and reach out to immune cells to structure the inflammatory habitat. The identification of such a critical regulator as *Itga11* further supports the notion that reprogramming stroma might provide an effective approach for managing chronic inflammatory disorders.

4 Paper 3: Inhibition of interferon gamma impairs induction of experimental epidermolysis bullosa acquisita

In the present study, we investigate EBA, a rare autoimmune blistering skin disease with autoantibodies targeting type VII collagen (COL7) as the major component of the dermal-epidermal junction. EBA is a notoriously therapy-resistant disease, and its chronic relapsing course is associated with considerable morbidity. Prior studies in experimental mouse models of the disease support that Treg depletion worsens EBA, that is associated with, upregulation of IFN-γ in the skin. Based on this finding, the present study examines whether pharmacologic blockade of IFN-γ can ameliorate severity of disease in a murine model of antibody transfer-induced EBA.

Rabbit anti-mCOL7C IgG was injected into C57BL/6J mice to create EBA, and then the mice were treated with neutralizing monoclonal anti-IFN-γ antibody at different dosages (125, 250 or 500 μg per mouse) or 500 μg per mouse isotype control antibody. Treatment was initiated 24 h before the induction of the disease and antibodies were administrated every other day for a total of 13 days. The severity of the disease was evaluated by clinical score of skin lesions, histological examination, and immunological testing (IgG- and C3- deposition at the dermal-epidermal junction).

IFN-γ blockade dose-dependently attenuated disease severity: By day 12, mice at the highest dose showed lower clinical scores, determined by the affected body surface area. Histological analysis validated reduced dermal inflammation and infiltration by Ly6G+ neutrophils. In contrast, the numbers of macrophages and CD4+ T cells in the affected skin were not significantly changed. Epidermal proliferation, determined by Ki-67, was not altered, indicating that IFN-γ most likely influences leukocyte recruitment rather than keratinocyte function.

Analysis of tissue-bound IgG by immunofluorescence demonstrated comparable amounts of bound IgG in treated and control animals but an unexpected increase in the amount of C3 deposition in treated mice. A serum analysis showed a decrease in pathogenic rabbit IgG at the high dose, but the levels of the protective mouse IgG were stable. These observations indicate that IFN-γ may affect antibody clearance or distribution, possibly by changing the activity of the neonatal Fc receptor (FcRn), which has been shown to be inhibited by IFN-γ.

CXCL1, which is a chemoattractant for neutrophils, was markedly decreased at the level of protein in the skin of treated mice, while levels of mRNA remained unchanged. This implies a post-transcriptional regulation or a late cytokine response. Flow cytometric analysis showed a marked decrease in skin-infiltrated neutrophils, which function of IFN-γ induction of EBA pathology may be mediated by augmenting recruitment and activation of neutrophils.

Despite a clinical improvement, pair-wise comparison of global gene expression profiles of the skin biopsies from treated vs. non-treated animals did not reveal substantial differences. In addition, multiplex cytokine analysis of serum samples revealed only marginal changes, and the only significant differences were found for IFN-γ itself, as well as CXCL1. These findings suggest that the effects of IFN-γ blockade are most likely limited to the skin and independent from general immunosuppression.

This study provides mechanistic insight into the role of IFN-γ in autoimmune blistering diseases (AIBDs)such as EBA. Although IFN-γ is best known as a promoter of Th1 responses and macrophage activation, its role in neutrophil-dependent tissue injury remains poorly defined. In the present study, the results support that IFN-γ enhances neutrophilic inflammation in EBA, which might be achieved by activating chemokines, such as CXCL1, and possibly by affecting complement pathways.

There are two potential translational implications for these observations. First, they provide evidence that IFN-γ may be a promising therapeutic target in EBA and potentially other autoantibody-driven dermatoses. Second, they propose that cytokine blockade approaches should be context specific and might be more effective in combination with other treatments. For example, the concurrent targeting of CXCL1, FcRn, or complement pathway could potentially improve IFN-γ inhibitors-preventive/therapeutic effect.

Furthermore, this research also illustrates the advantages of hypothesis-driven experimental research in validating pathogenic mechanisms and in identifying therapeutic targets. Although human studies are crucial to clinical translation, mouse models offer a more controlled environment that can be genetically manipulated to dissect individual components of disease pathogenesis. Linking these models with more recent technologies, including single cell RNA

sequencing and spatial transcriptomics, could potentially improve our ability to translate discoveries to clinical use.

In summary, the study provides evidence that IFN-γ promotes autoantibody-mediated cutaneous inflammation in EBA through neutrophil infiltration.

5 General Discussion and Conclusion

Pathogenesis of CNISDs is a consequence of combined and complex systemic risk factors and genetic predisposition and local immune mediated events. This cumulative dissertation is comprised of three separate, but complimentary studies; all investigating different phases of disease pathogenesis of CNISD. Together, they begin to provide a multi-faceted picture of how chronic inflammation is modulated. Furthermore, it also provides evidence that novel insights on disease pathogenesis can be obtained through different approaches: In-depth investigation of RWD, unbiased genetic approaches and hypothesis-driven experimental work.

In the first study, a large RWD study, we utilized a large cohort of EHRs to investigate the association between obesity and the development of 46 CIDs. The findings underscore the notion that obesity is not merely a comorbidity of CNISDs but rather an active contributor to systemic inflammation and immune dysregulation. The higher prevalence of diseases such as hidradenitis suppurativa, urticaria, autoimmune hepatitis and even of less frequently explored dermatoses contributes to the theory of a systemic pro-inflammatory condition induced by adiposity. More importantly, we also discovered that disease risk varied depending on sex and race, thus emphasizing the significance of addressing sex- and racial disparities for a more nuanced risk assessment. For example, in individual with White ancestry and in females' obesity imposes a greater risk for the subsequent diagnosis of specific CNISDs compared to those with Black of African American heritage or men. These differences potentially reflect variations in local fat distribution, hormonal control, and immune system function. If confirmed by other studies in the future, the findings of this study could support preventive measures against inflammatory skin diseases by focusing on metabolic health.

Obesity is also a pathophysiologic condition that leads to chronic inflammation, in part, via secretion of adipokines, derangement of lipid metabolism, and the recruitment of inflammatory macrophages in adipose tissue. These modifications result in elevated serum levels of IL-6, TNF-a, and C-reactive protein (CRP) generating a systemic inflammatory scenario. Furthermore, two other obesity-related cytokines, leptin and resistin, have also been shown to be involved in the deviation of immune responses to the pro-inflammatory side. In the skin, such systemic

inflammation can affect local immune cells, change keratinocyte behavior and barrier function, favoring the generation or amplification of chronic inflammatory dermatosis.

The second study used an experimental mouse model of psoriasiform dermatitis to perform a forward genetic screen, leading to the identification of *Itga11* as a previously unreported mediator of the disease process. Using genetic variation between inbred strains and linking this to disease severity following Aldara® treatment, they identified *Itga11* as a major genetic locus. Functional validation in *Itga11* knockout mice showed that targeted ablation of *Itga11* provided profound protection from skin inflammation. At the molecular level, we demonstrated that *Itga11* was expressed mainly in fibroblast cells and conditioning ECM composition, which modulated recruitment of immune cells. These results are of particular interest because, although fibroblasts are now recognized as active players in immune regulation, they have only recently been studied and characterized in the context of acute inflammation. The possibility that the tissue microenvironment in particular, the stromal and ECM topology can shape immunity is of significant importance in our view with respect to understanding chronicity and its therapeutic targeting. The work also serves as an example of how unbiased, hypothesis-independent genetic approaches may lead to the discovery of new players in disease pathways that would be neglected by classical candidate-gene approaches.

Fibroblasts, historically considered a solely structural component of connective tissue, are emerging as regulators of immunity. They secrete cytokines, chemokines, and ECM proteins, together with further shaping the local immune microenvironment. For instance, in psoriasis, fibroblasts secrete IL-6, CXCL1 and CCL20 to attract neutrophils and T cells to the skin with the inflamed lesion. *Itga11*, a collagen-binding integrin, regulates fibroblast-ECM interplay and could be regulating the stiffness of the dermis. These mechanical signals have in turn been demonstrated to impact the function of immune cells via mechano-transduction signaling routes. In this regard, a protective phenotype in *Itga11*$^{-/-}$ mice could be indicative of a less-permissive, more reined-in tissue environment that is less accommodating to immune invasion and activation.

The third study used a hypothesis-driven approach to investigate whether blocking IFN-γ would suppress skin inflammation in a mouse model of EBA. Treg depletion was previously shown to be accompanied by elevated IFN-γ and exacerbated disease so neutralization of IFN-γ was a test for

reversal of its effect. The data showed a significant but modest decrease in the severity of the disease with a decrease in both neutrophil migration and CXCL1 levels within the skin. Strikingly, neither expression of genes nor cytokine levels were overall not significantly changed, indicating that the observed effects of IFN-γ are very likely driven at the level of cell trafficking and local tissue interactions but not by systemic immunosuppression. However, the results herein also question the extent of single cytokine targeting in diseases such as EBA, where overlapping or compensatory inflammatory pathways may restrict the likelihood of success for monotherapies.

This study also adds to an increasing appreciation for the contribution of Th1-mediated immunity to autoantibody-mediated cutaneous diseases. Although Th2-related cytokines, such as IL-4 and IL-13, have been involved in diseases such as atopic dermatitis, EBA is more Th1-mediated with IFN-γ being a dominant effector. The decreased expression of CXCL1 and neutrophil infiltration in response to blockade of IFN-γ adds mechanistic evidence for a relationship between T-cell cytokines and recruitment of reactive innate immune cells. These results were also corroborated by the finding that IFN-γ blockade did not alter systemic cytokine signatures or keratinocyte proliferation to a significant degree, further illustrating that the disease modulation was achieved via targeted suppression of local immune crosstalk rather than systemic suppression of the immune response.

Taken together, these three studies provide compelling evidence for the complex nature of CNISDs. The first study positions obesity as a potential systemic inducer of inflammation that may shift the balance toward onset of disease. The other points to an architectural tissue component - fibroblast-derived integrin alpha 11 - that directly controls disease severity through control of immune cell access to inflamed skin. The third one focuses on a specific cytokine IFN-γ as mediator of inflammatory perpetuation and demonstrates that its neutralization amelioration disease. Each study is based on another methodology-epidemiology, genetics and immunology indicating that an interdisciplinary approach is essential to decipher such a multifactorial pathogenesis of complex diseases such as CNISDs.

Critically, these findings also hold translational value. Public health interventions targeting obesity may have widespread impacts beyond cardiometabolic health, which include reducing the burden of autoimmune and chronic inflammatory diseases. Genetic testing might even be possible to

identify people who are at high risk of severe disease or of responding poorly to treatment. And immunomodulatory approaches that target cytokines or fibroblast-immune interactions could provide new options for treatment, especially in patients who do not respond to current biologic agents.

These studies also highlight the importance of using experimental models to test both mechanistic hypotheses and therapeutic strategies. Unbiased genetic discovery and candidate-directed cytokine targeting combine to form an effective translation for immunology. One major benefit of working with laboratory animals is the opportunity to undertake controlled experiments that are not possible in humans. Nevertheless, the interspecies diversity in immune responses, composition of microbiota, and skin architecture still represent obstacles to clinical translation. It will be a future challenge to fill these gaps through humanized model, organoids or ex-vivo skin explants.

In perspective, integration of genetic risk, metabolic measurements, immune phenotypes and skin microbiome in a systems biology approach may help to better understand disease heterogeneity. In addition to this, patient-derived organoid models and spatial transcriptomics might even facilitate unprecedented visualization and manipulation of fibroblast-immune crosstalk. Lastly, combination therapies may be more effective than monotherapies targeting independent components if metabolic, structural and immune effects are collectively targeted.

In conclusion, the studies presented in this thesis advance our knowledge on the pathogenesis of chronic inflammatory skin disease by detailing the importance of systemic risk factors, genetic modifiers, and immunological effectors. Together, these results show that CNISDs are not localized to the skin, but instead represent systemic abnormalities of multiple cell types and signaling pathways. In accepting this complexity, we inch that much closer to discovering real therapies that work for people suffering from these often-devastating diseases.

6 Zusammenfassung

Einleitung

Chronisch-entzündliche, nicht übertragbare Hauterkrankungen (chronic non-communicable inflammatory skin diseases, CNISDs) stellen weltweit eine zunehmende medizinische und gesellschaftliche Herausforderung dar. Zu diesen Erkrankungen zählen unter anderem Psoriasis, atopische Dermatitis, Hidradenitis suppurativa sowie seltene autoimmune und autoinflammatorische Dermatosen. Diese Krankheitsbilder sind häufig chronisch-rezidivierend, treten oftmals bereits im frühen Erwachsenenalter auf und gehen mit erheblichen Einschränkungen der Lebensqualität der betroffenen Patientinnen und Patienten einher. Darüber hinaus sind sie häufig mit systemischen Komorbiditäten wie metabolischem Syndrom, kardiovaskulären Erkrankungen oder psychischen Belastungen assoziiert.

In den vergangenen Jahren hat sich das Verständnis der Pathogenese chronisch-entzündlicher Hauterkrankungen grundlegend gewandelt. Während diese Erkrankungen früher primär als lokal begrenzte dermatologische Krankheitsbilder betrachtet wurden, wird zunehmend deutlich, dass sie Ausdruck komplexer systemischer Entzündungsprozesse sind. Die Krankheitsentstehung beruht auf einem vielschichtigen Zusammenspiel genetischer Prädisposition, umweltbedingter Einflüsse sowie fehlregulierter Immunreaktionen. Neben klassischen immunologischen Signalwegen rücken dabei zunehmend auch strukturelle Zellpopulationen der Haut – insbesondere Fibroblasten und andere stromale Zellen – als aktive Modulatoren entzündlicher Prozesse in den Fokus wissenschaftlicher Untersuchungen.

Vor diesem Hintergrund verfolgt die vorliegende kumulative Dissertation das Ziel, den Einfluss genetischer Faktoren und umweltbedingter Risikofaktoren auf die Pathogenese chronisch-entzündlicher Hauterkrankungen systematisch zu untersuchen. Hierzu wurden komplementäre methodische Ansätze kombiniert, darunter populationsbasierte epidemiologische Analysen, genetische Untersuchungen in experimentellen Tiermodellen sowie mechanistische immunologische Studien. Durch diese integrative Herangehensweise sollten sowohl systemische Risikofaktoren als auch molekulare und zelluläre Mechanismen der Krankheitsentstehung näher charakterisiert werden.

Studie I: Large-scale analysis highlights obesity as a risk factor for chronic non-communicable inflammatory diseases

Die erste Studie dieser Dissertation widmet sich der Untersuchung von Adipositas als systemischem Risikofaktor für chronisch-entzündliche Erkrankungen. Hierzu wurden elektronische Gesundheitsdaten aus dem internationalen TriNetX-Netzwerk analysiert, welches klinische Informationen von Millionen Patientinnen und Patienten aus verschiedenen Gesundheitssystemen umfasst.

In einer retrospektiven Kohortenanalyse wurden mehr als drei Millionen übergewichtige oder adipöse Personen mit einer entsprechend gematchten Kontrollgruppe ohne Adipositas verglichen. Ziel der Untersuchung war es, den Zusammenhang zwischen Adipositas und dem Risiko für die Entwicklung von insgesamt 46 chronisch-entzündlichen Erkrankungen zu analysieren.

Die Ergebnisse zeigen, dass Adipositas mit einem signifikant erhöhten Risiko für eine Vielzahl entzündlicher Erkrankungen assoziiert ist. Besonders ausgeprägt war dieser Zusammenhang bei dermatologischen Erkrankungen, insbesondere bei der Hidradenitis suppurativa. Darüber hinaus konnte auch für verschiedene systemische entzündliche Erkrankungen ein erhöhtes Erkrankungsrisiko nachgewiesen werden. Subgruppenanalysen deuteten zudem auf Unterschiede zwischen verschiedenen demografischen Gruppen hin, insbesondere zwischen Geschlechtern sowie zwischen unterschiedlichen ethnischen Populationen.

Pathophysiologisch lassen sich diese Befunde durch die chronische niedriggradige systemische Entzündung erklären, die mit Adipositas einhergeht. Fettgewebe fungiert nicht ausschließlich als Energiespeicher, sondern stellt ein metabolisch aktives Organ dar, das eine Vielzahl proinflammatorischer Mediatoren produziert. Hierzu zählen unter anderem Zytokine wie TNF-α und IL-6 sowie verschiedene Adipokine, die sowohl angeborene als auch adaptive Immunreaktionen modulieren können. Diese Prozesse können eine systemische inflammatorische Umgebung schaffen, die die Entstehung immunvermittelter Erkrankungen begünstigt.

Die Ergebnisse dieser Studie unterstreichen somit die Bedeutung metabolischer Faktoren für die Pathogenese chronisch-entzündlicher Hauterkrankungen und weisen darauf hin, dass Adipositas nicht lediglich als Begleiterkrankung, sondern als potenzieller pathogenetischer Faktor betrachtet werden sollte.

Studie II: Forward genetics identifies Itga11 as a modulator of psoriasiform dermatitis

Die zweite Studie dieser Dissertation untersucht genetische Determinanten entzündlicher Hauterkrankungen anhand eines experimentellen Mausmodells der psoriasiformen Dermatitis. In diesem Modell wird durch die topische Applikation des Immunmodulators Aldara® eine entzündliche Hautreaktion induziert, die zentrale histologische und immunologische Merkmale der humanen Psoriasis reproduziert.

Unterschiedliche Inzuchtstämme von Mäusen zeigten dabei erhebliche Unterschiede in der Ausprägung der entzündlichen Reaktion. Durch genomweite Assoziationsanalysen konnte das Gen Itga11 als potenzieller genetischer Modulator der Krankheitsstärke identifiziert werden. Itga11 kodiert für die Integrin-α11-Untereinheit, die gemeinsam mit der β1-Untereinheit einen Kollagenrezeptor bildet und vor allem in Fibroblasten exprimiert wird.

Zur funktionellen Validierung dieser Ergebnisse wurden Itga11-defiziente Mäuse untersucht. Diese Tiere zeigten im Vergleich zu Wildtyp-Tieren eine deutlich abgeschwächte entzündliche Hautreaktion. Insbesondere wurden eine reduzierte epidermale Hyperplasie, eine geringere Immunzellinfiltration sowie Veränderungen in der Zusammensetzung der extrazellulären Matrix beobachtet.

Diese Befunde deuten darauf hin, dass Fibroblasten über die Regulation der extrazellulären Matrix und der Gewebearchitektur eine zentrale Rolle bei der Steuerung entzündlicher Prozesse spielen können. Veränderungen in der Struktur der extrazellulären Matrix können die Migration, Aktivierung und Persistenz von Immunzellen im Gewebe beeinflussen und damit das lokale Entzündungsgeschehen modulieren.

Die Studie verdeutlicht somit die Bedeutung stromaler Zellpopulationen als aktive Regulatoren immunologischer Prozesse und erweitert das Verständnis der zellulären Mechanismen, die der Pathogenese entzündlicher Hauterkrankungen zugrunde liegen.

Studie III: Inhibition of interferon-γ impairs induction of experimental epidermolysis bullosa acquisita

Die dritte Studie befasst sich mit der Rolle des Zytokins Interferon-γ (IFN-γ) in der Pathogenese der Epidermolysis bullosa acquisita (EBA), einer seltenen autoimmunen blasenbildenden

Hauterkrankung. Diese Erkrankung wird durch Autoantikörper gegen Kollagen VII verursacht, ein strukturelles Protein der dermoepidermalen Junktionszone.

In einem experimentellen Mausmodell der antikörpervermittelten EBA wurde untersucht, ob die pharmakologische Blockade von IFN-γ den Krankheitsverlauf beeinflussen kann. Hierfür wurden Mäuse mit neutralisierenden Antikörpern gegen IFN-γ behandelt und anschließend klinisch sowie histologisch untersucht.

Die Ergebnisse zeigen, dass die Blockade von IFN-γ zu einer dosisabhängigen Reduktion der Krankheitsaktivität führt. Insbesondere wurde eine verminderte Infiltration neutrophiler Granulozyten in der Haut beobachtet. Diese Befunde sprechen dafür, dass IFN-γ eine wichtige Rolle bei der Rekrutierung und Aktivierung neutrophiler Immunzellen im Rahmen der EBA-Pathogenese spielt.

Die Ergebnisse liefern somit neue mechanistische Einblicke in die immunologischen Prozesse autoantikörpervermittelter Hauterkrankungen und weisen darauf hin, dass IFN-γ ein potenzielles therapeutisches Ziel darstellen könnte.

Gesamtdiskussion und Schlussfolgerung

Die in dieser Dissertation präsentierten Arbeiten verdeutlichen, dass chronisch-entzündliche Hauterkrankungen das Ergebnis eines komplexen Zusammenspiels systemischer Risikofaktoren, genetischer Determinanten sowie lokaler immunologischer Mechanismen sind.

Die erste Studie zeigt, dass metabolische Faktoren wie Adipositas einen wichtigen Beitrag zur Entstehung chronisch-entzündlicher Erkrankungen leisten können. Die zweite Studie identifiziert mit Itga11 einen neuen genetischen Modulator entzündlicher Hauterkrankungen und hebt die Bedeutung stromaler Zellpopulationen für die Regulation von Immunreaktionen hervor. Die dritte Studie liefert mechanistische Hinweise auf die Rolle von IFN-γ bei autoantikörpervermittelten Entzündungsprozessen der Haut.

Zusammenfassend verdeutlichen diese Arbeiten, dass chronisch-entzündliche Hauterkrankungen nicht ausschließlich durch immunologische Fehlregulationen bestimmt werden, sondern vielmehr das Ergebnis komplexer Interaktionen zwischen metabolischen Faktoren, genetischer

Prädisposition und gewebespezifischen Mechanismen darstellen. Die Kombination populationsbasierter Analysen mit experimentellen Modellen ermöglicht ein vertieftes Verständnis der zugrunde liegenden Krankheitsmechanismen.

Langfristig könnten integrative Forschungsansätze, die genetische, metabolische und immunologische Faktoren gleichermaßen berücksichtigen, zur Entwicklung neuer präventiver und therapeutischer Strategien für chronisch-entzündliche Hauterkrankungen beitragen.

Acknowledgments

First and foremost, I would like to express my deepest gratitude to Prof. Dr. Ralf Ludwig for his invaluable guidance, support, and encouragement throughout the course of my dissertation. His expertise, insightful feedback, and continuous motivation have played a crucial role in shaping this work. It has been an honor to learn under his supervision.

I would also like to extend my sincere thanks to Prof. Dr. Walter Raasch, PD. Dr. Katja Bieber and Dr. Anika Kasprick for their helpful advice, constructive discussions, and generous support during various phases of this project. Their input has been essential in enriching the quality and depth of my research.

A special thanks goes to PD. Dr.Tatiana Sezin, and Dr. Yask Gupta whose support and assistance in a significant part of the project were greatly appreciated. They collaboration and help made a meaningful difference in the completion of this work.

Above all, I want to express my heartfelt appreciation to my beloved family, “my wife Monir and my beautiful children Parmida and Samyar” for their unwavering love, patience, and support during this challenging and demanding time. Their strength and understanding gave me the determination to persevere and complete this journey.

Finally, I am grateful to everyone who contributed directly or indirectly to the success of this dissertation. Your support has meant a great deal to me.

Seyed Sadegh Mousavi

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Qualifications Summary

- Dedicated doctoral researcher at the Lübeck Institute for Experimental Dermatology.
- **Scientific areas of expertise include skin immunology, autoimmunity, complement diet and host-microbe interactions in autoimmunity**.
- My extensive publication record includes **17 peer-reviewed** articles in prestigious journals, with **an h-index of 9 and 270 citations.**

Education

Oct2021– Present

Doctoral Researcher at the Lübeck Institute for Experimental Dermatology, University of Lübeck, Germany.

Topic: "*Diet as intervention in autoimmune pre-disease*"

In this project, I investigate the influence of diet on the development of the autoimmune disease in C57BL/6J mice. Through the course of the experiments, I examined the development of any disease under different dietary compositions and caloric intakes by studying temporal histological changes in the kidney, proteinuria-development, emergence of antinuclear antibodies and analyzing the composition of the gut microbiome.

Core research methodologies:

- *In vivo* mouse work
- Histology
- Immunohistochemistry
- ELISA
- RNA-seq
- Flowcytometry
- 16S rRNA sequencing
- GraphPad Prism

Jan 2007– Aug 2010

Master of Industrial Biotechnology, in the Department of Bioprocess Technology, Laboratory of Industrial Microbiology, Biotechnology and Fermentation Technology Unit (FTU) (PD. Dr. Rosfarizan Mohammad) at University Putra Malaysia, Malaysia.

Topic: "*Influence of medium formulation and cultural conditions on folate production by lactic acid bacteria*"

Core research methodologies:

-
- Microbiology
- Medium Optimization
- Vitamin extraction method
- ELISA
- HPLC
- Sigma plot and ESL software

Grade: GPA=3.768 out of 4 (A)

Feb 2000- July 2002 **Bachelor's Degree, "2.5 year study"** in Medical Laboratory Science in Tehran University of Medical Science, Tehran, Iran

Graduation Project in Microbiology, in Laboratory of Microbiology at Tehran University of Medical Science, Tehran, Iran

Topic: *"Antimicrobial Gradient Strip Method, E-Test"*

Core research methodologies:

- Clinical Microbiology
- Antibiogramm

Sep 1990- Nov 1992 **Associate Degree, "2.2 year study"** in Medical Laboratory Science in Tabriz University of Medical Sciences, Tabriz, Iran

Core credits course:

- Biology, Immunology, Histology, Hematology, Clinical Biochemistry, Microbiology, Parasitology, Mycology, Histology, Pathology, Virology and Physiology in Theoretical and Practical.

Professional experience

Feb 2014 – Oct 2021 **Biol. Research Technician**
In working group of Prof. Dr. Sadik (AG Innate immunity) in Department of Dermatology, Allergology and Venereology University of Lübeck.

Topic: *"Role of the innate immune system in the pathogenesis of autoimmune diseases such as psoriasis, Epidermolysis bullosa acquisita (EBA), pemphigoid disorders*"

July 2013– Feb2014 **Internship** in the laboratory of Prof Ralf Ludwig, Department **of** Dermatology, Allergology and Venereology University of Lübeck.

2007 – July 2010	**Research Assistant,** in the laboratory of industrial Biotechnology and Microbiology, Department of Bioprocess Technology University Putra Malaysia **Topic:** ***"****lecture in the Lab for Bachelors student"*
Sep 1995 – Dec 2006	**Executive Assistant** in the Equipment office, Shahed University, Tehran Iran
Nov !994 – Sep 1995	**MTA** in Diagnostic Laboratory in Hospital Shahid Beheshti , Bandar Lengeh (Persian Gulf), Iran

Key knowledge and Skills

Languague skills:

- English — Fluent
- German — Intermediate
- Persian — Native
- Azeri Turkish — Native

Experimentally skills

- Animals handling- Mouse model
- Immunohistochemistry
- Histology
- Fluorescence microscopy
- Protein Purification
- Bacteriology
- ELISA
- Fermentation
- Cell culture
- Chemical management
- RNA and DNA
- PCR, SDS-PAGE, ELISA
- Flow cytometry
- Lab Managing
- HPLC
- Bioreactor operation,
- Kinetic and Modeling

IT Skills:

- MS office
- GraphPad
- FlowJo
- Biological online data
- Sigma plot and ESL

Courses & Professional Memberships

- FELASA course (FTA Physiologie und Versuchstiere), University of Lübeck, Lübeck, Germany.
- German Society for Immunology (DGFI).

Peer-Reviewed Publications

- Mousavi, S., Bieber, K., Zirpel, H., Vorobyev, A., Olbrich, H., Papara, C., De Luca, D. A., Thaci, D., Schmidt, E., & Riemekasten, G. (2025). Large-scale analysis highlights obesity as a risk factor for chronic, non-communicable inflammatory diseases. *Frontiers in Endocrinology*, *16*, 1516433.
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- Mousavi, S., Kasprick, A., Boakye-Dankwa, P., Scheppan, D., Schmidt-Jiménez, L., Vorobyev, A., Bieber, K., Raasch, W., & Ludwig, R. (2024, May). Metabolomics and Immunologic Profiling Unravel the Impact of Diet on Autoimmune Disease Susceptibility. 14th International Congress on Autoimmunity, Ljubljana, Slovenija.
- * S. Mousavi, , M. Kamaguchi, , K. Izumi, , S. Dräger, , L. F. SchmidtJiménez, , A. Kasprick, , S. Patzelt, , S. Emtenani, M. Pigors , K. Bieber, & , E. Schmidt, R. J. Ludwig. (2024, March). Involvement of Alternative C5-Convertases in Inducing Skin Inflammation in Experimental Pemphigoid Diseases. ADF 2024, Düsseldorf, Germany. https://doi.org/10.1111/exd.14994.
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Hobbies

- Swimming
- Traveling
- Gardening

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- Prof. Dr. Walter Raasch, Institute of Experimental and Clinical Pharmacology and Toxicology University of Lübeck, Germany

- PD. Dr. Tatiana Sezin, Institute for Inflammatory Medicine, University of Lübeck, Germany

List of Original Articles

Article 1

Title:
Large-scale analysis highlights obesity as a risk factor for chronic, non-communicable inflammatory diseases

Full bibliographic citation:
Mousavi, S., Bieber, K., Zirpel, H., Vorobyev, A., Olbrich, H., Papara, C., De Luca, D. A., Thaci, D., Schmidt, E., & Riemekasten, G. (2025). *Frontiers in Endocrinology*, *16*, 1516433.

DOI link:
https://doi.org/10.3389/fendo.2025.1516433

Abstract:

Background: Overweight and obesity are a global pandemic, contributing to death and disability-adjusted life-years. Obesity is a major factor in the onset of chronic inflammatory diseases (CIDs). Yet, several knowledge gaps remain: For several CIDs, inconsistent results have been reported, relating to their obesity-imposed risk, data on most rare CIDs remain unavailable, sex differences and racial disparities remain mostly unaddressed.

Methods: A large-scale cohort study compared the risk of developing 46 CIDs in individuals with overweight/obesity (n=3,101,824) to an equal number of non-overweight/obese individuals. Propensity score matches optimized between group comparability, and sensitivity analyses assessed study robustness.

Results: The risk of developing any CID was 28.48% in overweight/obese individuals versus 17.55% in non-overweight/obese controls, with a hazard ratio (95%-confidence interval) of 1.52 (1.509-1.521, $p<0.0001$). This risk was consistent across all sensitivity, sex-, and race-stratified analyses. Overweight and obesity were associated with an increased risk for 24 of 46 CIDs in the primary analysis and all sensitivity analyses. For 12 diseases, increased risks were confirmed to one of the two sensitivity analyses, while for 10 diseases, results were discordant. No increased risk was observed for one disease. In sex-stratified analysis, overweight and obesity posed a more pronounced risk for four CIDs in female individuals. In race-stratified analysis, overweight and obesity were linked to a higher risk for seven CIDs in White individuals and to one CID in “Black or African American” individuals.

Conclusion: Overweight and obesity increase the risk for the majority of CIDs in a sex- and race-specific manner.

Article 2

Title:

Forward genetics and functional analysis highlight Itga11 as a modulator of murine psoriasiform dermatitis

Full bibliographic citation:

Bieber, K., Bezdek, S., Gupta, Y., Vorobyev, A., Sezin, T., Gross, N., Prüssmann, J., Sayegh, J., Becker, M., & Mousavi, S. (2023). *The Journal of Pathology*, *261*(2), 184–197.

DOI link:

https://doi.org/10.1002/path.6162

Abstract:

Psoriasis is a chronic inflammatory skin condition. Repeated epicutaneous application of Aldara® (imiquimod) cream results in psoriasiform dermatitis in mice. The Aldara®-induced psoriasiform dermatitis (AIPD) mouse model has been used to examine the pathogenesis of psoriasis. Here, we used a forward genetics approach in which we compared AIPD that developed in 13 different inbred mouse strains to identify genes and pathways that modulated disease severity. Among our primary results, we found that the severity of AIPD differed substantially between different strains of inbred mice and that these variations were associated with polymorphisms in Itga11. The Itga11 gene encodes the integrin α11 subunit that heterodimerizes with the integrin β1 subunit to form integrin α11β1. Less information is available about the function of ITGA11 in skin inflammation; however, a role in the regulation of cutaneous wound healing, specifically the development of dermal fibrosis, has been described. Experiments performed with Itga11 gene-deleted (Itga11 _/_) mice revealed that the integrin α11 subunit contributes substantially to the clinical phenotype as well as the histopathological and molecular findings associated with skin inflammation characteristic of AIPD. Although the skin transcriptomes of Itga11_/_ and WT mice do not differ from one another under physiological conditions, distinct transcriptomes emerge in these strains in response to the induction of AIPD. Most of the differentially expressed genes contributed to extracellular matrix organization, immune system, and metabolism of lipids pathways. Consistent with these findings, we detected a reduced number of fibroblasts and inflammatory cells, including macrophages, T cells, and tissue-resident memory T cells in skin samples from Itga11_/_ mice in response to AIPD induction. Collectively, our results reveal that Itga11 plays a critical role in promoting skin inflammation in AIPD and thus might be targeted for the development of novel therapeutics for psoriasiform skin conditions.

Article 3

Title:

Inhibition of interferon gamma impairs induction of experimental epidermolysis bullosa acquisita

Full bibliographic citation:

Gross, N., Marketon, J., Mousavi, S., Kalies, K., Ludwig, R. J., & Bieber, K. (2024). *Frontiers in Immunology*, *15*, 1343299

DOI link:

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Abstract:

Epidermolysis bullosa acquisita (EBA) is a muco-cutaneous autoimmune disease characterized and caused by autoantibodies targeting type VII collagen (COL7). The treatment of EBA is notoriously difficult, with a median time to remission of 9 months. In preclinical EBA models, we previously discovered that depletion of regulatory T cells (Treg) enhances autoantibody-induced, neutrophil-mediated inflammation and blistering. Increased EBA severity in Treg-depleted mice was accompanied by an increased cutaneous expression of interferon gamma (IFN-g). The functional relevance of IFN-g in EBA pathogenesis had been unknown. Given that emapalumab, an anti-IFN-g antibody, is approved for primary hemophagocytic lymphohistiocytosis patients, we sought to assess the therapeutic potential of IFN-g inhibition in EBA. Specifically, we evaluated if IFN-g inhibition has modulatory effects on skin inflammation in a pre-clinical EBA model, based on the transfer of COL7 antibodies into mice. Compared to isotype control antibody, anti-IFN-g treatment significantly reduced clinical disease manifestation in experimental EBA. Clinical improvement was associated with a reduced dermal infiltrate, especially Ly6G+ neutrophils. On the molecular level, we noted few changes. Apart from reduced CXCL1 serum concentrations, which has been demonstrated to promote skin inflammation in EBA, the expression of cytokines was unaltered in the serum and skin following IFN-g blockade. This validates IFN-g as a potential therapeutic target in EBA, and possibly other diseases with a similar pathogenesis, such as bullous pemphigoid and mucous membrane pemphigoid.