Name of Principal Investigator(s)
Peter Wolf

Department
Dermatology

Title
Mediators of systemic pathophysiology in psoriasis

Background
Psoriasis, a very common inflammatory skin disease, is nowadays considered a systemic condition affecting beyond the skin and joints. In particular, metabolic syndrome associated with obesity and comorbidities such as diabetes, hyperlipidemia, and atherosclerosis has been linked to psoriasis. However, how anti-psoriatic treatment of skin lesions affects psoriasis as a systemic disease remains to be determined. Our work using a K5.hTGF-β1 psoriasis-like mouse model has disclosed platelet-activating factor (PAF) as an essential proinflammatory lipid mediator of psoriatic skin hyperplasia and systemic abnormalities, such as elevated TNF and cytokine levels of the IL-23/Th17 axis and their transcription factor STAT3. We hypothesize that proinflammatory lipid mediators as well as cytokines driven from the skin play a role in psoriasis as a systemic disease and their affection by anti-psoriatic treatment will reduce comorbidities.

Objectives
To investigate in psoriasis patients and mouse models how anti-psoriatic treatment with TNF blockade, anti-IL12/23 antibody, or photo(chemo)therapy affects proinflammatory cytokines (including TNF, IL-17/23 and others), immune function, parameters of atherosclerosis and oxidative stress, including plasma lipids and PAF. A better understanding of the therapeutic mechanisms of anti-psoriatic treatment should help improving overall treatment strategies in psoriasis.

Methodology
The PhD candidate will learn how to perform the assays and methods necessary to study the objectives above. She/He will learn how to use mouse models and a human skin xenotransplantation SCID model to investigate psoriasis. Blood and skin samples will be provided by an ongoing clinical study. The techniques include photobiologic methods such as UV light treatment and dosimetry, flow cytometry, RT-PCR, western blot, multiplex ELISA, immunobead technology, immunohistochemistry, immunofluorescence microscopy, and microarray technology. The student will also isolate and expand T cells and apply T cell transplantation and cellular assays of immune function. In addition, she/he will learn to isolate lipoproteins, quantify their protein composition and posttranslational modifications, and determine cholesterol efflux potential and activity of HDL-associated anti-inflammatory enzymes.

References
1. Singh, T.P., Schon, M.P., Wallbrecht, K., Michaelis, K., Rinner, B., Mayer, G., Schmidbauer, U., Strohmaier, H., Wang, X.J., and Wolf, P. 2010. 8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. *J Immunol* 184:7257-7267.
2. Singh, T.P., Huettner, B., Koefeler, H., Mayer, G., Bambach, I., Wallbrecht, K., Schon, M.P., and Wolf, P. 2011. Platelet-activating factor blockade inhibits the T-helper type 17 cell pathway and suppresses psoriasis-like skin disease in K5.hTGF-beta1 transgenic mice. *Am J Pathol* 178:699-708.

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