PhD position within RESIST-II: The role of thymic stromal lymphopoietin (TSLP) and other epithelial mediators in herpes simplex virus (HSV) infections of human skin

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PhD candidate: We are looking for a highly motivated PhD candidate to join our interdisciplinary team. The PhD candidate will work at the interface of virology, dermatology, and cell biology investigating the role of the cytokine thymic stromal lymphopoietin (TSLP) and other epithelial mediators in herpes simplex virus infections of human keratinocytes and skin. We are looking for an applicant with a master´s degree in biochemistry, biology, biomedicine, or a closely related field with interest in host-pathogen interactions and skin biology. Prior experience in virology, molecular biology, microscopy, or dermatological research will be considered a plus. To apply, please submit a motivation letter and your CV as single PDF. Applications should be sent to: Doehner.Katinka@mh-hannover.de

Funding: This project will be funded by the Cluster of Excellence RESIST (EXC 2155), E13 65% for 3.5 years, start: as soon as possible.

Research Group and Proposed Project

The group of Prof. Werfel focuses on chronic inflammatory skin diseases including atopic dermatitis (AD). AD renders people more susceptible to infections. About 22% of patients with moderate to severe AD have a history of eczema herpeticum (EH), a disseminated skin infection usually caused by herpes simplex virus type 1 (HSV-1) (1). If untreated, EH can develop into a potentially life-threatening systemic infection (2).

The fact that EH affects only a subgroup of AD patients despite the high prevalence of HSV infections suggests a role for genetic determinants. Several single nucleotide polymorphisms (SNPs) in genes involved in skin barrier function, inflammation, and antiviral defense are associated with EH risk, and we found a SNP in *COL23A1* to be linked to EH risk (2, 3). Subsequently, we have examined the presence of 900 candidate SNPs in a cohort of 750 age- and sex-matched AD patients, half of whom with a history of EH. We found 45 SNPs that were significantly associated with the risk of EH, including multiple SNPs in *IFNG*, *IL23R*, *CYP24A1*, *SPINK5*, and the aforementioned *TSLP*. Humans express two TSLP variants: long-form TSLP (lfTSLP), which is a pro-inflammatory cytokine, and short-form TSLP (sfTSLP), a constitutively expressed antimicrobial peptide (AMP) (4).

Immune determinants also influence EH risk. Compared to AD patients without a history of EH, AD patients with a history of EH are less capable of inducing AMPs in their lesional skin, indicating that AMPs protect not only against microbes, but also against EH (2). In the first RESIST funding period, we showed that the AMPs RNase 7 and sfTSLP directly restrict HSV infection of human keratinocytes (5, 6).

Effect of EH-associated SNPs on transcript and protein levels and HSV susceptibility

Our SNP array revealed that several SNPs in *TSLP* were associated with EH risk. Transcriptome analysis revealed that genotypes associated with a higher EH risk correlated with higher TSLP expression (7). We hypothesize that, in individuals with genotypes that are more prevalent in EH patients, increased expression of the pro-inflammatory lfTSLP may drive atopic inflammation. This inflammation weakens the skin barrier, making individuals more susceptible to disseminated infections. Upregulation of lfTSLP in lesional AD skin co-occurs with downregulation of the AMP sfTSLP (8).

To test whether this is also the case for AD patients carrying these TSLP SNPs, the PhD candidate will use long-read transcriptomics and develop methods to specifically label sfTSLP. Furthermore, he/she will examine how several cytokines and AD-relevant therapeutics modulate the expression of lfTSLP, sfTSLP and other AMPs. To study the effect of TSLP SNPs on

different stages of HSV-1 infection, we will either use keratinocytes isolated from respective SNP carriers or introduce these SNPs into human keratinocytes.

Identification of sfTSLP interaction partners and characterization of its antiviral mechanism

Recombinant sfTSLP, but not lfTSLP, restricts HSV-1 infection of human keratinocytes (6). To identify potential cellular or viral interaction partners, we will use mass spectrometry. Moreover, we will use transcriptomics to assess sfTSLP-induced changes in gene expression in uninfected cells as well as after HSV-1 infection. Potential candidates identified by these assays will be characterized by HSV-1 infection experiments in 2D or 3D cultures of human keratinocytes.

As recombinant sfTSLP reduces immediate-early HSV-1 transcripts but not the number of incoming HSV-1 capsids at the nuclear rim (6), we will examine whether sfTSLP interferes with the nuclear import of incoming viral genomes or the transactivation of immediate-early genes. Moreover, we will also test whether sfTSLP promotes the repression of viral genomes, affects transcription regulated by HSV-1 promoters or promotes the degradation of viral transcripts. In addition, we will use single- and multi-step growth kinetics to study whether sfTSLP affects the release of infectious HSV-1.

Since several endogenous proteases present in inflamed skin cleave TSLP (4), we will examine the anti-HSV-1 effect of TSLP cleavage products. As self-DNA, which is present in increased amounts on lesional AD skin, modulates the function of several AMPs (9), we will investigate whether it also affects the antibacterial and antiviral activity of sfTSLP. We will also test whether sfTSLP acts synergistically with other AMPs such as hBD-3, LL-37, or RNase 7 against HSV-1 infection. Tezepelumab, which blocks the interaction between lfTSLP and its receptor, is approved for the treatment of severe asthma and also relieves AD (4). As tezepelumab also binds to a region region shared by sfTSLP and lfTSLP, we will test whether it interferes with the anti-HSV-1 activity of sfTSLP. Moreover, we will determine whether sfTSLP also restricts the related α-herpesviruses, HSV-2, which causes most cases of genital herpes, and varicella-zoster virus, which causes chickenpox in primary infection and shingles after reactivation.

Within this project, the PhD candidate will analyze the effect of EH-associated TSLP SNPs on expression and secretion of sfTSLP and lfTSLP as well as HSV-1 infection of keratinocytes. In addition, he/she will elucidate the molecular mechanisms by which sfTSLP influences HSV-1, HSV-2 and VZV infection and characterize their function especially in the context of AD, EH, and severe herpes zoster infections.

References

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