Infection Biology

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Host pathogen interaction in infectious diseases

The infection biology research group explores host- and pathogen-specific aspects of infectious diseases in a strong translational setting. Our main focus is to understand the interaction of innate and adaptive immune responses in the context of bacterial, fungal and viral infections with the aim at elucidating key mechanisms of immune protection, thus fostering personalized treatment – with the overarching goal to improve clinical outcome.

Host response to fungal infections

Invasive fungal infections are devastating in immune compromised patients and associated with high mortality rates despite treatment. Risk assessment and diagnosis remain a major challenge leading to administration of broad-spectrum antifungal prophylaxis and over-treatment, which in turn is associated with high costs, drug interactions and, most importantly, limited clinical efficacy with emergence of resistant strains. Hence, reliable tools to identify patients at risk and tailored treatment strategies to improve patient outcome are urgently needed.
We recently found that functional neutrophil, NK-cell and *Aspergillus fumigatus*-specific Th1 immunity is associated with a better outcome in patients after allogeneic hematopoietic stem cell transplantation (HSCT) with invasive aspergillosis (Fig. 1A).
To get a broader knowledge about immunological factors increasing the susceptibility to fungal infections in other patient populations, we further studied risk factors for development of *Candida* esophagitis in HIV-infected patients. We found that HIV-1-infected patients with *Candida* esophagitis had an accumulation of multiple, partly *Candida*-specific immunological defects (Fig. 1B). In addition, long-term immune recovery was impaired even after introduction of combination antiretroviral therapy, illustrating that specific immunological gaps persist in these patients. These data clearly support the rationale for early combination antiretroviral therapy initiation to prevent irreversible immune defects.

Adoptive T-cell therapy for infectious diseases

Adoptive transfer of pathogen-specific donor-derived T cells is to date the most promising and feasible immunotherapeutic strategy in transplant recipients restoring the lacking T-cell function. Its potential as prophylactic or therapeutic treatment has been demonstrated for viral infections after transplantation. We recently initiated a clinical trial of adoptive T-cell therapy for treatment-refractory viral infections with cytomegalovirus, Epstein Barr virus and adenovirus after HSCT using the cytokine capture assay® (Miltenyi Biotec) at the University Hospital of Basel (ClinTrials ID NCTO2007356), which is so far unique in Switzerland.
The fact that higher *Aspergillus fumigatus*-specific Th1 responses correlate with a better clinical outcome in HSCT recipients with invasive aspergillosis encourages the development of antifungal T-cell transfer. We recently identified immunogenic *Aspergillus fumigatus* antigens, which are likely protective by inducing Th1-cell responses in healthy individuals and HSCT recipients with well-controlled invasive aspergillosis (Fig. 2A,B). We were further able to select these antigen-specific cells based on activation-dependent expression of CD137 or CD154 with a GMP-compliant protocol (Fig. 2C). Moreover, cell lines containing T cells specific for all three proteins cross-reacted to the most relevant human-pathogenic molds (Fig. 2D). These results greatly foster adoptive T-cell therapy for these problematic infections.

Staphylococcal implant infections

Bacterial infection of implanted devices is a major health care problem occurring in about 5 % of patients. These infections are mainly caused by biofilm-forming staphylococci, which are generally tolerant to antibiotic treatment. We could recently demonstrate that silver-coating can efficiently prevent implant-associated infections and thus can be considered for clinical application (Fig. 3). Further studies are on the way investigating the host pathogen interaction in biofilm-associated infections.

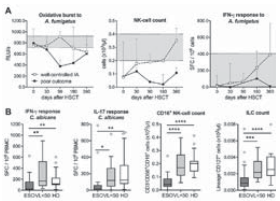

Fig. 1: Antifungal immune response in patients with invasive aspergillosis after allogeneic hematopoietic stem cell transplantation (A) and HIV-1-infected patients with *Candida* esophagitis (B). RLU/s = relative light units per second, IA = invasive aspergillosis, ILC = innate lymphoid cell count, ESO = *Candida* esophagitis, VL < 50 = viral load < 50 c/ml HD = healthy donors For details: Stuehler C, J Infect Dis. 2015 Sep 15;212(6): 959–67; Stuehler C and Bernardini C et al, AIDS May 5, 2016.

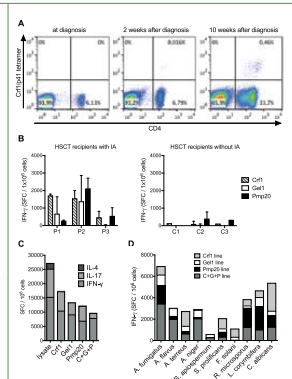

Fig. 2: Hematopoietic stem cell transplant (HSCT) recipients with active invasive aspergillosis (IA) show expansion of Crf1/p41-specific cells over time (A) and respond to *Aspergillus fumigatus* antigens irrespective of absolute CD4+ T-cell counts (B). The antigen-specific T-cell lines can be expanded (C) and show cross-reactivity to different filamentous molds (D). IFN-γ = interferon-gamma, PBMC = peripheral blood mononuclear cells, C+G+P = all antigens Crf1, Gel1 and Pmp20 were used for stimulation (J Infect Dis. 2015 Apr 15;211(8):1251–61).

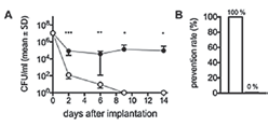

Fig. 3: Infection of uncoated (closed circles) or silver-coated (open circles) TiAlNb tissue cages with *S. epidermidis* strain 1457 in C57BL/6 mice. Planktonic bacteria indicated as colony forming units (CFU) per cage in the tissue cage fluid after perioperative infection (A). Prevention rates for silver-coated (open columns) or uncoated (closed columns) tissue cages (B). TiAlNb = titanium-aluminum-niobium alloy (Kuehl R, Antimicrob Agents Chemother 2016 Mar 25;60(4):2467–75).

Connection to Clinical Practice

Fungal and viral infections have become a leading cause of morbidity and mortality in immunosuppressed patients. Pharmaceutical agents are often less effective in the setting of immunodeficiency, may cause substantial side effects, are expensive and may generate resistance. To overcome these issues, understanding the host-pathogen interaction and exploring strategies such as adoptive T-cell transfer that boost and induce long-term immunity may be promising in these patients.

Selected Publications

Schürmann N, Forrer P, Casse O, Li J, Felmy B, Burgener AV, Ehrenfeuchter N, Hardt WD, Recher M, Hess C, Tschan-Plessl A, Khanna N, Bumann D. Myeloperoxidase targets oxidative host attacks to pathogens and prevents collateral tissue damage. Nature Microbiology. 2016, accepted 13 December 2016
Stuehler C, Bernardini C, Elzi L, Stoeckle M, Zimmerli S, Furrer H, Gunthard HF, Leibundgut-Landmann S, Battegay M, Khanna N, *et al.* (2016) Immune recovery in HIV-infected patients after candida esophagitis is impaired despite long-term antiretroviral therapy. AIDS
Kuehl R, Brunetto PS, Woischnig AK, Varisco M, Rajacic Z, Vosbeck J, Terracciano L, Fromm KM, Khanna N. (2016) Preventing Implant-Associated Infections by Silver Coating. Antimicrob Agents Chemother 60, 2467–2475
Nowakowska J, Stuehler C, Egli A, Battegay M, Rauser G, Bantug GR, Brander C, Hess C, Khanna N. (2015) T cells specific for different latent and lytic viral proteins efficiently control Epstein-Barr virus-transformed B cells. Cytotherapy 17, 1280–1291
Stuehler C, Kuenzli E, Jaeger VK, Baettig V, Ferracin F, Rajacic Z, Kaiser D, Bernardini C, Forrer P, Weisser M, *et al.* (2015a) Immune reconstitution after allogeneic hematopoietic stem cell transplantation and association with occurrence and outcome of invasive aspergillosis. J Infect Dis
Stuehler C, Nowakowska J, Bernardini C, Topp MS, Battegay M, Passweg J, Khanna N. (2014) Multispecific Aspergillus T Cells Selected by CD137 or CD154 Induce Protective Immune Responses Against the Most Relevant Mold Infections. J Infect Dis