leukemia cells transfected with human CD20. Activity of this combination was lost in Fc alpha-R-1- mice. Furthermore IL-15 augmented the ADCC of alemtuzumab in a xenograft model of human adult T-cell leukemia (ATL). These studies support our clinical trial involving IL-15 with alemtuzumab in patients with acute ATL.

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A functional FAS polymorphism links CD4 T stem cell memory levels and IFN-induced apoptosis in both healthy controls and Adult T-cell Leukemia patients

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Introduction: Adult T-cell leukemia (ATL) is an aggressive, chemotherapy-resistant CD4+ CD25+ leukemia caused by HTLV-1 infection, which usually develops in a minority of patients several decades after infection. Recently, CD4 T stem cell memory (Tscm) cells have been identified as the hierarchical cellular apex of ATL. IFN-α, in combination with AZT, is currently the major treatment option for ATL, but therapeutic success is limited and no bona fide biomarkers for therapeutic failure are currently available.

Results: In a prospective study with a five-year clinical follow-up, we found significant ex vivo antiproliferative, antiviral and immunomodulatory effects of IFN-α treatment in short-term culture of primary mononuclear cells from ATL patients ($n = 28$). We detected a genotype/phenotype interaction for the −670 FAS A/G promoter polymorphism, apoptosis and proliferation in ATL patients. Surprisingly, IFN-induced apoptosis occurred only in carriers of the functional A allele (corresponding to a functional STAT1 binding site), which we experimentally validated in an independent cohort of healthy controls ($n = 20$). This Fashigh proliferating and chemotherapy-resistant leukemic phenotype is in agreement with the recently discovered CD4 Tscm hierarchical apex of ATL. The same FAS −670 polymorphism also determined CD4 Tscm levels in a genome-wide twin study ($p = 7 \times 10^{-11}$, $n = 669$), confirming our hypothesis. Finally, we provide in vivo evidence that CD4+ Fashigh leukemic cells can be eliminated by IFN-α +AZT combination therapy, but not AZT monotherapy.

Conclusion: A genetically determined IFN/STAT1/FAS axis underscores the CD4 Tscm ATL model and helps explain the observed in vivo IFN + AZT responsiveness and chemotherapy resistance in ATL patients.

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HCMV infected human monocyte-derived macrophages and DC produce type I IFN in a cGAS-dependent manner

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The majority of the human population is latently infected with human cytomegalovirus (HCMV). In the immunocompromised host HCMV reactivation can lead to serious symptoms and vertical infection can cause severe disabilities in the infant. We addressed the susceptibility of primary human antigen presenting cells to HCMV infection and their capacity to mount type I interferon (IFN-I) responses. HCMV treated plasmacytoid dendritic cells (pDC) did not efficiently support viral gene expression, while abundant to intermediate viral gene expression was detected in M-CSF macrophages (M-CSF MΦ), monocyte-derived DC (moDC), and GM-CSF macrophages (GM-CSF MΦ) in descending order. Even though HCMV encodes multiple evasion mechanisms, several of which exploit the interferon system, the magnitude of IFN-I responses mounted by the different monocyte-derived subsets correlated with the degree of infection. In contrast, pDC that were largely resistant to HCMV infection showed the highest IFN-I expression. These data implied that pDC sensed HCMV in a different manner than monocyte-derived cells. Since microbial dsDNA can activate cyclic GMP/AMP synthase (cGAS) to produce cyclic GMP-AMP dinucleotides (cGAMP), which trigger the stimulator of interferon genes (STING) that in turn induces IFN-I, we analyzed cGAS-dependent IFN-I responses in pDC, moDC, GM-CSF MΦ, and M-CSF MΦ. We found that upon HCMV infection monocyte-derived macrophages and DC, but not pDC, showed enhanced cGAMP production as a measure of cGAS activity. Moreover, monocyte-derived cells devoid of cGAS showed impaired IFN-I responses. Thus, HCMV stimulated primary monocyte-derived macrophages and DC, but not pDC, showed cGAS dependent cGAMP formation that triggered IFN-I.

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Failure to control a neonatal measles viral infection in the brain despite immune cell infiltration and cytokine production

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Viral infections in the central nervous system (CNS) are associated with devastating neurological consequences, particularly in newborns. Neonates are often unable to control viruses in the brain and suffer extensive neuronal loss, despite mounting an immune response. To study viral CNS infections, we use a transgenic mouse model of neuronally-restricted measles virus (MV) infection (NSE-CD46 mice), where the human isoform of CD46, a MV receptor, is expressed under the control of the neuron-specific enolase promoter. Adult CD46+ mice survive infection and clear MV in an interferon gamma (IFNg)- and T cell-dependent manner. Neonatal CD46 mice succumb by 15 days post infection (dpi) despite T cell infiltration. Neonatal mice lacking IFNg succumb more rapidly (100% mortality by 10 dpi) despite higher T cell infiltration and equivalent natural killer cell infiltration and microglial activation compared to CD46+ neonates. CD46+ adults show greater CD4 T cell infiltration compared to neonates, despite lower levels of virus in the brain. Quantitative RT-PCR analysis demonstrated expression of pro-inflammatory cytokine genes such as IFNg, IFNα2, IL-1α, IL1β, IL-6, and TNFα in MV infected neonates, as well as the anti-inflammatory Interleukin 1 receptor antagonist. Current experiments aim to compare anti-viral cytokines protein levels between MV-infected adults and neonates. These results suggest the neonates are capable of significant immune cell infiltration and cytokine production, but that the cytokine milieu is ineffective at controlling MV. These findings further suggest that the T cell response may contribute to neuropathology, as lower T cell infiltration is associated with prolonged survival in neonates.

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Combinatorial association and abundance of ISGF3 components dictate selectivity and kinetics of interferon responses

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IFNα induces ISG expression by phosphorylating STAT1 and STAT2. STAT1 homodimers facilitate transcriptional responses by directly activating ISGs containing GAS element. Combinatorial association of STAT1 and STAT2 with the additional DNA binding protein IRF9 (forming ISGF3) induce ISRE-containing ISGs. Evidence is accumulating for the existence of a STAT2/IRF9-dependent, STAT1-independent IFNα signaling pathway that generates ISGF3-like response. However, no detailed insight exists in the genome-wide transcriptional regulation and the biological implications of STAT2/IRF9 dependent IFNα signaling as compared to ISGF3 and how WT- and alternative responses are dictated.

In hST2-U3C IFNα-induced expression of classical ISGs correlated with the kinetics of STAT2 phosphorylation, and the presence of STAT2/IRF9 complex. Expression profiling of IFNα treated 2fTGH and hST2-U3C identified 120 known antiviral ISRE-containing ISGs commonly up-regulated by STAT2/IRF9 and ISGF3. The STAT2/IRF9 directed expression profile of these ISGs was prolonged as compared to the transient response mediated by ISGF3. ChIP-seq analysis confirmed binding of STAT2 to the ISG