How human cytomegalovirus influences acute myeloid leukemia

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Background and central scientific questions or problem

Over half of the global population is latently infected with the human cytomegalovirus (HCMV, also known as human betaherpesvirus). While primary and recurrent HCMV infections in healthy adults are effectively controlled by the immune system, individuals with immature, impaired or senescent immunity are prone to life-threatening HCMV diseases. The continuous fight between HCMV and our immune system enforces remarkable adaptations. Accordingly, twin studies revealed that 119 of 204 assessed immune parameters differ between healthy monozygotic twins discordant for an HCMV infection (PMID: 25594173). The combination of HCMV disease in individuals with impaired immunity together with aforementioned immune modulatory capacities render HCMV highly relevant for the clinical outcome of neoplastic diseases, especially in the context of immune checkpoint blockade and cell therapies such as hematopoietic cell therapy (HCT). Clinicians observed a significantly reduced AML relapse probability associated with an early intermediate peak titer HCMV reactivation in patients who received HCT as therapy for AML (see e.g., PMIDs: 33439488, 34619756, 21540462, 3015193). We call this effect *HCMV versus leukemia* (HCMVvL). Our goal is to establish a molecular understanding of HCMVvL, and -in the long-range- to develop HCMV-based anti-relapse biologicals.

Technical and conceptual approach to address the research question

We established an in vitro model that recapitulates HCMVvL. Using fluorescence-based cell cycle reporters, classic as well as automated cell counting, cytometry, and calorimetric assays, we investigate how and by which mechanisms HCMV affects the cell cycle of various AML cells. Luminex assays and mass-spectrometry are applied to assess which cytokines are secreted by HCMV-infected AML cells and to characterize global proteome alterations occurring upon HCMV infection. Based on the clinical finding that anti-thymocyte globulin treatment abrogates HCMVvL (see e.g., PMIDs 24120526 & 34619756), we also study the effects of cytokines produced by activated HCMV-specific CD4+ T cells on AML cells (in collaboration with ►PI Fleischhauer). We aim to identify the HCMV-encoded as well as the cytokine-stimulated host proteins that influence AML and contribute to HCMVvL. For this purpose, we apply a panel of doxycycline-inducible cell clones expressing individual proteins derived from HCMV or the host.

Specific scientific and technical expertise of the research group

Virology; cytomegalovirus; interferon; antibody responses, viral immune modulation

Our websites:

HIV-AAD; IVE

Link to our publications:

PUBMED; bioRxiv; LOOP; Google Scholar