1. Introduction

The complement system is a complex part of the innate immune system and consists of more than thirty different proteins present in the plasma and on cell membranes. Complement can be activated via three different pathways and may play a role in triggering the NLRP3 inflammasome [1]. Inflammasomes are essential components in innate immunity. A group of inflammasome disorders has been associated with Autoinflammatory Diseases (AIDs). Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Chronic Infantile Neurological, Cutaneous and Articular syndrome/Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID) were originally described as three distinct conditions. After the identification of their common genetic origin, i.e., mutations in the NLRP3 gene on chromosome 1q44, they are categorized as a continuum of one disease entity and labeled Cryopyrin-Associated Periodic Syndromes (CAPS). This preliminary study on a patient with MWS aimed to investigate the interplay between the complement system and this autoinflammatory disorder. PBMCs (Peripheral Blood Mononuclear Cells) were isolated from blood of a healthy donor and an MWS patient by density gradient centrifugation using a Ficoll Paque Premium (GE Healthcare). After washing, PBMCs were incubated with anti-human CD14 Magnetic Beads (BD) to obtain CD14+ monocytes. These were stimulated with cytokines (IL-4 and GM-CSF) for five days to generate immature monocyte-derived DCs (iDCs). iDCs were stimulated with either LPS or differentially opsonized HIV-1 preparations (non-opsonized HIV-1, HIV; complement-opsonized HIV-1, HIV-C). After two days in culture, iDCs and low and high LPS concentrations (10 ng/ml and 100 ng/ml) or HIV-exposed DCs were used for cytokine ELISAs and flow cytometric analyses. IL-1β and IL-6 ELISAs were analyzed and phenotypical characterization of pathogen-exposed DCs was performed by analyzing characteristic surface markers (CD11c, DC-SIGN, CD86) by multicolor flow cytometry [3]

2. Results

IL-1β and IL-6 production of iDCs in the patients’ cells was significantly higher upon stimulation with non- and complement-opsonized HIV-1, with complement-opsonized HIV-1 being the most potent stimulator (Figure 1a and 1b). In contrast, the bacterial stimulus LPS mediated a non-significant increase in IL-1β at the high concentration in the individual suffering from MWS, while IL-6 was only slightly upregulated by the higher LPS concentration in both the healthy and MWS individual (Figure 1a and 1b). We recently described CD11c, the alpha chain of CR4, as a trigger of pro-inflammatory cytokines and type I interferon production [4]. From these findings we conclude that the complement system may play an essential role in the development of an overshooting pro-inflammatory milieu in patients with autoinflammatory disorders. The phenomenon shown in a patient with MWS should be reproduced in more MWS patients as well as in patients with other autoinflammatory disorders.
Figure 1a: IL-1β and IL-6 production of iDCs in the patients’ cells was significantly higher upon stimulation with non- and complement-opsonized HIV-1. In contrast, the bacterial stimulus LPS mediated a non-significant increase in IL-1β at the high concentration in the individual suffering from MWS, while IL-6 was only slightly upregulated by the higher LPS concentration in both the healthy and MWS individual (Figure 1a and 1b).

References


