Differential responsiveness to IL-2, IL-7, and IL-15 common receptor gamma chain cytokines by antigen-specific peripheral blood naive or memory cytotoxic CD8+ T cells from healthy donors and melanoma patients


Common receptor gamma chain (c-gamma) cytokines (CKs) support proliferation of CD8+ T cells in presence or absence of antigen triggering and help maintaining the immunologic memory. We addressed the effects of low (< or ≥ 5 ng/mL)-dose interleukin (IL)-2, IL-7, or IL-15 on human naive and memory antigen-specific CD8+ T cells. Peripheral blood CD8+ lymphocytes proliferated with decreasing efficiency in response to IL-15, IL-7, and IL-2. Of note, IL-15 preferentially promoted expansion of CD45RA/CD8+ T-cell memory subset. Accordingly, cytotoxic T lymphocytes specific for cytomegalovirus-derived antigens from seropositive donors proliferated in response to IL-15 and, to lesser extent to IL-7, but poorly to IL-2. CD8+ T cells were then pretreated with CK before antigen stimulation using, as read out, specific cytotoxic activity. After the pretreatment with IL-15, but not IL-2, previously experienced viral antigens induced vigorous cytotoxic responses. Minor effects of IL-7 were also detectable. In contrast, IL-2 best supported the cytotoxic T lymphocyte generation from prevailing naive CD8 T cells from HLA-A*0201 healthy donors, specific for L27Melan-A/MART-126-35 melanoma-associated antigen. Cells from melanoma patients were tested before and after Melan-A/MART-1-targeted antigen-specific immunotherapy. Untreated patients showed heterogeneous patterns of responsiveness to c-gamma CK. However, when naive patients whose CD8+ T cells best responded to IL-2 were vaccinated, a modified responsiveness pattern was detectable. After immunization, cells displayed a significantly higher response to IL-15 than to IL-2 pretreatment. Thus, responsiveness to c-gamma CK is critically influenced by naive or memory status of peripheral blood CD8+ T cells.