Guifen Shen
Dr. med.

Polymorphonuclear neutrophil-derived apoptotic microparticles selectively suppress $CD4^+CD25^-CD127^+$ T cells

Promotionsfach: Innere Medizin
Doktorvater: Prof. Dr. med. Hanns-Martin Lorenz

Polymorphonuclear neutrophils (PMNs) are short-lived effector cells of the innate immune system which play an important role in the early defense against extracellular pathogens. Increasing evidence indicates that PMNs interact with various cell populations of both the innate and the adaptive immune system in a bidirectional way. For instance, PMNs are described to indirectly and directly modulate the activation and proliferation of T lymphocytes. The short lifespan of PMNs ensures their integrity, since apoptosis prevents the release of its noxious molecules. During the dynamic process of apoptosis, dying cells start to release microparticles. Cell-derived membrane-coated microparticles are known to be important mediators of intercellular communication and microparticles derived from PMNs are described to have immunomodulatory properties. Since PMNs are the most abundant type of leukocytes in the peripheral blood and due to their very short lifespan, they are the source of massive amounts of apoptotic microparticles. While the interaction between PMN and T cells has been focus of extensive research, the influence of neutrophil-derived apoptotic microparticles (NdAMPs) on T cells has not been analyzed so far and its detailed investigation was the aim of this study.
We could show that NdAMPs significantly suppressed the proliferation of a subset of T lymphocytes, namely of $CD4^+CD25^-CD127^+$ T cells, in a dose-dependent manner, while other $CD4^+$ T cell subsets were not affected. Interestingly, apoptotic PMNs or apoptotic microparticles derived from other cell types did not mediate comparable suppressive effects. Co-culture with NdAMPs also significantly reduced the secretion of tumor necrosis factor alpha, but not of interferon gamma, by $CD4^+CD25^-CD127^+$ T cells. On the surface of non-proliferating T cells, NdAMPs prevented the upregulation of CD25 and induced the maintenance of CD127 expression. Confocal microscopy revealed that NdAMPs, but not apoptotic PMNs, adhere tightly to the T cell surface. The suppression of T cell proliferation by NdAMPs was not mediated by arginase or indoleamine 2,3-dioxigenase activation, or by the induction of T cell apoptosis. Remarkably, the addition of interleukin (IL)-2 and IL-7, or the presence of other T cell subsets dramatically abrogated the suppressive effect of NdAMPs on $CD4^+CD25^-CD127^+$ T cells. High concentrations of IL-15, but not of IL-4, could also reverse the inhibitory effect of NdAMPs to some extent.
In conclusion, NdAMPs suppress the proliferation specifically of quiescent $CD4^+CD25^-CD127^+$ T cells under conditions of limiting IL-2 and IL-7 concentrations. We hypothesize that NdAMPs elevate the signaling threshold necessary for the activation and proliferation of such resting T cells. This could represent an important mechanism to prevent inappropriate T cell activation in the absence of sufficient stimulation and cytokine production, and to maintain the peripheral tolerance to self.