Einfluss von Thrombozyten auf die NK Zell-vermittelte Immunüberwachung von Tumoren
(Modulation of NK cell-mediated tumor immunosurveillance by platelets)

The development of clinically apparent malignancy following cell-intrinsic oncogenic events is largely dependent on the interaction of the transformed cells with the immune system. This reciprocal process substantially influences whether tumor cells are eliminated or progress to a life-threatening disease. Indeed, induction of tolerance of innate and adaptive immune effector cells seems to be a required factor in tumorigenesis. In particular metastasized cancer caused by disseminating tumor cells is, with very few exceptions, an incurable disease. Therefore, a better understanding of the mechanisms that influence tumor propagation is key to improve therapeutic options of tumor patients.

NK cells, which play an important role in the immunosurveillance of tumors, recognize and eliminate malignant cells thereby preventing both local tumor progression and metastatic spread. While being initially described as lymphocytes capable to lyse cells with low or absent expression of MHC class I without prior sensitization, it has meanwhile been recognized that NK cell reactivity is governed by a balance of multiple inhibitory and activating receptors. NK cell reactivity is thus dependent on various immunoregulatory molecules far beyond MHC class I–specific inhibitory KIR receptors. Apart from the direct interaction with their target cells, NK cell activity is further influenced by the reciprocal interplay with various other hematopoietic cells like dendritic cells (DC), monocytes/macrophages, and lymphocytes. The complex nature of this crosstalk has been exemplified by numerous studies demonstrating that e. g. interaction of NK cells and DC causes multiple and potentially opposite effects on the activity of both involved cell types depending on factors like cellular context or maturation state. However, up to now no detailed study, especially in humans, has addressed the molecular mechanisms and consequences of the crosstalk of NK cells with platelets, another central component of the blood, which is physiologically in direct proximity of NK cells. This is even more surprising since murine tumor models document a strong dependence of tumor progression and metastasis on quantitatively and qualitatively normal thrombocytopoiesis. Furthermore, inhibition of metastasis caused by antibody-induced thrombocytopenia has been shown to be reversed by additional depletion of NK cells. Thus, thrombocytopenia may “indirectly” inhibit tumor dissemination by allowing NK cells to exert their anti-tumor effector functions. However, beyond mechanistic hypotheses which propose a “tumor-protective effect” of platelets by preventing immune cells from accessing tumor cells, nothing is yet known regarding the molecular mechanisms underlying these finding obtained in mouse models. Even less is known regarding the influence of platelets on NK cell anti-tumor reactivity in humans. However, there is ample evidence that both disseminating tumor cells and leukemic blasts do not travel through the blood alone, but surround themselves by coating platelets. This may not only enable a “molecular mimicry” of tumor cells “hiding” behind platelets, but also leads to platelet activation causing release of their granules, which contain various factors that can alter NK cell reactivity. Indeed, platelet releasate has been found to inhibit PBMC cytolytic activity. Recently, a paradigm shift occurred in platelet biology: platelet releasate was found to differ substantially depending on which receptor on platelets was stimulated. For example, upon activation of proteinase-activated receptor 1 (PAR1) a proangiogenic releasate containing high amounts of VEGF-A and bFGF was secreted, while triggering PAR4 caused release of well-known inhibitors of angiogenesis such as endostatin and...
thrombospondin-1. These findings provide an explanation for the meanwhile established ambivalent role of platelets in angiogenesis. They further suggest that secretion of functionally differing platelet releasates, in addition to the direct effect of coating platelets on NK-tumor cell interaction, could play an analogous dual role systemically affecting NK cell mediated tumor immunosurveillance.

Taken together, the described observations raise several questions: Is immunosurveillance by NK cells modulated by a platelet-derived “neo-surface”? If yes, which immunoregulatory molecules expressed by platelets influence NK cell reactivity? Do humoral substances released by platelets exert (differential) effects on NK cell anti-tumor reactivity? If yes, what are the molecular mechanisms? And above all: can we modify the obviously occurring platelet-NK cell interactions to achieve an anti-tumor effect in patients?

Accordingly, the following points are addressed:

2. Functional characterization of immunoregulatory molecules on the platelet surface influencing NK cell reactivity.
3. Research into a specific platelet “phenotype” in patients with tumor disease as compared to normal donors.
4. Determination of the in vivo relevance of NK-platelet-tumor cell interaction in immunodeficient mice xenotransplanted in order to provide human hematopoiesis and growing human tumors.
5. Evaluation of therapeutic compounds for the modulation of platelet-NK cell interactions in favor of an enhanced anti-tumor response in vitro and in vivo.

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