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Transplantation-induced cancers

Emerging evidence that clonal CMV-specific NK cells are causal immunogenic factors

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Solid cancers are a major adverse outcome of liver transplantation. Recent reassessments have revealed insights into causal factors, primarily centering on modulations of the natural killer (NK) cell compartment in liver transplant recipients. In the presence of cytomegalovirus, the clonal expansion of differentiated NK cells could restrict the diversity of the NK repertoire favoring the development of certain tumors.

Malignancy has become one of the three major causes of death after transplantation in the past decade and is thus increasingly important in all organ transplant programs. The overall risk of cancer in transplanted patients is increased between two- and 3-fold compared with the general population of the same age and sex. Reasons for the increased risk of most cancers after transplantation are likely owing to the interplay of several factors: the organ transplanted, prior and new exposure to viral infections, and duration of immunosuppression. While the use of a prolonged immunosuppressive regimen is known to play a role in T-cell impairment, recent insights into the specificities of natural killer (NK) cells led us to reassess the potential modulation of this innate immune cell compartment after solid transplantation.

As an integral part of innate immunity, NK cells are critical in protecting the host for viral infections and tumor growth.[1] They distinguish their cellular targets from healthy cells via a very large panel of activating and inhibitory cell surface receptors. NK cell inhibitory receptors, like killer-cell immunoglobulin-like receptors (KIRs), recognize specific HLA class-I molecules that are readily expressed in the steady-state on most cells, and required for maintenance of self tolerance whereas, the activating receptors are rather implicated in the immunosurveillance. The presence of this vast array of NK receptors underlies the enormous diversity of NK cells, with a prediction of between 6000 and 30 000 distinct NK-cell phenotypes within an healthy individual.[2] This phenotypic diversity could explain how NK cells maintain self-tolerance through the strict genetic control of inhibitory receptor expression, while concurrently maintaining the flexibility to respond to infections and cancers. However, recent investigations, including our own and those of other groups, have revealed a rapid and vigorous "clonal" expansion of fully differentiated $CD56^{dim}NKG2C^{+}$ NK cells that preferentially express KIR self-reactive HLA class-I molecules in cytomegalovirus (CMV)-positive individuals. This was recently described upon additional encounters with viruses, including HIV-1, hantavirus, and hepatitis B and C viruses.[3] In immunocompromised individuals, the reactivation of latent virus or the development of an acute CMV infection is associated with the promotion of a lasting increase in differentiated $CD56^{dim}NKG2C^{+}$ NK cells, as observed in a child with a Severe Combined Immunodeficiency (SCID) infected with CMV,[4] or after organ transplantations.[5] Altogether, these data suggested that the repertoire of NK cells differs greatly from one person, or patient, to another after CMV infection, and that in some peculiar situations, the dramatic expansion of CMV-specific "clonal" NK cells could bias the diversity of the NK-cell repertoire, and consequently subvert the NK-cell recognition of other pathological situations, like the development of neoplastic cells (**Fig. 1**).

Recently, we performed an extensive study of NK cells in patients after orthotopic liver transplantation (OLT), from the French K-GREF cohort, enrolled at the time of diagnosis for the development of de novo non-cutaneous tumors and compared with OLT patients without tumors.[6] In this

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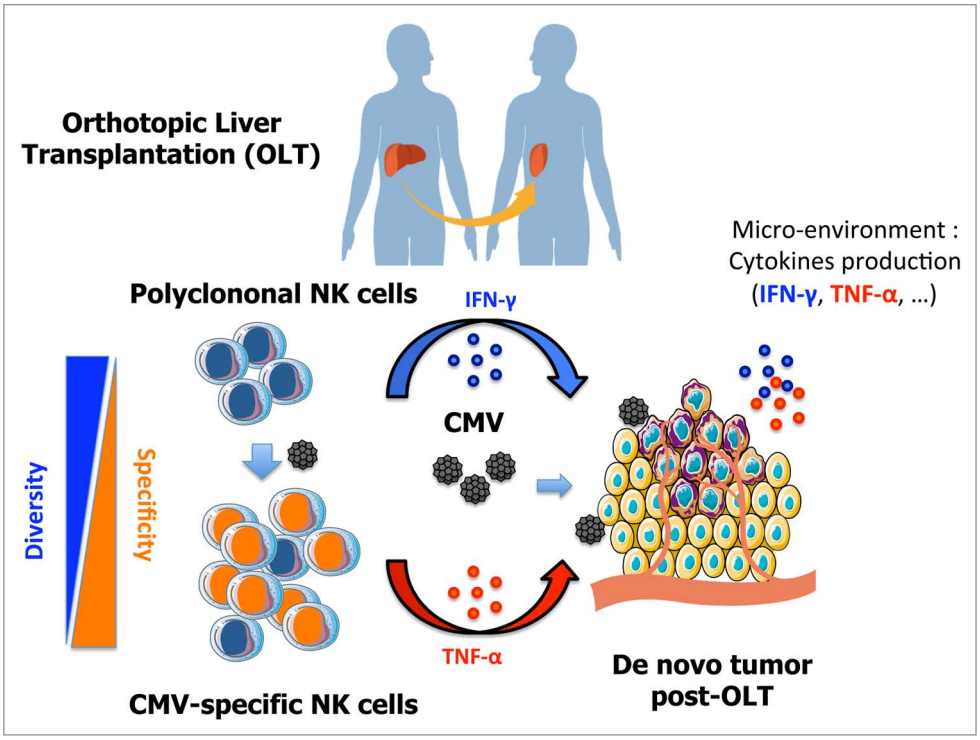

Figure 1. Putative role of expanded CMV-specific "clonal" NK cells in the development of de novo tumors in OLT patients. Natural killer (NK) cells are clonally expanded in the presence of cytomegalovirus (CMV), thereby decreasing NK cell diversity, altering the cytokine milieu and fostering cancer development in patients receiving orthotopic liver transplant (OLT). IFNγ, interferon; TNFα, tumor necrosis factor.

study, a hierarchical clustering of NK cell markers reveals that CMV infection is associated with the expansion of non-conventional fully differentiated $NKG2A^{low}CD62L^{low}CD57^{high}NKG2C^{+}$ "clonal" NK cells, whereas CMV^{-} patients present a classical immature $NKG2A^{high}CD62L^{high}CD57^{low}NKG2C^{-}$ NK cells, as currently observed in immunocompromised patients.[6] The overall polyfunctionality of NK cells, measured by their capacities to degranulate and to produce cytokines such as interferon γ (IFNγ) and tumor necrosis factor α (TNFα), reveals that CMV-specific "clonal" NK cells produce large amount TNFα,[6] an inflammatory cytokine that plays a key role in the control and (or) the development of de novo tumors both in shaping adaptive T-cell responses and in enhancing inflammatory responses in tissues. In contrast, immature NK cells from CMV^{-} patients mainly produced IFNγ, a cytokine that enhances adaptive T helper type 1 (Th1) responses. Popivanova et al.[7] showed that blocking TNFα reduced carcinogenesis of colorectal tumors, whereas increased IFNγ levels (as mediated by NK cells) predicts long-term survival in patients with gastrointestinal stromal tumors after treatment with imatinib mesylate.[8] The most intriguing result of our study was the exclusive development of de novo colorectal and head/neck tumors in patients with unconventional CMV-specific "clonal" NK cells, whereas, genitourinary tumors were only observed in CMV^{-} patients with immature NK cells. In contrast, gynecological tumors and lymphoproliferative disorders were diagnosed in OLT patients, irrespective of their CMV status.[6] It is widely recognized that virus infection is implicated in several cancers in the general population, and also through study in patients with acquired immune dysfunction, such as those with AIDS. Similarly, transplant patients are also vulnerable to viral infection or reactivation of latent infection. The rapidity of development of some malignancies after transplantation is also consistent with the concept of a viral action. Di Cocco et al.[9] have recently described a case of de novo gastric cancer after kidney transplantation with a concomitant diagnosis of CMV disease. There is also evidence in kidney recipients that after transplant failure and reduction or cessation of immunosuppression, the risk of virus-related cancers decreases back to levels seen in pre-transplant dialysis patients.[10]

Altogether these data suggest that reactivation or primary infection with CMV in immunocompromised OLT patients induces the expansion of differentiated CMV-specific "clonal" NK cells, which could partially bias the NK repertoire and subsequently favor the development of specific malignancies (**Fig. 1**). Whether CMV is causative or simply represents an epiphenomenon in the development of specific malignant tumors in immunocompromized patients urgently requires further elucidation and raises clinically relevant questions regarding better control of CMV in liver transplant patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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