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COMMENTARY

Calreticulin arms NK cells against leukemia

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ABSTRACT

Calreticulin (CALR) exposed on the surface of cancer cells succumbing to therapy delivers robust phagocytic signals that support the activation of adaptive anticancer immune responses. Recent data from our group demonstrate that spontaneous CARL exposure on leukemic blasts also supports innate anticancer immunity by natural killer (NK) cells via an indirect mechanism relying on myeloid $CD11c^{+}CD14^{+}$ cells.

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Malignant cells responding to selected stressors, including some chemotherapeutics agents (*e.g.*, anthracyclines, oxaliplatin, cyclophosphamide), radiation therapy, some variants of photodynamic therapy, and high hydrostatic pressure, expose on their surface or release in their microenvironment numerous molecules that deliver a signal of danger to the host immune system.[1] These molecules, which are collectively known as "damage-associated molecular patterns" (DAMPs), are responsible for the recruitment and activation of antigen-presenting cells (APCs) or their precursors to sites of cancer cell death, culminating with the local or nodal cross-presentation of tumor-associated antigens to naïve T cells and hence initiation of adaptive anticancer immunity.[2] The term "immunogenic cell death" (ICD) has been widely employed to refer to instances of cancer cell death associated with the release of DAMPs in amounts and according to kinetics that are compatible with the initiation of adaptive tumor-targeting immunity.[3] Importantly, DAMP emission by cancer cells undergoing ICD occurs downstream of stress responses that are initiated when cells are still alive in support of cellular homeostasis.[3]

ICD-relevant DAMPs encompass soluble molecules, including ATP, the non-histone chromatin-binding protein high mobility group box 1 (HMGB1) and the cytokine interferon beta 1 (IFNB1), as well as molecules ectopically associated with the plasma membrane, such as the endoplasmic reticulum (ER) chaperone calreticulin (CALR). While soluble DAMPs generally deliver chemotactic and immunostimulatory signals, CALR exposed on the membrane of dying cells and dead cell corpses supports their uptake by APCs in the context of type I IFN production.[4,5] Consistent with this notion, elevated levels of CALR on surface of malignant blasts has been linked with improved prognosis in patients with acute myeloid leukemia (AML),[6,7] correlating with superior T-cell dependent immunity.[6]

As the contribution of lymphoid cells other than T cells to anticancer immunity driven by membrane-exposed CALR was unclear, we set to investigate the potential involvement of natural killer (NK) cells, which are gaining considerable momentum as actionable items for cancer immunotherapy.[8] Previous findings suggested indeed a link between the exposure of ER chaperones on the surface of malignant blasts and NK cells activation in leukemia.[9]

We demonstrated that high levels of membrane-exposed CALR on malignant blasts correlates with increased amounts of circulating NK cells in patients undergoing post-chemotherapy hematopoiesis restoration. Moreover, NK cells from patients with CALR-exposing blasts exhibited increased secretory and cytotoxic functions, which were unrelated to increased expression of NK cell-activatory ligands by cancer cells.[10] However, we were unable to document the direct effects of membrane-exposed CALR on the functional and secretory profile of NK cells. Rather, we found that CALR on the surface of malignant blasts favors the accumulation of a population of $CD11b^{+}CD14^{+}$ myeloid cells exhibiting numerous markers of activation, including CD86 and MHC Class II molecules, chemokine receptors such as C-C motif chemokine receptor 7 (CCR7), membrane-exposed interleukin 15 receptor, alpha chain (IL15RA), and type I IFN secretion.[10] Thus, AML patients in whom malignant blasts spontaneously expose CALR on the cell surface manifest the accumulation of an activated APC population with an elevated potential to migrate to lymph nodes (via CCR7)[11] and activate NK cells (via IL15RA, which is required for IL15 trans-presentation)[12] (Figure 1). Supporting the clinical relevance of these findings, patients with high levels of CALR on the surface of malignant blasts and high levels of the NK cell activatory receptor (best known as NKGD2)[13] on the NK cell surface had superior overall survival as compared to all other patient subgroups.[10]

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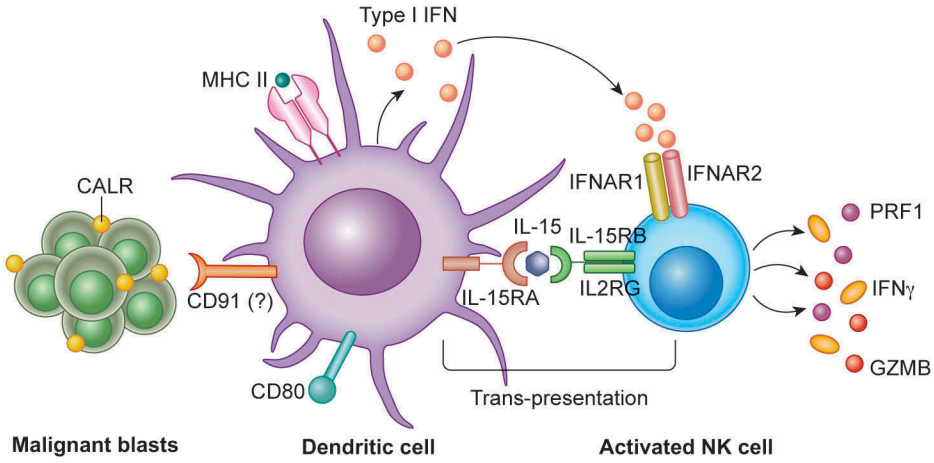

Figure 1. Calreticulin and NK cell activation. The exposure of calreticulin (CALR) on malignant blasts from patients with acute myeloid leukemia (AML) favors the accumulation of an activated, poly-functional population of $CD11b^{+}CD14^{+}$ myeloid cells that support natural killer (NK) cell anticancer functions. CCR7, C-C motif chemokine receptor 7, IL15RA, interleukin 15 receptor, alpha chain (IL15RA); IFN, interferon.

In summary, our results suggest that monitoring CALR exposure on malignant blasts and NK cell activation markers may improve current prognostic and predictive assessments in patients with AML. Additional studies are required to elucidate the precise prognostic and predictive value of these parameters.

Disclosures

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