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INSIGHTS

AC/DC: Highway to cell

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Apoptotic cell (AC) corpses can be taken up by certain types of dendritic cell (DC), which cross-present dead cell-derived antigens. In this issue of JEM, Tam et al. (https://doi.org/10.1084/jem.20250887) reveal that GPR34, a lysophosphatidylserine receptor, promotes AC uptake and cross-presentation by type 1 DCs (cDC1s).

Billions of cells die each day through programmed apoptosis. The uptake of these apoptotic corpses, termed "efferocytosis," is a key process for maintaining organ homeostasis (Morioka et al., 2019). Efferocytosis has been extensively studied in macrophages, gravediggers par excellence. However, apoptotic cells (ACs) can also be taken up by dendritic cells (DCs), particularly type 1 DCs (cDC1s), which are highly adept at rescuing antigenic information from corpses by (cross-)presenting dead cell-derived antigens to CD8+ and CD4+ T cells (Cabeza-Cabrerizo et al., 2021). Phosphatidylserine (PS) exposure marks ACs for clearance, and macrophages express numerous PS receptors, such as TIM-4, MERTK, and AXL, that facilitate efferocytosis (Morioka et al., 2019). However, cDC1s lack many classical PS receptors, pointing to alternative efferocytosis pathways that remain elusive.

Tam et al. (2025) identify GPR34, a G protein-coupled receptor, as a key mediator of efferocytosis by mouse cDC1s. Notably, GPR34 does not recognize PS, but its derivative, lysophosphatidylserine (lysoPS), generated when phospholipases such as PLA1A and ABHD16A remove one of the PS fatty acid chains (Hosono et al., 2001). In mouse spleen, stromal cell-derived PLA1A appears key for generating lysoPS from exposed PS on AC membranes, providing a chemotactic and/or recognition cue for cDC1 efferocytosis.

Using bone marrow chimeric models, the authors show that GPR34-deficient cDCls display reduced efferocytosis compared with their wild-type counterparts. This

defect is specific to cDC1s, as macrophages lacking GPR34 display no impairment in AC uptake. Conversely, a gain-of-function GPR34 allele enhances efferocytosis by cDC1s. Importantly, reduced uptake in GPR34-deficient cDC1s translates into impaired cross-priming of CD8+T cells when mice are immunized with ACs bearing a model antigen. Together, these findings reveal a specialized lysoPS-GPR34 axis that enables cDC1s to carry out efferocytosis and cross-present AC-derived antigens.

The elegant work by Tam et al. raises important mechanistic and conceptual questions. How exactly does GPR34 promote efferocytosis by cDC1s? It could act at several levels: guiding cDC1s toward ACs (chemotaxis), facilitating corpse tethering, and/or signaling for engulfment (see figure). Further investigation into the molecular machinery engaged by GPR34 may illuminate its mechanism of action. Incomplete loss of efferocytosis by GPR34-deficient cDC1s suggests the existence of other, as-yet unidentified receptors. Such redundancy mirrors that seen in macrophage efferocytosis, which involves the coordinated activity of multiple PS receptors.

Another avenue for exploration concerns physiological consequences. In steady state, AC uptake by cDC1s drives a homeostatic maturation program that includes migration to lymph nodes (Bosteels et al., 2023; Cummings et al., 2016). Combined with MHC presentation of corpse-derived antigens, this pathway is thought to reinforce peripheral tolerance to tissue-restricted self-antigens. It may also influence cancer immunity, where AC uptake by cDC1s has







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been suggested to induce an "mregDC" state that correlates with impaired anti-tumor T cell activity (Maier et al., 2020). It will be interesting to assess the impact of the lysoPS-GPR34 pathway in both tumor immunity and in peripheral tolerance settings. Moreover, whether GPR34 selectively detects ACs or also contributes to uptake of other cargo is unknown. Pinpointing when and where GPR34 contributes to immune physiology, and how it integrates with other receptor signals, will be key to translating the insight of Tam et al. into therapeutic potential.

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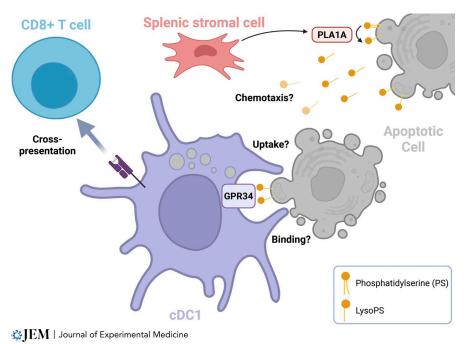
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LysoPS and GPR34: A new axis for DC efferocytosis and cross-presentation. Stromal cell–derived PLA1A converts PS on ACs to lysoPS. LysoPS binds GPR34 on cDC1s, promoting efferocytosis through chemotaxis, corpse tethering, and/or engulfment. AC-derived antigens can then be cross-presented to CD8 $^{+}$ T cells. Figure created with BioRender.

Reis e Sousa is a visiting professor at Imperial College London and King's College London and holds an honorary professorship at University College London, all unrelated to this work. No other disclosures were reported.

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