

ONLINE SUMMARY

- As cells are infected by microorganisms, they can preemptively die to avoid replication and spreading of the pathogen. Cell death associated with the presence of pathogen-associated molecular patterns (PAMPs) can stimulate vigorous immune responses.
- In the absence of PAMPs, damage-associated molecular patterns (DAMPs) associated with cell death may stimulate an immune response that can elicit the specific recognition of antigens expressed by dying cells (for instance tumor antigens).
- The nature of the immune response to cell death depends on what cells die, where they die, how they die, who engulf them, and when (or if) associated antigen has been or will be recognized. Variations in these factors can have consequences that range from effective anti-pathogen or tumor responses to autoimmune pathology.
- The simple idea that apoptosis is tolerogenic or non-immunogenic and necrosis is immunogenic is likewise an oversimplification. Thus, the apoptosis of tumor cells induced by chemotherapy can prime an efficient immune response, which in turn may contribute to the efficacy of anticancer regimens.
- Various factors contribute to the immunogenicity of apoptotic cell death. Such DAMPs include the surface exposure of chaperones (such as calreticulin) or the release of proteins (such as protein high-mobility group box 1 protein, HMGB1, and spliceosome-associated protein 130, SAP130), among others. The catabolic action of caspases and macroautophagy can also contribute to the immunogenicity of cell death.
- The tolerogenic effect of cell death depends on multiple factors including the absence of T cell help, the location of the dying cells, which in part dictates their engulfment by distinct DC cell subtypes, the maturation state of DC, the production of immunosuppressive factors (such as TGF- β), or modification of DAMPs (such as oxidation of HMGB1 resulting in its inactivation).
- In conclusion, the mechanisms that determine the immune response against dead and dying cells are complex. Understanding (and possibly manipulating) these mechanisms can have important implications for cancer biology, infectious disease, tissue injury and autoimmunity.