IMMUNE MEMORY

Inflammasomes drive NK cell memory

S. Bradbrook/NPG

Immunological memory was traditionally associated with B and T cell responses, but an increasing number of studies show that natural killer (NK) cells can possess traits of adaptive immunity and acquire immune memory. Now, Van den Boorn, Hornung and colleagues report in *Immunity* that the contact-sensitizer monobenzone induces pigment cell-specific memory NK cells and that this memory response requires the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome in tissue-resident macrophages.

Monobenzone is specifically activated in pigmented cells and was used to investigate the immune responses that occur in contact hypersensitivity. Monobenzone was applied on the shaved abdomen of mice (sensitization) and reapplied on their ear 1 and 2 weeks later (rechallenge), which led to ear swelling (used as a surrogate marker of contact hypersensitivity). The authors found that monobenzone led to the recruitment of a hapten-specific CD45⁺ cell population that consisted of CD49B⁺NK1.1⁺ NK cells that were positive for LY49C and LY49I lectin-type receptors and CD18, indicating that these NK cells have effector functions. Of note,

mice lacking functional T and B cells (*Rag*^{-/-} mice) could mount a similar ear swelling response upon monobenzone sensitization and rechallenge whereas this response was abolished in wild-type mice depleted of NK cells. Thus, monobenzone induced the formation of a memory NK cell population.

Hapten-induced memory NK cells have previously been shown to reside in the liver so the authors purified NK cells from the liver and spleen of monobenzone-sensitized mice and transferred them to naive wild-type mice that were then challenged with monobenzone. Only adoptively transferred liver NK cells could induce a recall contact hypersensitivity response after monobenzone challenge. Tracking of the adoptively transferred NK cells showed that these cells homed back to the liver of recipient naive mice and could not be detected at any other sites, but readily homed to the ear after monobenzone challenge. Subsequent experiments showed that the local NK cell activation after monobenzone treatment coincided with migration of tissue-resident macrophages from the challenge site into the local draining lymph nodes and that macrophage depletion abrogated the monobenzone-induced contact hypersensitivity. Hence,

monobenzone-induced memory NK cell formation requires the migration of macrophages into the local lymph node.

Finally, the authors investigated if the inflammasome could have a role in the induction of monobenzone-triggered memory NK cells as the NLRP3 inflammasome has previously been shown to be required for the induction of contact hypersensitivity by various haptens. Indeed, mice lacking NLRP3 or its adaptor ASC were unable to establish monobenzone-dependent contact hypersensitivity and NK cells were not recruited into the ear during monobenzone rechallenge in these mice. Adoptive cell transfer experiments showed that the inflammasome was required for both memory induction and the recall response. Furthermore, transfer of bone marrow from sensitized wild-type mice to *Nlrp3*^{-/-} mice enabled monobenzone-triggered contact hypersensitivity only when the skin-resident macrophages were depleted from the recipient mice, whereas depletion of macrophages in wild-type mice receiving *Nlrp3*^{-/-} bone marrow abolished the establishment of contact hypersensitivity. Thus, inflammasome activation in tissue-resident macrophages drives the monobenzone-induced formation of memory NK cells.

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“memory NK cell formation requires the migration of macrophages”

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FURTHER READING Cerwenka, A. & Lanier, L. L. Natural killer cell memory in infection, inflammation and cancer. *Nat. Rev. Immunol.* **16**, 112–123 (2016)