Macrophage activation unveiled

In the early 1960s, George Mackaness showed that macrophages from mice infected with intracellular bacteria could launch an indiscriminate attack against unrelated bacteria. Thus began an explosion of research on the biology of what Mackaness first termed “macrophage activation.”

Although Mackaness coined the term in 1962, the concept of macrophage activation is a century old. In 1905, Elie Metchnikoff reported that phagocytic mononuclear cells from animals resistant to certain bacterial infections were more adept at killing those bacteria (1). But how macrophages became better killers remained mysterious until Mackaness embarked on his pioneering work with the intracellular bacterium Listeria monocytogenes.

Macrophages get worked up

Resistance to infectious organisms was long thought to depend primarily on antibodies that help to lyse pathogens in the presence of complement and promote microbe ingestion by phagocytic cells. But antibody responses to intracellular pathogens didn’t always correlate with the level of protection against that organism, hinting at the existence of an antibody-independent form of antimicrobial resistance.

Mackaness, then an immunologist at the John Curtin School of Medical Research in Australia, was interested in studying one such pathogen: Mycobacterium tuberculosis. But rather than wrestle with the slow-growing M. tuberculosis, he turned to L. monocytogenes, against which mice developed a robust, antibody-independent resistance.

Mackaness soon discovered that infection with L. monocytogenes rendered the mice temporarily resistant to subsequent infection with both L. monocytogenes and unrelated bacteria. He referred to this phenomenon as acquired cellular resistance. Careful analysis of the lesions in resistant mice led Mackaness to attribute the phenomenon to macrophages, which accumulated in the lesions where they ingested bacteria. When taken out of resistant mice, these cells could kill a range of bacteria with heightened efficiency compared with macrophages from uninfected mice.

This broad resistance waned over time, but could be reacquired by challenging the mice with a second dose of the original bacteria. This second offense activated the macrophages almost immediately, but this did not occur if the mice were challenged with an unrelated organism. Hence, the macrophage-dependent resistance appeared to be antigen-specific in its elicitation but indiscriminate in its expression. These seminal results were published in two articles in The Journal of Experimental Medicine (2, 3).

Timing is everything

Mackaness noted that the timing of acquired resistance paralleled the development of delayed-type hypersensitivity (DTH), a cell-dependent inflammatory reaction of the skin. Based on this, Mackaness boldly (and prophetically) hypothesized that acquired resistance might be directly dependent on the hypersensitive state.

His later studies showed that the transfer of cyclophosphamide-sensitive spleen cells (now recognized as T cells) from Listeria-immune mice simultaneously induced protection and DTH in naive mice. However, the protection was immunologically specific; lymphoid cells alone did not transfer nonspecific cellular resistance. This required both immune lymphoid cells and an eliciting dose of the corresponding microbe (4, 5), suggesting that the macrophages needed to interact directly with the challenge organism to evoke resistance. Thus, acquired cellular resistance hinged on the coordinated response of antigen-specific lymphocytes and nonspecific macrophages.

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Demystifying activation

This was as far as Mackaness got. “We still had no idea how a lymphocyte could communicate a property to a macrophage,” says Carl Nathan (Cornell University Weill Medical College, New York), whose own research on macrophage activation was inspired in part by the observations of Mackaness. Nathan, then a medical student at Harvard University, soon established that a soluble product made by antigen–stimulated lymphocytes could activate macrophages (6). His later studies identified the T cell–derived cytokine interferon-γ as the primary instigator of this activation (7).

“Mackaness was the first to assign the specificity [of an immune reaction] to one cell and the execution to another cell,” notes Nathan. His work also helped pave the way for other areas of research including cytokine biology, tumor immunology, and the biochemistry of macrophage killing.