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Myeloid cells function as major bridges between the innate and adaptive immune systems. First, dendritic cells orchestrate an appropriate adaptive immune response through Ag presentation, a landmark finding that garnered a Nobel Prize for Ralph Steinman (1). Less well known are the findings of George Mackaness from the John Curtin School of Medical Research in Australia, who demonstrated a second intersection between the innate and adaptive immune responses: that macrophages can serve as effector cells for acquired cell-mediated immunity. In 1962, his article titled "Cellular Resistance to Infection" was published in *The Journal of Experimental Medicine* (2), highlighted here along with a second seminal article by Mackaness from 1964 (3) as a *Pillar of Immunology*. At the time, Ab-dependent immune responses were well appreciated, but cellular immunity was not generally accepted. However, there were a number of lines of evidence that pointed to a major role for cellular immunity. For example, the humoral response alone did not correlate with protection in all infections, especially ones caused by intracellular pathogens (4).

Mackaness used *Listeria monocytogenes*, a facultative, intracellular pathogen, to investigate cellular resistance (2). His decision to use this pathogen was based on previous observations suggesting that the clearance of *L. monocytogenes* was not dependent on humoral immunity (5, 6). Because the parental strain of *L. monocytogenes* was unable to persist in mouse macrophages, Mackaness used serial passaging, a technique described in the original discovery of *L. monocytogenes* (7), to enhance its virulence. Interestingly, the bacterium increased in virulence regardless of whether it had been passaged in vivo or in cultured macrophages. This observation legitimized the in vitro infection model that was used in parallel with the mouse model. With *L. monocytogenes* as the pathogen and outbred mice as the host, Mackaness demonstrated acquired cellular immunity by primary infection and secondary challenge. Whereas naive animals were susceptible to *Listeria* infection, previously infected animals could withstand a secondary infection of 10 LD_{50} (2). This acquired resistance persisted for at least 13 wk after primary infection. The role of Abs in acquired resistance to *Listeria* was ruled out when serum from immunized animals failed to reduce bacterial growth in recipient animals. Mackaness also observed that the emergence of delayed-type hypersensitivity, now known as a surrogate for assessing cell-mediated immunity, coincided with the antibacterial response. Detailed histological studies of the spleen and liver identified mononuclear cells as the dominant population during secondary challenge. Macrophages isolated from previously infected animals were distinct morphologically and phenotypically from macrophages isolated from naive animals. These ex vivo macrophages from immunized animals were also resistant to *Listeria* infection in vitro. The data led him to conclude that macrophages from mice previously infected with intracellular pathogens were resistant to secondary challenge. In subsequent work also highlighted here, using *L. monocytogenes*, *Brucella abortus*, and *Mycobacterium tuberculosis*, Mackaness demonstrated that these activated macrophages have nonspecific resistance to unrelated pathogens, but only when cellular immunity has been established in vivo (3). This resistance was due to enhanced nonspecific bactericidal activities within the macrophage. Finally, he demonstrated that lymphocytes transferred from immunized animals altered the bactericidal activity of the recipient macrophages (8, 9). Thus, the interdependence of the innate and adaptive immune responses in successfully protecting the host against intracellular pathogens was revealed. Mackaness' seminal work set the stage for the molecular characterization of macrophage activation, such as the 1983 publications by two groups, first-authored by Carl Nathan and Robert Schreiber, demonstrating that T cell–secreted IFN-γ was the factor that stimulated macrophages to increase their bactericidal activity during cellular immunity (10, 11). Mackaness' work clearly demonstrated the involvement of macrophages in the complex interactions between cells that play key roles in innate and adaptive immunity, and it laid the foundation for current research focused on dissecting the mechanisms that drive this crosstalk.

Disclosures

The authors have no financial conflicts of interest.

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