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MUCOSAL IMMUNOLOGY

Battle scars

It has been proposed that acute infections could serve as triggers for the development of chronic inflammatory diseases. However, supporting evidence for this idea has been lacking. Yasmine Belkaid and colleagues now show that an acute gastrointestinal infection in mice can lead to tissue remodelling and the long-term impairment of immune function. They suggest that such ‘immunological scarring’ may result in the breakdown of tissue homeostasis and subsequent disease development.

The authors infected mice orally with the Gram-negative bacterium *Yersinia pseudotuberculosis*, using a dose that causes a transient infection. Although most animals cleared the infection by 3 weeks, 70% of the mice developed a chronic lymphadenopathy of the mesenteric lymph nodes (MLNs) that was still detectable at 9 months post infection. Notably, this remodelling of the MLNs resulted in the impaired induction of regulatory T cells and prevented systemic tolerance induction in a model of oral tolerance. In addition, mice with *Y. pseudotuberculosis*-induced chronic lymphadenopathy showed defects in the induction of T helper 17 cells in a model of oral

vaccination. Therefore, a single acute enteric infection can lead to tissue remodelling that impairs the subsequent induction of both tolerogenic and effector immune responses in the intestine.

Closer analysis suggested that these immune abnormalities were linked to defects in dendritic cell (DC) trafficking. MLNs of mice with chronic lymphadenopathy showed reduced numbers and proportions of DCs, and migratory CD103⁺CD11b⁺ DCs were virtually absent. By contrast, DC subsets in the lamina propria were unchanged, suggesting that DCs were failing to migrate or accumulate properly in the MLNs of mice with chronic lymphadenopathy. Experiments with fluorescently labelled long-chain fatty acids showed that the lymphatics were ‘leaky’ in these animals, and this loss of lymphatic integrity was associated with a massive infiltration of neutrophils and macrophages into the surrounding mesenteric adipose tissue (MAT). Notably, CD103⁺CD11b⁺ DCs, which are not normally found in MAT, accumulated in the MAT of mice with chronic lymphadenopathy, suggesting that these cells were prematurely exiting the leaky lymphatics.

So what prevents the resolution of inflammation and a return to tissue homeostasis? The authors found that the intestinal microbiota is necessary for sustaining the lymphadenopathy that occurs following acute infection. Germ-free mice still showed remodelling of the MLNs following *Y. pseudotuberculosis* infection, but this was not associated with subsequent defects in the accumulation of migratory CD103⁺CD11b⁺ DCs in the MLNs. Moreover, antibiotic treatment of mice with chronic lymphadenopathy reduced their levels of MAT inflammation, prevented accumulation of CD103⁺CD11b⁺ DCs in the MAT and restored oral vaccination responses.

Taken together, these data indicate that the microbiota has a role in sustaining mesenteric remodelling that is initiated by an acute enteric infection. Importantly, these findings suggest a model for how an acute infection can leave an ‘immunological scar’ that leads to chronic immune dysfunction.

Yvonne Bordon

“an acute infection can leave an ‘immunological scar’ that leads to chronic immune dysfunction”

ORIGINAL RESEARCH PAPER Morais da Fonseca, D. *et al.* Microbiota-dependent sequelae of acute infection compromise tissue-specific immunity. *Cell* **163**, 354–366 (2015)