Journal Club

NRI AT 20: DISEASE TOLERANCE

IMMUNOLOGY'S INTOLERANCE OF DISEASE TOLERANCE

There is an old, theoretical and practical concept from plant ecology that proposes that infected hosts can differ in their ability to reduce pathogen load (called resistance) and the amount they suffer in response to varying pathogen loads (called disease tolerance).

Disease tolerance is most clearly observed in cases where different responses to a pathogen either save or kill the host, but do not alter pathogen load. Looking back through the literature, there are clear examples of this effect in the animal world. For example, a study by Dionne et al. (2006) showed that *Mycobacterium marinum* infection in *Drosophila* leads to a wasting disease that usually results in death. However, an alteration in insulin signalling prolonged survival without affecting pathogen load. Like many tolerance mechanisms, this did not involve a physiological mechanism that we normally think of as part of 'the immune system', despite being critical for surviving an infection.

In 2007, a study by Pamplona et al. reported that haem oxygenase, the enzyme that metabolizes haem into bilirubin, can enhance survival in mice with cerebral malaria without affecting parasite load. Again, haem oxygenase was not a typical immunological effector, but it was critical for survival.

At the time, there was no overarching theoretical way of describing disease tolerance in animals. Raberg et al. (2007), in an elegant paper that makes many say "I wish I had thought of that!", imported the idea of disease tolerance from plant ecology and applied it to animals. In their study, the authors concluded that different mouse strains, which were known to differ in their responses to rodent malaria, could be described as differing in terms of their disease tolerance. This was an important insight as it opened the door to applying decades of theory and practice from plant science to animal biology.

Around the same time, Ayres et al. (2008) showed that roughly equal numbers of resistance and tolerance mutations can be found in *Drosophila* when screening for factors affecting their survival to infections. Oddly, genetic screens for fly immunity had been ongoing for about 10 years and no disease tolerance effects had been reported — which was likely due to the fact that early screens looked for changes in immune effectors but not host survival. The study by Ayres et al. is important because it suggested that it should be easy to find tolerance effects if we bother looking for them.

At the beginning of the COVID-19 pandemic, we faced a pathogen for which we had no effective antiviral treatments and no vaccine. Our only hope was to promote disease tolerance to save lives, and that is what we did; oxygen

> "it opened the door to applying decades of theory and practice from plant science to animal biology"

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NRI AT 20: NEUROIMMUNOLOGY

THE COMPLEMENT CASCADE REPURPOSED IN THE BRAIN

Over the past two decades it has become clear that the complement cascade — best known for its roles in innate immunity and in the clearance of pathogens and immune complexes — has distinct functions in the brain, in both healthy development and in disease. Surprisingly, complement proteins were shown to be abundant in the central nervous system (CNS), and this led to the discovery of non-inflammatory functions for complement in regulating structural plasticity and functional homeostasis of synapses in the developing brain. For example, our study was among the first to implicate C1q and downstream C3 in synaptic pruning (Stevens et al., 2007), a process in which subsets of synapses are eliminated while the remaining synapses are preserved and strengthened. Studies initiated in the laboratory of the late Ben Barres showed that C1q and C3 are not only widely expressed in the CNS, but localize to subsets of immature synapses in the developing visual system, leading to elimination of these 'tagged' axons and synapses.

How are complement-tagged synapses eliminated? We and others subsequently found that microglia mediate synaptic pruning via phagocytosis, recognizing complement-tagged synapses using complement receptors, including CR3 (Schafer et al., 2012). We observed fragments of presynaptic terminals within microglia lysosomes during critical periods of synaptic pruning. Mice lacking C3 or CR3 showed reduced synaptic pruning, indicating that deficient complement signalling during brain development results in long-term defects in synaptic connectivity. Later, we and others characterized additional immune-related pathways — including the CD47–SIRPα 'don't-eat-me' signal — that also regulate microglial pruning of synapses, helping to determine which are preserved and which are eliminated (Lehrman et al., 2018).

Such studies in the developing mouse brain have also led to new insights into the molecular pathways that mediate pathological synapse loss, a hallmark of many neurodegenerative diseases and brain disorders. For example, there is evidence of region-specific deposition of complement onto subsets of synapses in mouse models of Alzheimer disease and in other neurodegenerative diseases, even in the absence of overt inflammation or pathology. Inhibiting the classical complement cascade by deleting the genes for C1q, C3 or CR3 rescues synapse loss and some cognitive impairment, including learning and memory defects, independently of amyloid plaques (Hong et al., 2016). These and other studies challenge the view that complement and microglial activation are a side-effect of neuronal damage and instead provide evidence that immune mechanisms are early mediators of synaptic loss and dysfunction. This model is corroborated by human genetics data that implicate complement and microglia as risk factors for Alzheimer disease as well as schizophrenia (Sekar et al., 2016), the pathogenesis of which has been hypothesized to involve aberrant synaptic pruning. Validation of this

treatment and anti-inflammatories are tolerance treatments. Given its obvious importance, I had hoped that the idea of disease tolerance would gain traction, but it has encountered resistance. Part of the problem is its name, yet we already deal with many types of tolerance in immunity – one more should not be a problem. The most important barrier might be that understanding tolerance requires the study of the whole physiological response of a body, not just isolated immune cells; perhaps the time has come to study organismal function in parallel to biological mechanisms.

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disease mechanism in humans will be an important next step for translating these findings into new therapies and early biomarkers.

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Competing interests
B.S. is on the Advisory Board of Annexon Biosciences.

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NRI AT 20: MACROPHAGES

TISSUE MACROPHAGES BREAK DOGMA

At the turn of the twenty-first century, macrophage biology appeared to be a mundane topic in research, as the field gave way to rapid growth in the study of dendritic cells. The blood monocyte was scarcely questioned as the de facto precursor for macrophages, but even the popularity of monocytes as a topic of research relied on their potential to differentiate into dendritic cells. Twenty years ago, entrenched dogma in the field was that proliferation of end-stage differentiated cells within the haematopoietic lineage was rare, so the concept that fully mature macrophages could proliferate while maintaining their differentiated status was akin to heresy. However, elegant work in 2009 by Aziz et al. upended that dogma by showing that macrophages were capable of self-renewal as fully differentiated cells. This proliferation occurred in the context of impaired expression of the transcription factor MafB, so the physiological context of when macrophage proliferation might occur in vivo was not entirely clear.

Nonetheless, these findings set the stage for the breaking of another dogma in the field — that of the widely accepted paradigm that adult bone marrow-derived monocytes were the precursors of all tissue macrophages. Employing a clever lineage tracing strategy, Ginhoux, Merad and colleagues (2010) revealed that primitive macrophages from the embryonic yolk sac gave rise to microglia, the macrophages of the brain. Indeed, these cells were sustained locally through self-proliferation so that even adult mice did not require monocytes for replenishment of this macrophage population.

Next, whereas direct origins from yolk sac macrophages turned out to be atypical for other tissue-resident macrophages, Schulz, Geissmann and co-workers (2012) broadened the paradigm of macrophages arising from embryonic progenitors when they revealed that most organs of the body, not just the brain, housed resident macrophages that derived from embryonic progenitors, maintaining lifelong or near-lifelong independence from bone marrow progenitors. The laboratory went on to show that the yolk sac gave rise to erythroid–myeloid progenitors that homed to the liver and later seeded the organs of the developing embryo with proliferation-competent macrophages that would take up residence in the tissue.

Each tissue macrophage developed a distinct imprint. That is, microarray analysis revealed that the tissue-resident macrophages in different organs bore distinct gene expression profiles that fit the functional needs of the organ but also distinguished them from monocytes recruited during inflammatory reactions. This set the stage for many studies to come on the complex interplay between tissue-resident and recruited monocytes in disease states. For example, during type 2 immunity induced by helminths, Jenkins, Allen and colleagues (2011) found that resident macrophages in body cavities proliferated and accounted for the inflammatory expansion of macrophages that once were assumed to arise only from the migration of blood monocytes into the tissue. In another example, tumour macrophages expanded through proliferation of the tissue-resident macrophages, whereas other macrophages with a different gene expression profile and function in the same tumours arose from bone marrow-derived monocytes, supporting the concept that the origin of macrophages is linked to their distinct functions (Zhu et al., 2017).

Collectively, these studies broke major dogma in the field on the origins and nature of macrophage progenitors, the state in which they are capable of renewal, and their overall identity in the tissue niche. Later work showed that, while dogma was broken by these foundational new works, there are several more nuanced scenarios. Adult bone marrow-derived monocytes do sometimes give rise to tissue-resident macrophages that closely resemble those arising from embryonic origins, including the capacity to renew through proliferation. And epigenetic loss of tissue macrophage identity can arise during inflammation to leave tissue-resident macrophages that are more similar to inflammation-induced, monocyte-derived macrophages than the cells started out as. Future studies will no doubt continue to reveal exceptions to the 'new dogma'. Nonetheless, there is broad consensus that our view of macrophage origin and identity has been forever changed by works of the past 10–15 years.

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