DAMed in (Trem) 2 Steps

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The role of microglia in neurodegenerative diseases has been controversial. In this issue, Keren-Shaul et al. identify a unique population of disease-associated microglia (DAM) that develop in two steps and may help to restrict damage in Alzheimer and related diseases.

In the early 1920s, Pio del Rio Hortega identified microglia and their phenotypes in different pathologies. Thereafter, progress in understanding of microglial development and function was gradual until a seminal study identified primordial macrophages as precursors of microglia, whose arrival in the central nervous system coincides with development of the blood vasculature (Ginhoux et al., 2010). Subsequent studies confirmed that under physiological conditions peripheral monocytes do not engraft the brain parenchyma, but rather that throughout life the microglial pool is maintained by self-proliferation (Goldmann et al., 2013). After CNS injury or neuroinflammation (as in experimental autoimmune encephalomyelitis), peripheral monocytes invade the parenchyma but do not persist there. The role of microglia versus engrafted peripheral monocytes in Alzheimer’s disease (AD) (Boissonneault et al., 2009), amyotrophic lateral sclerosis (ALS) (Butovsky et al., 2012), and other neurodegenerative diseases is still under debate, in part because of how heterogeneous these populations could be. To begin to understand the diversity of immune cells in the brain and how they may affect diseases, Keren-Shaul et al. (Keren-Shaul et al., 2017) in this issue of Cell use single-cell transcriptomics, to comprehensively map all immune populations in the brains and meninges of normal mice and animal models of Alzheimer’s-like pathology.

One of the problems with previous studies is that isolation of microglia has been based on only two markers, CD45 and CD11b. Whereas meaningful data can be obtained from microglia isolated from normal brains, the characteristic heterogeneity of microglia in diseased brains precludes accurate isolation of their subtypes based on so few markers, since possible microglial subpopulations associated with a particular pathology would be missed. This is exactly what the current Cell paper shows. The authors exploit single-cell genomics to better understand which microglial subtypes are associated with AD and other pathologies. In their unbiased analysis of thousands of cells, they happen upon two unique microglial populations found in the brain cortex of AD mice, but not in healthy mice (wild-type or AD mice in an early phase of disease) or in brain areas less affected by amyloid pathology. They call these cells disease-associated microglia (DAM).

The role of the Trem2 protein, one of the major risk factors for AD, much as the role of microglia in animal AD models, has also been hotly debated (Ulrich et al., 2017). Keren-Shaul et al. new data show that as disease progresses, microglia evolve into DAM in a two-step process. In the first step, which is Trem2-independent, the homeostatic microglial signature is lost, and in the second, Trem2-dependent step, the cells acquire a phenotype associated with phagocytosis and lipid metabolism (Figure 1). It remains to be tested whether DAM depletion affects disease initiation.

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Sonneault et al., 2009), amyotrophic lateral sclerosis (ALS) (Butovsky et al., 2012), and other neurodegenerative diseases must be protected by reduced intake (anorexia) and by endogenous hepatic glucose production (gluconeogenesis). The levels of glucose that benefit cell survival may be missed. This is exactly what the current Cell paper shows. The authors exploit single-cell genomics to better understand which microglial subtypes are associated with AD and other pathologies. In their unbiased analysis of thousands of cells, they happen upon two unique microglial populations found in the brain cortex of AD mice, but not in healthy mice (wild-type or AD mice in an early phase of disease) or in brain areas less affected by amyloid pathology. They call these cells disease-associated microglia (DAM).

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and/or progression in AD and ALS models. It would also be interesting to test if inducing the DAM phenotype in healthy young mice or even in developing mice produces changes in behavior and cognitive function. The authors also state that the mechanism for sensing the environment and activating microglia is not understood, and the molecular trigger that activates microglia is unknown. Presumably such a trigger is common to neurodegenerative diseases like AD and ALS and present in aged brains. The immediate suspects for environmental sensing would be Toll-like and NOD-like receptors. Thus, a plausible future target for neuroprotective therapies might be the identification of molecular cues that trigger the DAM phenotype.

The role of peripherally engrafting monocytes is not addressed directly in the current study (Keren-Shaul et al., 2017) because the cells were isolated from the entire brain, including the choroid plexus and meninges, which harbor monocytes (among other peripheral immune cells). Therefore, the changes observed here in myeloid cells, other than microglia, with disease progression are not necessarily parenchymal, but may be meningeal or a combination of both. Future studies should aim at deciphering the distinctive phenotypes of parenchymal immune cells in order to determine whether peripheral cells engraft the parenchyma, and if so, how this affects their phenotype and function.

Another recently explored, yet still contradictory, aspect of microglial biology is their homeostatic function. Pharmacological treatment of microglia using M-CSF receptor antagonists results in their almost complete depletion but with no cognitive deficits (Elmore et al., 2014). Microglial depletion using alternative (genetic) method does yield cognitive deficits, supposedly owing to lack of microglia-derived BDNF (Parkhurst et al., 2013). Thus, although these studies showed quantitatively similar microglial depletion, their behavioral outcomes were opposite. These and other discrepancies may be attributable to different microbiota to which the mice are exposed. Microglia are brain-resident immune cells that constantly change in response to their environment, which includes the well-established gut–brain axis (Erny et al., 2015). Therefore, single-cell sequencing of brain pathology-associated microglia in mice housed under different conditions (germ-free versus specific-pathogen free) may reveal different microglia phenotypes between different laboratories and thus explain some discrepancies.

Microglia have long been the Cinderella of the CNS, but there is hope that novel tools emerging in the recent years, such as these used in the current study, will serve as the magic wand that confers on these cells their rightful elevated status.
Sex at Atomic Resolution

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Interspecies fertilization is rare, partly due to species separation enforced at the molecular level. In this issue, Raj et al. now reveal the crystal structures of mollusk egg coat protein, VERL, complexed with cognate sperm protein lysin. Given that VERL is structurally similar to mammalian ZP2, the mechanism elucidating species-specific gamete recognition likely exists in mammals.

To sexually reproduce, life must solve one of many fundamental problems: the egg must allow a foreign cell, a sperm, to penetrate its thick egg coat. The free-spawning marine mollusks, abalones, overlap breeding seasons and habitats yet fertilize species specifically. How is this species-specific gamete recognition achieved?

An abalone egg is coated with a heavily glycosylated, outer protective layer called the vitelline envelope (VE), which is analogous to the zona pellucida (ZP) in mammals. Sperm must penetrate these egg coats—the main block against cross-species fertilization—to reach the egg plasma membrane. The initial sperm-egg recognition was conceptualized as lock-and-key, species-specific binding between sperm proteins and receptors on the egg (Lillie, 1914). The VE receptor for lysin (VERL) and ZP2 are the egg coat proteins that recognize sperm proteins in abalone and mammals, respectively. Abalone sperm lysin, which is named after its VE dissolving activity, was identified as a 16-kDa protein released from the acrosome (Lewis et al., 1982), an organelle at the tip of the sperm head. Lysin creates a hole in the egg VE in a non-enzymatic, species-specific manner (Vacquier et al., 1990). VERL was identified as the VE receptor for lysin, with the surprisingly large molecular weight of ~2 MDa (Swanson and Vacquier, 1997).

Although lysin’s crystal structure has been determined (Shaw et al., 1993), the structural details of VERL and its interaction with lysin have been unknown. The highly glycosylated VERL has been resistant to crystallographic determination, limiting our understanding of the mechanism by which VERL and lysin interact to disrupt the egg VE. In this issue of Cell, Raj et al. (2017) present the first atomic-resolution structures of domain repeats of VERL, separately and in complex with lysin. The study describes the molecular and structural basis of species-specific sperm-egg coat recognition. Interestingly, VERL repeats are structurally similar to a functional domain of mammalian ZP2, despite their sequence divergence and evolutionary distance.

VERL is a rod-like tandem array of 22 VERL repeats (VR1–VR22), with a polymerization module that is conserved in all egg coat proteins, the C-terminal ZP domain (Galindo et al., 2002). VR1 and VR2 are highly variable in sequences, whereas VR3–VR22 have almost identical sequences. The investigators cleverly noticed that the N terminus of VERL is under high evolutionary pressure, similar to mammalian ZP2, the molecular component responsible for sperm recognition in the mammalian cell.