Salman and Libchaber, does fit with a growing appreciation of the advantages of slow-growing or static 'persister' cells in a population[10]. However, the nature of the signals that mediate the thermotactic switch suggests yet another interpretation. Both glycine and aspartate have been implicated in self-attraction of *E. coli* cells leading to a cooperative motile behaviour[7,11]. So the cryophilic switch may promote bacterial self-aggregation to form stress-resistant multicellular communities, or biofilms. Cryophilic taxis before or during bacterial self-aggregation would lead to preferential biofilm formation in regions with a lower temperature, where slower metabolism would provide an additional level of self-protection to the bacterial community.

In the best-studied model for thermotaxis — the nematode *C. elegans* — the thermotaxis set-point is tunable, being defined by previous experience[3]. Nematodes can remember the previous cultivation temperature, with a memory lasting for several hours. Salman and Libchaber provide evidence that, despite an apparently much simpler organization, bacteria display patterns of behaviour that can be similarly sophisticated. And this is likely to be just the tip of the iceberg: much more work is needed to understand the full complexity of how the environment alters bacterial thermotaxis and chemotaxis.

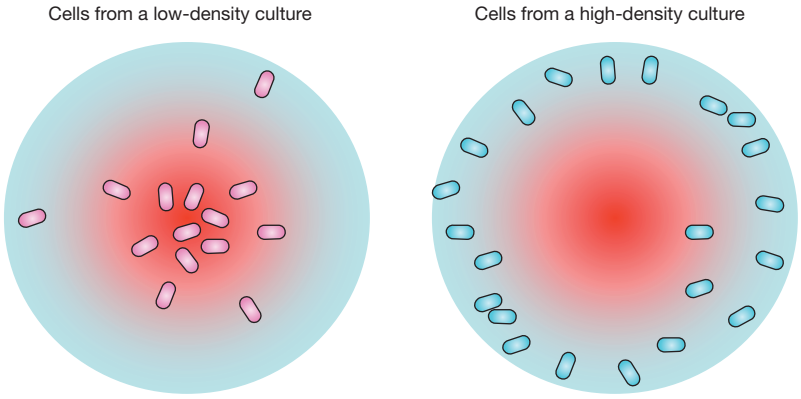

Figure 2 Density-dependent cryophilic switch observed by Salman and Libchaber[4]. *E. coli* cells taken from a low-density culture (left) have low levels of Tsr methylation and accumulate towards a laser-heated region (thermophilic response). For these cells, the dominant receptor Tsr mediates a thermophilic response. By contrast, cells taken from a high-density culture (right) avoid the heated region (cryophilic response). In growing to a high density, these cells have adapted to secreted glycine as well as to aspartate present in the medium, leading to a high level of methylation of both major receptors, accompanied by a sharp rise in the ratio of Tar to Tsr. Methylation renders Tsr temperature insensitive and inverts the temperature response of the now dominant Tar receptors to cryophilic.

COMPETING FINANCIAL INTERESTS
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Neural stem cells: guardians of the brain

Gianvito Martino and Stefano Pluchino

Toll-like receptors participate in the inflammatory response and are now shown to act in neural precursor cells to regulate adult hippocampal neurogenesis. The dialogue between inflammatory components and neural precursor cells might have important consequences for central nervous system homeostasis and repair.

The central nervous system (CNS) has long been viewed as exempt from the effects of the immune system. The brain has physical barriers for protection, and it is now clear that cells in the nervous system respond to inflammation and injury in unique ways. Neural precursor cells (NPCs) — the self-renewing and multipotent cells that reside within major germinal niches of the CNS — are among these cells. On page 1081 of this issue[1], Schwartz and colleagues show that NPCs express two Toll-like receptors (TLRs) and that these receptors control the cells' proliferation and differentiation properties. This suggests that TLR activation on NPCs regulates neurogenesis in response to injury and inflammation.

Seminal work by Peter Medawar in the late 1940s showed that skin homografts transplanted to the brain were well tolerated[2]. Since then, the CNS has been regarded as a privileged site that escapes immune surveillance. This peculiar trait was initially thought to depend solely on the presence of tightly regulated and rather impermeable barriers — the blood-brain and the blood-cerebrospinal fluid barriers — and on the virtual absence of a developed CNS lymphatic system. Since the

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early 1980s, however, increasing evidence has challenged this view by revealing that active cellular mechanisms support the existence of a more complex innate self-maintenance programme known as 'the brain-repair system'[3]. These mechanisms are crucial for promoting tissue healing following inflammatory and/or degenerative damage. For example, neural cells express a negligible amount of major histocompatibility complex (MHC) molecules[4], and blood-borne inflammatory effector cells invading the CNS rapidly undergo apoptosis[5]. Humoral and cellular inflammatory components may also shift function over time and switch from a tissue-damaging mode to a mode that promotes tissue repair. In addition, alternative neuronal pathways can undergo functional activation and promote axonal branching and synaptogenesis to bypass damaged areas[3]. More recently, it has been shown that endogenous NPCs modulate their migratory and differentiation potential in response to inflammatory and degenerative damage to promote tissue repair[6]. It is still controversial whether or not brain repair also takes place as a consequence of the recruitment within the CNS of trans-differentiating stem cells from a different embryonic tissue origin[7] or, in the case of fetomaternal microchimerism, from a different organism[8].

The functional response of NPCs to inflammation has stimulated new avenues of research aimed at identifying the precise relationship between the immune and the nervous systems. The first evidence strongly supporting the concept that NPCs interact with immune cells came from transplantation experiments aimed at using NPCs as therapeutic weapons against CNS inflammation[9,10]. NPCs express immune-relevant molecules, such as cell-adhesion molecules, integrins and chemokine receptors that enable them to functionally interact with an inflamed CNS microenvironment. More recently, it was found that inflammatory signals provided by activated microglia and/or antigen-specific T cells regulate neurogenesis and gliogenesis within germinal CNS areas[11–13].

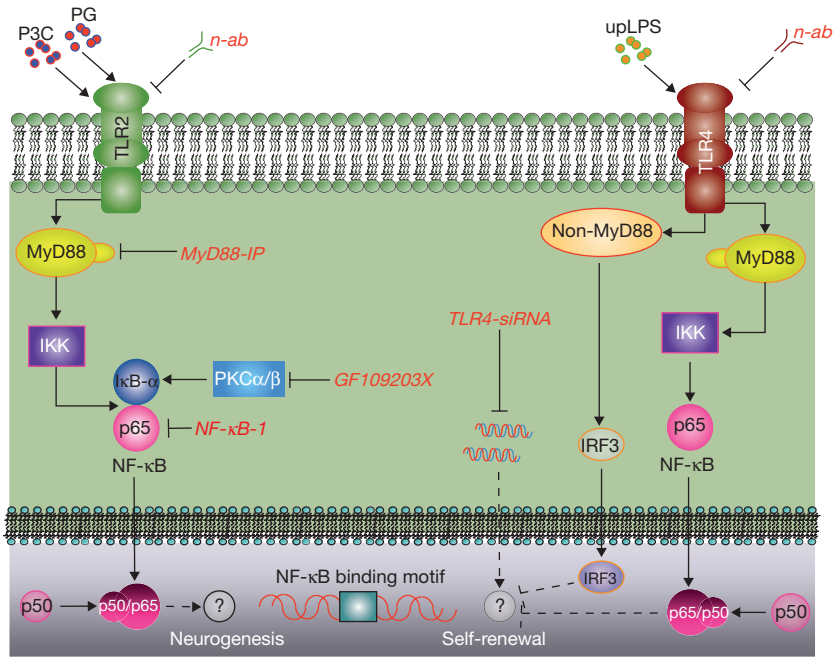

Figure 1 Signalling pathways induced by TLR activation in NPCs. TLR2 activation with the lipopeptide Pam3CysSK$_4$ (P3C) and the peptidoglycan (PG) promotes neuronal differentiation although it does not affect self-renewal. Inhibition of TLR2 signalling at different levels — directly with TLR2 neutralizing antibodies (n-ab) or indirectly with an MyD88-inhibitory peptide (MyD88-IP), a protein kinase C (PKC) α/(inhibitor (GF109203X) or a NF-κB-inhibitor (NF-κB-I) — results in a significant decrease in neuronal differentiation. Activation of TLR4 with ultra-purified lipopolysaccharide (upLPS) inhibits both neuronal differentiation and self-renewal of NPCs. Suppression of TLR4-dependent signalling with either TLR4 n-ab or TLR4 small interfering RNA (TLR4-siRNA) overcomes the inhibition. Stimulation of TLR4 activates both MyD88-dependent and MyD88-independent (acting through phosphorylation of IRF3) pathways. The identification of signals (?) downstream of the nuclear translocation of NF-κB will be required to understand the differential effect of TLR2 and TLR4 on NPC self-renewal and differentiation.

Now, the study from Schwartz and colleagues identifies a novel molecular mechanism by which NPCs might react to inflammatory pathogens[1]. They show that TLR2 and TLR4, which regulate the immune response through the recognition of pathogen-derived molecules or pathogen-associated molecular patterns[14,15], are expressed in NPCs and act as key regulators of adult hippocampal neurogenesis in rodents. The authors observe that, *in vitro*, TLR2 activation with pharmacological activators promotes neuronal differentiation although it does not affect self-renewal. Conversely, inhibition of TLR2 signalling, which normally leads to nuclear factor-κB (NF-κB) activation, results in a significant decrease in neuronal differentiation in parallel with an increase in (astro)glial differentiation (Fig. 1). TLR4 seems to have distinct effects: its activation inhibits both neuronal differentiation and self-renewal of NPCs. Again, suppression of TLR4-dependent signalling overcomes the inhibition triggered by activation of the receptor. The inhibition of both TLR2 and TLR4 results in a predominant effect on TLR4-dependent pathways, a finding that will need further investigation. These *in vitro* experiments are corroborated by *in vivo* observations showing that TLR2-deficient mice have impaired hippocampal neurogenesis, whereas the absence of TLR4 resulted in enhanced NPC proliferation and neuronal differentiation. TLR2 and TLR4 signal through a similar pathway in NPCs. They both activate the intracellular adaptor myeloid differentiation primary response protein 88 (MyD88), which leads to IκB kinase (IKK) phosphorylation and consequently to the nuclear translocation of RelA to form active NF-κB p50–RelA heterodimers.

NF-κB activation is temporally similar in TLR2- and TLR4-stimulated cells, and so one could attribute the specificity of their different effects on neurogenesis to elements downstream of NF-κB, such as other transcription factors that are necessary for regulating NF-κB-mediated gene transcription. For instance, TLR4 activation in NPCs also triggers a MyD88-independent pathway leading to phosphorylation of the interferon regulatory factor (IRF)3 (Fig. 1). Whether this alternative pathway (or IRF3 itself) is responsible for the difference in the downstream effects of TLR4 on neurogenesis remains to be investigated. Finally, from these *in vitro* studies, we cannot exclude at this stage the idea that polyclonal NPCs contain distinct subpopulations of cells expressing only TLR2 or TLR4, each responding differently to activation.

IKK phosphorylation and nuclear translocation of NF-κB is essential for neuronal differentiation despite direct engagement of TLR2 and TLR4. It is therefore tempting to suggest that other inflammatory molecules aside from TLR ligands are capable of activating NF-κB and also regulate NPC biological properties *in vivo*. Inflammatory cytokines (for example, tumour necrosis factor α, interleukin 1 and leukaemia inhibitory factor) and neurotrophic growth factors (for example, fibroblast growth factor-II, epidermal growth factor, platelet-derived growth factor, insulin-like growth factor and vascular-endothelial growth factor)[14,15] are likely candidates because some of their receptors[6,10] have already been found to be expressed in NPCs.

TLR2 and TLR4 orchestrate proliferation and differentiation of NPCs. Pulse-chase experiments reveal that most TLR-expressing NPCs are doublecortin $(DCX)^+$ fast-cycling progenitors. Although it needs to be corroborated further, the fact that fast-proliferating NPCs react to TLR activation by undergoing terminal differentiation into neurons or glia can be interpreted as preliminary evidence for a flexible brain-defence programme that uses specific subtypes of NPCs (for example, regionally specialized NPCs) to limit the extent of CNS damage. Although (astro)gliogenesis contributes to scar formation — a pathophysiological phenomenon aimed at limiting tissue damage — neurogenesis contributes to the replacement of damaged cells (Fig. 2).

The brain has to protect itself from injuries more than any other organ in the body, and the ways in which this can be accomplished are still being elucidated. The fact that NPCs within major germinal niches adapt their proliferative and differentiation capacities upon sensing invading inflammatory agents (possibly through TLRs) is one of the most fascinating areas currently under active study. Understanding the proliferation and differentiation capacities of NPCs in response to inflammatory signals may also be useful for the medical treatment of acute and chronic CNS inflammatory diseases by cell transplantation. In these disorders, it has already been shown that NPCs not only replace damaged cells but also promote neuroprotection through the release of immunomodulatory molecules[6,9,10]. From now on, NPCs may also be considered as *bona fide* immune-relevant cells of the brain. Is this a relic of an early developmental mechanism that regulates

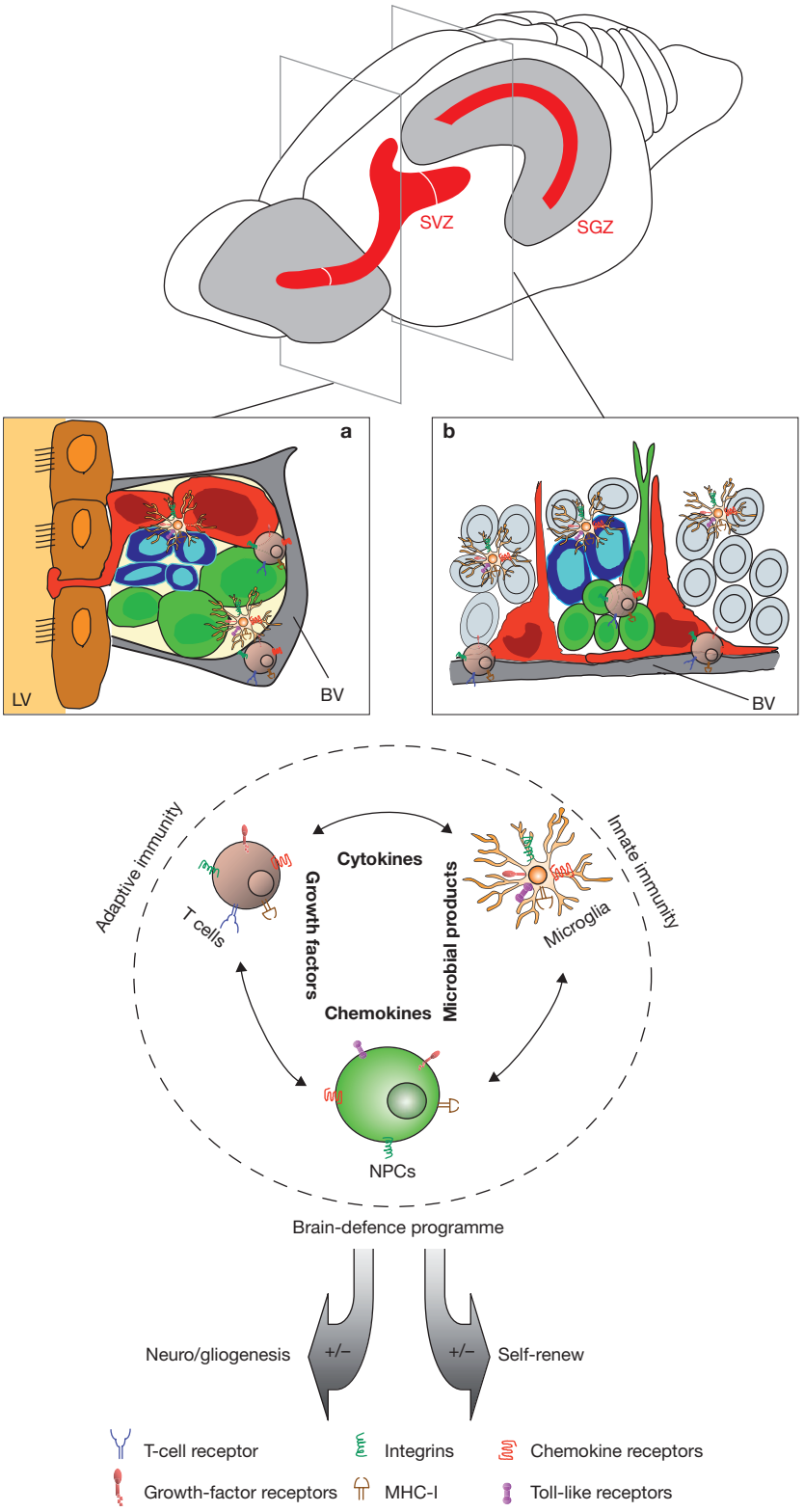

Figure 2 A 'brain-defence programme'. (**a**) NPCs in the subventricular zone (SVZ) of the lateral ventricle (LV) (**a**) and in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus (**b**) reside in intimate contact with blood microvessels (BV). (**b**) NPCs produce cytokines, chemokines and growth factors and express chemokine, cytokine and growth factor receptors as well as MHC class I molecules and TLRs. This immune signature allows them to react to inflammation through a cross-talk with immune-competent cells (for example, CNS-resident microglia and blood-borne CNS-invading T cells). The net effect of this cross-talk is the activation of a 'brain-defence programme' within which NPCs adapt their self-renewal and differentiation potential to efficiently protect the CNS from invading agents.

tissue formation and regeneration in the embryo or is it merely a question of cells that serendipitously express molecules with an immune-relevant function? NPCs constitutively express not only TLR2 and TLR4, but also all other TLRs. Because TLRs have evolved not only to recognize a wide array of invading agents (for example, microbial products from bacterial, fungal and viral pathogens) but also to detect injury and initiate tissue repair[15], we favour the hypothesis that NPCs have also evolved to defend the brain from danger signals (Fig. 2). Although, at first glance, the immune and the neural stem-cell systems seem quite separate in their aims and operations, deeper reflection leads to the realization that interactions between the two systems, either protective[13] or detrimental[11], might have important consequences for evolution and health.

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