Review

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Effects of inflammation on stem cells: together they strive?

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Abstract

Inflammation entails a complex set of defense mechanisms acting in concert to restore the homeostatic balance in organisms after damage or pathogen invasion. This immune response consists of the activity of various immune cells in a highly complex manner. Inflammation is a double-edged sword as it is reported to have both detrimental and beneficial consequences. In this review, we discuss the effects of inflammation on stem cell activity, focusing primarily on neural stem/progenitor cells in mammals and zebrafish. We also give a brief overview of the effects of inflammation on other stem cell compartments, exemplifying the positive and negative role of inflammation on stemness. The majority of the chronic diseases involve an unremitting phase of inflammation due to improper resolution of the initial pro-inflammatory response that impinges on the stem cell behavior. Thus, understanding the mechanisms of crosstalk between the inflammatory milieu and tissue-resident stem cells is an important basis for clinical efforts. Not only is it important to understand the effect of inflammation on stem cell activity for further defining the etiology of the diseases, but also better mechanistic understanding is essential to design regenerative therapies that aim at micromanipulating the inflammatory milieu to offset the negative effects and maximize the beneficial outcomes.

Keywords disease; inflammation; neural stem cell; proliferation; regeneration
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See the Glossary for abbreviations used in this article.

Introduction

Etymologically, inflammation (*in* + *flammō*) denotes a metaphoric blaze caricaturized as sumptuous mythological creatures. A tale about Phoenix for instance narrates the fire devouring its body into ashes, from which a new bird arises. Thus, the state of torrid heat in the myths is both devastating and revitalizing. In biological systems, the situation may be quite similar. Inflammation in organisms points to a non-homeostatic response of the vascular tissues to various stimuli such as pathogens, injury or xenobiotics [1]. During evolution, inflammation was developed as a mechanism of self-defense and survival pertaining to both beneficial and detrimental outcomes depending on the timing, cell types involved and the severity of the insult to the tissue. Generically, the effect of inflammation on tissues is therefore closely linked to how inflammation is initiated, maintained and resolved (Fig 1).

Different phases of the inflammatory reaction are well defined [1]. Acute period is the initial phase where the earliest reactions to the insult set on with the help of resident immune cells such as macrophages and dendritic cells [2]. Secretion of pro-inflammatory cytokines such as IL-8 and TNF-α initiates a cascade of molecular events in neutrophils, fibroblasts and endothelial cells: Macrophages are recruited to the site, and the complement system is concomitantly activated [3]. Acute inflammation contains an ensuing phase of active resolution by anti-inflammatory agents such as steroids, IL-10, nitric oxide, TGF-β or regulatory T cells [3]. During the acute inflammation phase, the exudative component from the blood plasma-containing immunoglobulins or fibrins flushes into the inflamed site causing edema. This tissue swelling is relinquished by the lymphatic system where antigens are recognized by the T and B cells of the adaptive immune system, which is a recent evolutionary invention in vertebrates [4]. Acuity of the reaction can be succeeded by chronicity based on the resolution dynamics of the inflammatory response. Chronic inflammation is hazardous to tissues, as exemplified by its involvement in the onset or progression of neurodegenerative disorders, cardiovascular diseases, autoimmunity, cancer and various metabolic diseases [5]. Therefore, the regulation of inflammatory response is of utmost importance for restoration of tissue integrity and homeostasis.

In this review, we will focus specifically on the crosstalk between inflammation and stem cells. Various tissue stem cells react differently to inflammation, and the interplay between inflammation and stem cell activity is an immense research field. Here, we will mainly concentrate on the relationship between neural stem cells and inflammation, molecules known to be mediating this reciprocity and the effect of the inflammatory milieu on the ability to regenerate tissue.

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Glossary

CCR2	C-C chemokine receptor type-2
CNS	central nervous system
Cr	complement receptor
Cystlr1	cysteinyl leukotriene receptor 1
EAE	experimental autoimmune encephalomyelitis
FasL	Fas ligand; tumor necrosis factor superfamily member 6
Gata3	GATA family zinc-finger transcription factor 3
IFN-γ	interferon gamma
IGF-1	insulin growth factor-1
IKKβ	nuclear factor NFκB inhibitor kinase beta
IL	interleukin
JAK	janus kinase
JNK	c-Jun N-terminal kinase
LTC4	leukotriene C4
MCP-1	monocyte chemoattractant protein-1
MSC	mesenchymal stem cell
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NSPC	neural stem/progenitor cell
SOCS3	suppressor of cytokine signaling 3
STAT3	signal transducer and activator of transcription 3
TGF-β	transforming growth factor beta
TLR	toll-like receptor
TNF-α	tumor necrosis factor alpha

Tissue microenvironment and stem cells during inflammation

Inflammation in a tissue is profoundly affecting the homeostatic measures thereof and thus has a strong impact on nearby cells. In adult organisms, tissues contain resident niches of stem cells that are specialized to form new cells contingent with their surrounding [6]. Stem cell activity is regulated by intrinsic mechanisms and extrinsic cues that emanate from the niche environment, and inflammation is one of them. Inflammation was documented to be negatively affecting tissue restoration in various systems [7–10]. Therefore, understanding the crosstalk between inflammation and stem cells is important to elucidate the mechanisms of how stem cells respond to tissue damage. Additionally, tweaking the effects of inflammation on stem cell behavior will constitute a possible intervention point for regenerative therapies.

Inflammation was shown to regulate several stem cell niches non-exhaustively including mesenchymal stem cells (MSCs), intestinal stem cells (ISSs), satellite cells or myogenic precursors of the muscle (MPCs), liver progenitor cells (LPCs), epidermal stem cells and neural stem/progenitor cells (NSPCs). In this review, we will mainly focus on NSPCs and their regulation by inflammation.

Neural stem progenitor cells

Neural stem/progenitor cells (NSPC) are multipotent cells that generate the cell types of the nervous system: neurons, glia and oligodendrocytes [11]. In vertebrate development, multipotent neuroepithelial cells progressively differentiate into cell types of the nervous system, while sparing undifferentiated cells that maintain glial identity and act as resident stem/progenitor cells of the adult nervous system [12–15]. Stem cell niches in vertebrates show diverse localizations. In adult mammalian brain, neurogenic stem cell niches are restricted to the telencephalon [13], where neural stem cells are found in the subventricular zone (SVZ) of the lateral ventricles and in the subgranular zone of the dentate gyrus in the hippocampus (SGZ) [12,16]. Non-mammalian vertebrates contain a more widespread activity and distribution of stem cells in their brains. Zebrafish, for instance, possesses sixteen different stem cell niches that are distributed along the entire rostro-caudal brain axis [17]. As a result, the regulation of the neural stem cell activity in vertebrates is a highly complex interplay between intrinsic and extrinsic cues [18–20].

Nervous system contains cells of immune system origin, called microglia—the resident macrophages [21,22]. These cells have various functions such as regulating developmental synaptogenesis [23], homeostatic surveillance of the nervous tissue throughout life [24], managing neuronal cell death [25] and eliciting an innate immunity reaction upon various forms of pathogenesis [26]. Microglia are main modulators of the inflammatory milieu in the nervous system [25,27–29]. Homeostatically, microglia are ramified in shape to fulfill its surveillance function. Upon pathology, pathogen invasion or insults, they retract the protrusions, become amoeboid, increase their migratory behavior and secrete molecules to retract peripheral immune cells [30]. In mammals, the early phase of the inflammation entails subsequent infiltration of neutrophils, microglia/macrophages and T cells, while the later phase is an extended prevalence of various cell types and consequent resolution of inflammation over long periods of time (reviewed in [31]). In regenerating organisms such as zebrafish or newt, initial events of acute inflammation manifest similar to mammals, while prolonged inflammation response is not observed [32,33]. In regenerating organisms, neural stem/progenitor cells are also activated even in inflammation conditions and fulfill regenerative neurogenesis—as a striking difference to mammalian tissues [32,34–36]. Therefore, the mutual interaction between inflammation and neural stem cells has emerged as an important research area not only because inflammation might exert different effects on stem cells in different species, but also because a majority of neurological disorders or neurodegenerative diseases in humans involve varying levels of inflammation in the neural microenvironment [27,37]. Hypothetically, what we learn from regenerating organisms in terms of the interplay between inflammation and stem cells could help design regenerative therapies.

First studies elaborating on the instructive crosstalk of inflammation on neural stem cells showed that in a mouse model of multiple sclerosis and experimental autoimmune encephalomyelitis (EAE), transplantation of non-inflamed neurospheres ameliorated the demyelination phenotype in various regions of the brain, suggesting that inflammation impairs the neurophysiological properties of neural stem cells and their descendants, such as oligodendrocytes [38–40]. The exact role of inflammation on neural stem/progenitor cells (NSPCs) has been controversial, because both detrimental and beneficial effects have been assigned to inflammation [31,41], suggesting that the interactions between immune cells and NSPCs are context dependent. Interestingly, a recent study in adult mouse brain showed that neural stem cells can improve the neuronal survival at the host by transforming microglia from a harmful to a neuroprotective phenotype [42].

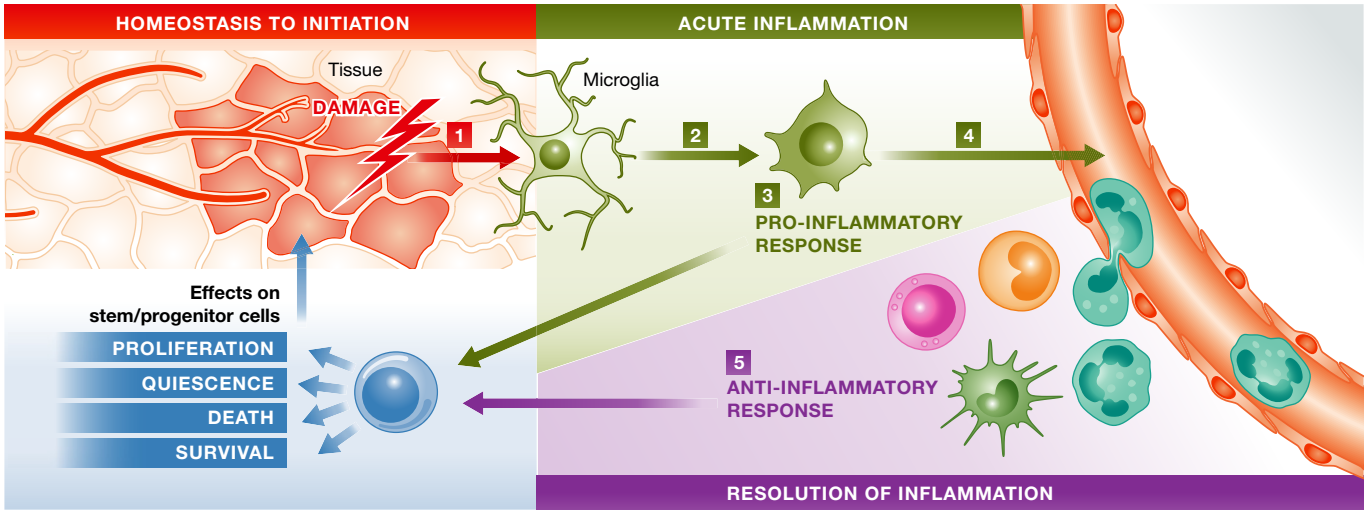

Figure 1. A simplified generic scheme of initiation and resolution of inflammation in six steps.
1) A tissue when compromised during its homeostatic state initiates inflammation programs, through damage cues (such as intracellular content, apoptosis and cytokines). 2) Breach of homeostasis triggers the morphological and functional transformation of the resident macrophages (green). 3) Acute inflammation is initiated upon secretion of several pro-inflammatory cytokines and chemokines such as TNF-α, IL-1β, IL-6 and MCP-1. Complement system is also activated. 4) This process calls for peripheral immune cells, and recruited immune cells potentiate the inflammation by secreting more pro-inflammatory factors. 5) The immune cells also partake in active resolution of inflammation through secretion of anti-inflammatory factors such as IL-4, IL-10, C5a, IFN-γ, TGF-β and NO. A stem/progenitor cell undergoes the influence of the dynamic inflammatory milieu. The final outcome on the tissue manifests depending on the context.

Negative role of inflammation on neural stem cells

Several studies indicate that inflammation exerts a negative regulation of NSPC proliferation [43–45] (Fig 2). In fetal mouse, maternal inflammation reduces ventricular cell proliferation in developing brain [46]. In a medial cerebral arterial occlusion model of mice, chronic immunosuppression was shown to reduce the activation of macrophages, which increased the number of newborn neurons in mouse hippocampus [47]. TNFR1 null mice showed significantly elevated levels of cell proliferation in the dentate gyrus and increased number of newborn neurons in the granular zone [44], suggesting that the pro-inflammatory cytokine TNF-α hampers NPSC activity. NSPCs were shown to express the receptors for proinflammatory cytokine IFN-γ, which is secreted predominantly by cytotoxic T cells and reduces the proliferative ability of NSPCs through STAT1 signaling [48,49]. NSPCs of the hippocampus also express the complement receptor 2 (Cr2) that binds to C3d and INF-α. Cr2 null mouse showed increased basal neurogenesis in adult hippocampus [50], suggesting that complement system might suppress neural stem cell activity. In the adult subventricular zone (SVZ) of the mouse brain, anti-inflammatory cytokine IL-10 keeps NSPCs in undifferentiated proliferative state at the expense of neurogenic differentiation [51], an observation that could partially explain why regenerative neurogenesis does not take place after injuries in rodent brains while SVZ cells increase their proliferation as a reaction to damage [48]. Leukotrienes were implicated in suppression of NPSC activity in rodents, because blockage of cysteinyl leukotriene receptor 1 (CYSTLR1) using the antagonist montelukast enhanced NSPC proliferation in cultured rat neurospheres [52], suggesting that lipid modifiers of inflammation negatively regulate NSPCs, possibly due to post-inflammatory brain damage through upregulation of TNF-α and IL-1β [53]. Consistent with this finding, in Parkinson's disease (PD) patients and MPTP-induced PD model in mice, $CD8^+$ and $CD4^+$ T cells were shown to contribute to dopaminergic toxicity through expression of FasL and exacerbate the pathology [54]. Inflammation was also suggested to cause NSPC dysfunction and lead to neurodegenerative disorders [55]. In an experimental autoimmune encephalomyelitis model, inflammation results in reduced neuroblast generation and alleviated olfactory bulb neurogenesis, a phenotype reminiscent of multiple sclerosis (MS) patients [56]. One reason of impaired neurogenesis in such an inflammatory condition was suggested to be the hampered cell cycle progression of NSPC and reduced migratory behavior of neuroblasts [57].

Positive role of inflammation on neural stem cells

Neural stem/progenitor cells were also shown to be positively affected by inflammatory conditions. In several disease models of mice, grafting efficiency of transplanted NSPCs was shown to be promoted by the inflammation milieu [58,59]. In hippocampal slice cultures, grafted NSPCs migrate to the site of injury upon presentation of cytokines in the tissue and activation of the CCR2 signal cascade [60]. In addition, monocyte chemoattractant protein-1 (MCP-1) knockout mice display deficient NSPC migration *in vivo* and in neurosphere cultures [60,61]. NSPCs require stromal-cell-derived inflammatory chemoattractant SDF1/CXCR4 signaling to migrate to the infracted area of the brain upon lesions or neurodegenerative conditions [62,63]. NSPCs also increase proliferation upon inflammation. After an immune response upon bacterial enterotoxins, adult mice increase progenitor cell proliferation in the hippocampus [64]. In postnatal rats, intrauterine infection using *E. coli* increases NSPC proliferation at developmental stage P7 by increasing the expression levels of BDNF, TrkB, p-Akt and survivin

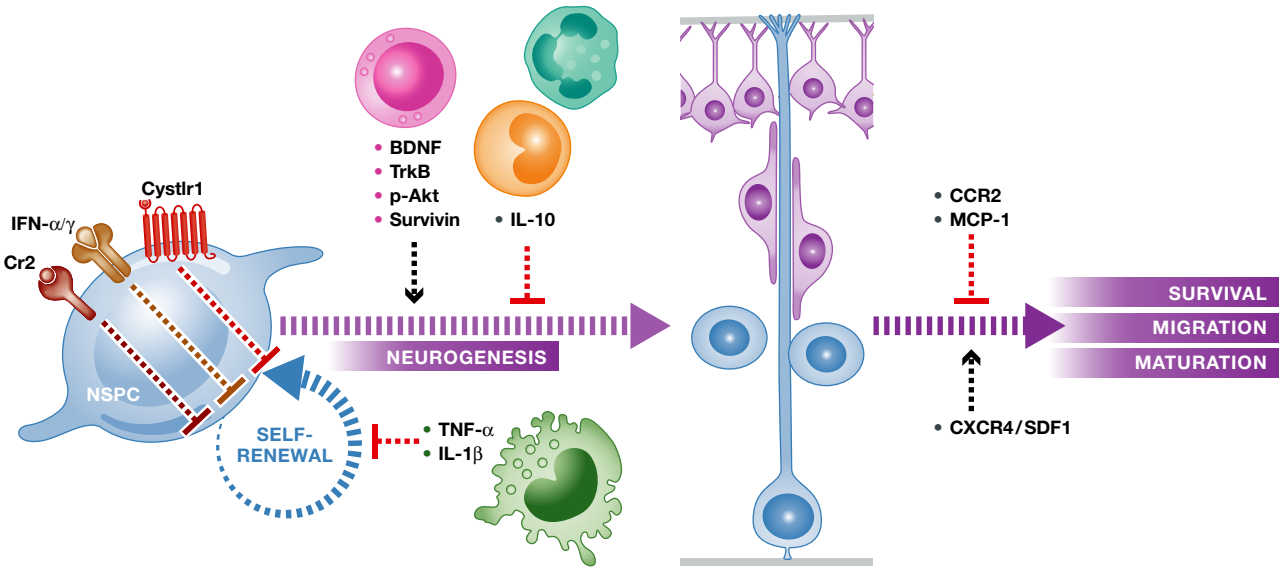

Figure 2. Mammalian neural stem/progenitor cells are generally negatively affected by inflammation.
Signaling cascades through Cystlr1, IFN-α and IFN-γ receptors and Cr2, which are expressed by neural stem/progenitor cells (orange, NSPC), as well as macrophage-derived TNF-α and IL-1β, suppress self-renewal. IL-10 secreted by monocytes blocks neuronal differentiation, while CCR2 and MCP-1 hamper neuronal survival, migration and maturation. T cells secrete BDNF to positively regulate neurogenesis from stem cells through its receptor TrkB and intracellular cascades of phosphorylated Akt and survivin. CXCR4/SDF1 chemokine signaling is required for directed migration of neural stem/progenitor cells and neurons.

[65]. *In vitro* studies also suggest that inflammatory signals such as TNF-α or IL-1β could trigger proliferation of NSPCs through NFκB and JNK signaling pathways, respectively [61,62]. Interestingly, NPSCs were also shown to exert immunomodulatory effects in a way to promote NSPC activity. In a chemically induced demyelination assay in rats, transplanted NSPCs inhibited the proliferation and activation of T lymphocytes through peripheral immunosuppression, which resulted in attenuated experimental autoimmune encephalomyelitis [66]. In a mouse model of chronic CNS inflammation, systemically injected NSPCs start expressing antigens of immune cells such as α4 subunit of integrin and various chemokine receptors. These proteins were shown to be required for proliferation and long-term persistence of those stem cells *in vivo* through induction of selective apoptosis of CNS-infiltrating pro-inflammatory Th1 but not anti-inflammatory Th2 cells [65]. This effect is mediated through inhibiting IL-2-mediated phosphorylation of JAK3 in Th1 lymphocytes [44], suggesting that NSPCs might hijack molecular programs of immune cells to positively favor their own proliferation and survival. In a mouse model of EAE, chronic inflammation was suggested to impose a fate switch in spinal cord-derived neural progenitor cells as they transit from being gliogenic to neurogenic [67]. Several studies also showed that inflammatory cells exert a protective effect on the neural stem cell function through helping the resolution of the acute inflammation in an orchestrated manner [68,69]. Thus, taken together, documented detrimental and beneficial effects of inflammation clearly demonstrate a context- and time-dependent contribution of inflammatory response to stem cell activity (Table 1). The effect of inflammation on NSPCs is binary as it can either support or inhibit proliferation, survival or differentiation depending on the onset of the inflammation, the cell types involved in the process and the chronicity of the response [58,70]. Therefore, studies aiming to determine the correct time of intervention to inflammatory environment will provide an important insight for designing therapeutic clinical strategies which could be customized to individual stem cell niches.

Inflammation in zebrafish nervous system

In zebrafish, several studies showed that chemokine signaling is required for activity of NSPCs at different locations of the nervous system [71–74], suggesting that an immune-neural crosstalk similar to that of mammals might exist in non-mammalian vertebrates (Fig 3). In adult zebrafish brain, acute inflammation through leukotriene C4 (LTC4) binding to its receptor Cystlr1 is sufficient and necessary for activating NSPCs and priming them for regenerative neurogenesis [32]. LTC4 seems not to be required for homeostatic NSPC function, but it is necessary for injury-activated proliferation response of the radial glial cells [32] that are the neurogenic progenitors in the adult zebrafish brain [75,76]. Upon cerebroventricular microinjection into the brain fluid [77,78], LTC4 is also sufficient to induce a regeneration-specific molecular program of zebrafish telencephalon that includes the injury-induced activity of the zinc-finger transcription factor *gata3* [35]. *gata3* is not expressed in the homeostatic NSPCs of the adult zebrafish telencephalon but is induced after injury and is required for regeneration of lost neurons as *gata3* knockdown inhibits the reactive proliferation response of the NSPCs [35]. In case of sterile inflammation using pathogenic cell wall extract or LTC4 itself, *gata3* expression can be induced [32]. Furthermore, partial immunosuppression using dexamethasone significantly reduces the reactivity of NSPCs to injury and suppresses the induction of *gata3* expression in NSPCs [32],

Table 1. An overview of the effects of inflammatory cues on various stem cell niches.

Stem cell niche	Model	Cytokine/chemokine signaling involved	Effect on stem cell proliferation, migration or engraftment	References
Neural stem/progenitor cell	Rodent	TNF-α	–	[44,114,115]
		IFN-γ	–	[48,49]
		C3d, IFN-α	–	[50]
		LTC4	–	[52]
		IL-1β	–	[53]
		IL-2	–	[44,65]
		CCR2	+	[60,61]
		SDF1	+	[63,138]
		IL-10	+	[51]
	Zebrafish	LTC4	+	[32]
		SDF1	+	[71]
		Cxcr5	+	[72]
Satellite cells	Rodent	CX3CR1, IL-10, CCL2	+	[86]
		TNF-α	–	[112,113]
Pancreatic β-cell	Rodent	IL-1β, IL-6, TNF-α, CXCL8	–	[88,139]
		TGF-β	+	[93]
Intestinal stem cells	Rodent	IL-6, epimorphin	+	[94]
		IL-17	+	[95,98]
Liver progenitor cell	Rodent	IL-22	+	[102]
		C3, TNF-α, IL-6	+	[103,104,120,121]
		IFN-γ	+	[105]
Hair stem cell	Rodent	TNF-α, MCP-1	–	[106,107]

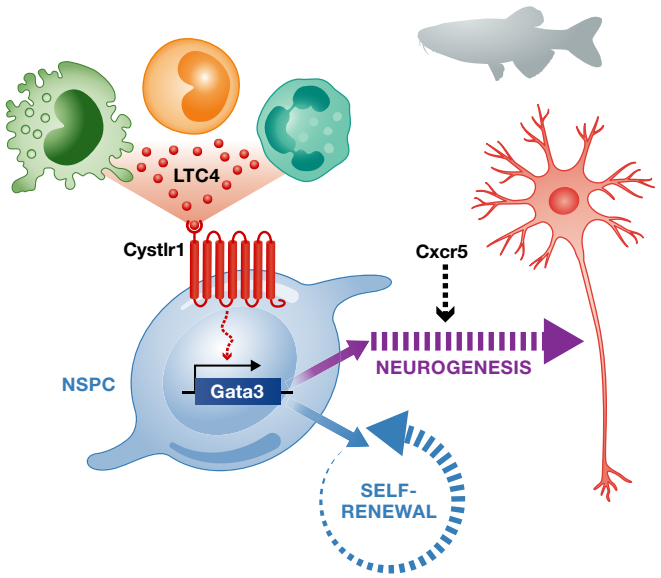

Figure 3. Inflammation promotes neurogenesis and regeneration in zebrafish.
In zebrafish, inflammation elicited by immune cells leads to secretion of leukotriene C4 (LTC4, green circles), which bind to its receptor Cystlr1 on neural stem/progenitor cell (NSPC). LTC4/Cystlr1 signaling leads to transcriptional activation of zinc-finger transcription factor Gata3, which is a key molecule that promotes proliferation and regenerative neurogenesis. Chemokine signaling through Cxcr5 is also required for differentiation of proliferating NSPCs into neurons.

demonstrating that acute inflammation is positively affecting the NSPCs in zebrafish brain and is involved in activating molecular programs that enable efficient tissue regeneration, which is poorly manifested in mammals.

Effects of inflammation on stem cells outside the nervous system

The binary role of inflammation in neural stem/progenitor cells also holds true for other stem cell niches. In this section, we will give brief information on the documented effects of inflammation in other stem cell niches outside the nervous system.

Mesenchymal stem cells are multipotent stromal cells that are found in a variety of tissues such as bone marrow, adipose, umbilical cord and muscle. They can differentiate into bone, cartilage and fat cells. *In vitro* studies showed that MSCs react to the inflammatory milieu. IL-1β-conditioned macrophage medium converts adipose-derived MSCs to smooth muscle cells through a prostaglandin F(2a)-mediated mechanism [79]. In an experimental allergic encephalomyelitis model of CD70-transgenic mice, endogenous MSCs were shown to be mobilized dependent on IFN-γ [8]. In another study using a mouse model of liver fibrosis, the regenerative role of MSCs was revoked upon immunosuppression with the steroid dexamethasone [80]. MSCs also prevent allorecognition and impede macrophage function to modulate different immune

phenotypes and cell fate decisions [81], indicating that inflammation orchestrates patterning of the local tissue and its restoration. One example to this phenomenon is seen in satellite cells, which are the resident stem cells of the adult skeletal muscle and give rise to myofibers. Monocytes/macrophages play an intricate role in regulating proliferation and differentiation capacities of satellite cells in muscle tissue [9,82]. Macrophages that are co-injected with myoblasts into injured skeletal muscle led to a significantly improved survival as well as expansion and migration to the dystrophic muscle [83]. Myogenic precursor cells crosstalk with monocytes/macrophages to recruit them to the site of injury in order to elicit a chemotactic response, which in turn favors muscle growth and fiber reconstitution [84,85]. This communication is established through chemokine and growth factor signaling such as CX3CR1, IL-10, CCL2/MCP-1 and IGF-1, suggesting that satellite cell behavior is licensed by inflammatory cues secreted by monocytes/macrophages [86].

The role of the inflammatory milieu in generating a micropatterning environment can also be observed in other organs, such as the pancreas. Elevated release of several pro-inflammatory chemokines and cytokines including IL-1β, IL-6, TNF-α and CXCL8 from the macrophages accumulated around the adipocytes results in activation of stress-induced kinases IKKβ and JNK [87,88] and initiates a signaling cascade involving NFκB and NLRP3 in β-cells [5,89]. This signaling, in turn, activates FAS ligand on the surface of β-cells, which consequently undergo apoptosis [90], suggesting a negative effect of inflammation in pancreas. Pathogen-related inflammation through TLR4/TLR9 signaling has also been shown to induce β-cell death and insulin resistance through induction of pro-inflammatory cytokines by M1 macrophages [91]. Several clinical studies aiming to block pro-inflammatory signaling have been designed to treat T2D [92], suggesting that inflammation has a profound effect on the progression of metabolic diseases. Interestingly, a recent study showed that TGF-β signaling is required for baseline β-cell proliferation by promoting the overall mass of β-cells [93], suggesting that homeostatic and pathological inflammatory state in pancreas might have different effects on progenitor cell proliferation and tissue homeostasis.

Inflammation has been described to play a crucial role in proliferation of intestinal progenitors. Upon damage, IL-6 is secreted by the intestinal myofibroblasts and dendritic cells leading to inflammation and increased proliferation of the crypt cells through epimorphin signaling [94]. IL-6 mediates STAT3 activation through SOCS3, which is required for bringing back the injury-induced crypt hyperproliferation to constitutive levels [10]. The proliferation of crypt epithelium is also regulated by the cytokine IL-17 secreted by T-helper lymphocytes in the intestine [95]. Similar to what leukocytes and other monocytes do, paneth cells, the niche-organizing secretory epithelial cells located at the apex of the crypts [96], secrete proteolytic enzymes and cytokines such as alpha-defensin, NOD2, and TNF-α into the lumen [7], suggesting that modulation of local inflammatory milieu in the intestines is important for stem cell function. In a recent study, it was shown that after intestinal tissue damage, the soluble IL-22 receptor (IL-22BP) was downregulated and thereafter its ligand IL-22 remained in excess in the surrounding environment. For the repair of the intestine, this is a crucial step, but in uncontrolled conditions, during the recovery phase, excess of IL-22 promoted tumor development [97]. In another study, by using a mouse model of colorectal tumorigenesis, it was shown that IL-23 signaling promotes tumor growth and initiates an IL-17-dependent neoplastic response [98]. A recent study identified STAT5 as a factor mitigating the effects of inflammation, namely reduced LGR5-positive intestinal epithelial stem cell proliferation and their regenerative capacity [99], suggesting context-dependent effects of inflammation on intestinal stem cells.

A well-known example of the supportive effect of inflammation in stem cell proliferation is seen in liver, which contains resident stem cells that generate a transient niche of precursor cells called liver progenitor cells (LPC) [100]. Macrophages and inflammatory response are potent determinants of liver progenitor cell (LPC) expansion [101]. Recent findings suggest that IL-22 produced by inflammatory cells promotes LPC proliferation via STAT3 [102]. TNF-α secreted from resident macrophages upon liver damage or pathology is required for the proliferation of liver progenitor cells through binding to TNFR1 [103]. Pro-inflammatory complement system signaling is also required for LPC proliferation. C3-null mice show impaired liver regeneration due to attenuated production of TNF-α and IL-6, which induces NFκB/STAT3-dependent priming of the hepatocytes [104]. A second wave of inflammatory signaling is initiated by cytotoxic T cells that secrete IFN-γ, which induces LPC proliferation [105]. Thus, the inflammatory milieu in liver is necessary for stem cell activity during growth and regeneration.

Finally, a clear negative effect of inflammation is seen in hair follicle stem cells. Inflammation has been shown to negatively regulate epidermal stem cell activity in keratin-15/CD34-positive hair follicle cells [106]. In a mouse model of permanent hair loss, immunoprivileged hair follicle sac shows elevated levels of inflammation with increased TNF-α and MCP-1 upon macrophage and dendritic cell invasion, whereas immunosuppression rescues the normal physiology of the stem cells [107]. Several chronic inflammatory states compromise the function of the hair stem cell niche through modulation of interferon-inducible cytokine expression [108], suggesting that inflammation negatively affects epidermal stem cell activity.

Collectively, inflammation entails a plethora of factors acting in concert in a highly context-dependent manner to regulate the behavior of various stem cell compartments. One practical conclusion emanating from these studies is that besides alleviating negative effects in a given tissue, systemic modulation of inflammation will certainly have other—possibly unwanted—collateral effects in other tissues and stem cells. Given that most age-related diseases manifest concomitantly, clinical therapies aiming at certain diseases should consider either local modulation of immune response or should take into account the effects in other stem cell niches. A more thorough understanding of spatiotemporal dynamics of individual inflammatory cells and stem cell compartments is likely to improve clinical practice as well as efforts toward regenerative therapies.

Inflammation as a regulator of stem cell activity underlying the regenerative capacity

Regeneration is a mechanism that restores lost cells or tissues analogous to the original forms of the precedent structures [109]. The capacity of regeneration differs widely among animals. In phylogeny, regeneration capacity tends to decrease or become more

restricted [110]. Inflammation is generally believed to be a by-product of damage or pathology, and it has been considered to impair tissue regeneration in vertebrates. For instance, TNF-α was shown to impair repair in liver [111], muscle [112,113] and nervous system [114,115]. Presence of inflammation was suggested to counteract the regenerative capacity in vertebrates [116–118]. Thus, regenerative therapies generally aimed to block inflammation for tissue restoration to take place. However, there is a growing body of evidence for positive regulation of regenerative capacity by inflammation in different tissues due to beneficial effects of the early inflammatory response. Hydrogen peroxide as a stable reactive oxygen species (ROS) is necessary for mounting a regeneration program via recruitment of leukocytes to the injured site in zebrafish [119]. TNF-α, IL-6 and complement system are required for regeneration of murine liver by the activation of liver progenitor cells [103,120,121]. Anti-inflammatory macrophages and their cytokine secretome promote muscle precursor cell proliferation and myogenesis [113] in part by CCR2 and IGF-1 signaling [122,123]. During zebrafish fin regeneration, ablation of macrophages impairs regenerative outgrowth through reduced resolution of inflammation [36,124]. After optic nerve crush, sterile inflammation enhances axonal regeneration in mice [125,126]. T-cell activity can protect nervous system from secondary damage after axotomy [127]. Acute inflammation in adult zebrafish brain through LTC4/Cystlr1 signaling initiates reactive proliferation of NSPCs and activates injury-induced molecular programs including *gata3*, which enables regenerative neurogenesis [32,35].

Inflammation has also been associated with various disease conditions, such as metabolic disorders, progressive neurodegeneration and cancer [128]. In all these conditions, rampant or elevated inflammation plays a role in either exacerbating the pathophysiology or eliciting the onset of the phenotypes. Regenerative therapies to circumvent the disease state largely aim to either supply cells externally or activate the endogenous stem cells of the patient to replenish the lost cell types. In both cases, the inflammatory milieu and its crosstalk to stem cells are important parameters to consider. Several studies addressed the interaction between inflammation and disease states in different contexts.

Specifically in the nervous system, non-resolving inflammation is associated with nervous system pathologies [129,130]. Macrophages—the resident immune cells of the CNS—switch to production of pro-inflammatory cytokines and chemokines (e.g. TNF-α, IL-1β and TGF-β) following pathogen invasion or damage [55]. This acute response impinges on neuronal viability by elevating the reactive oxygen species and subsequently causing apoptosis in neurons. When the acute inflammation is resolved, anti-apoptotic factors start to be expressed leading to increased neuronal survival [55]. In neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS), formation of non-physiological protein aggregates exacerbates the inflammation, which in turn leads to reduced NSPC activity despite neuronal death [55]. In AD, amyloid plaques recruit macrophages [131] and lead to elevated levels of pro-inflammatory cytokines and astrogliogenesis [132], which may lead to neuronal death [133]. In PD, microglia engulf extracellular α-synuclein aggregates and induce production of neurotoxic reactive oxygen species (ROS) [134], which potentiates the recruitment of $CD4^+$ T cells and expression of pro-apoptotic FasL in neurons [54].

Sidebar A: In need of answers

(i) What are the inflammatory factors affecting the stem cell activity?
(ii) What is the underlying reason why inflammation affects stem cell behavior differently in different tissues?
(iii) What are the molecular signaling cascades inflammation initiates in stem cells?
(iv) What is the relationship of inflammation with regeneration?
(v) Can regeneration be activated in mammals via immunomodulation?
(vi) What are the points of intervention to tweak the inflammation and increase the beneficial outcomes?
(vii) Can we learn from regenerating organisms how inflammation enables tissue restoration?
(viii) Can inflammation be harnessed for regenerative therapies?

Motor neuron degeneration in ALS also involves a feed-forward loop of inflammation through pro-inflammatory cytokines TNF-α and IL-1β, recruitment of M1 macrophages and $CD4^+$ and $CD8^+$ T-cell accumulation, nitric oxide (NO) synthesis, expression of FasL and cell death [135,136]. Several therapeutic applications for counteracting neurodegeneration are devised to reduce inflammation [130].

Conclusion and outlook

The role of inflammation on stem cells and tissue regeneration is multi-faceted. The general belief that early pro-inflammatory signaling is detrimental while anti-inflammatory signaling is beneficial for stem cell activity has been challenged by findings of positive consequences of pro-inflammatory cytokines and negative effects of anti-inflammatory signaling for tissue recovery. In zebrafish brain, upon deployment of immune cells into the tissue, leukotriene signaling—a part of the acute inflammatory response—mounts a special crosstalk to the stem cells urging them to generate more neurons even in the absence of damage [31,32] by initiating a special regeneration program that does not prevail during homeostasis [35,74,76]. Leukotriene signaling is an evolutionarily conserved mechanism that is also present in mammals [137]. This raises the question whether the crosstalk between immune system and stem cells in the organisms that have regenerative ability could be used to learn how mammalian immune system and inflammation should be tweaked to provide the stem cells a permissive environment and coax them into re-forming the lost cells. Such an approach would have profound ramifications in treatment of chronic diseases that involve progressive degenerative conditions. By performing an *in silico* comparison of the epistatic targets of inflammatory pathways (e.g. leukotriene signaling and *gata3*) and their interaction partners in high-throughput expression datasets in mammalian and zebrafish brain, several candidate genes and pathways that could constitute the difference between the regenerative capacities of mammals and zebrafish might be identified [74]. In conclusion, as we dwell more on the effects of inflammation on stem cells in various model organisms and disease models, possible spatiotemporal micromanipulation of the inflammatory milieu may emerge as a means of reactivating or unlocking the regeneration potential of mammalian tissues and herald new possibilities for regenerative therapies.

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CK, NK and MB wrote the manuscript. CK and MB revised the manuscript.

Conflict of interest
The authors declare that they have no conflict of interest.

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