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► **To cite this version:**

Candice Bohaud, Matt D Johansen, Christian Jorgensen, Laurent Kremer, Natacha Ipseiz, et al.. The Role of Macrophages During Mammalian Tissue Remodeling and Regeneration Under Infectious and Non-Infectious Conditions. *Frontiers in Immunology*, 2021, 12, pp.707856. 10.3389/fimmu.2021.707856 . inserm-03381916

**HAL Id: inserm-03381916**

**<https://inserm.hal.science/inserm-03381916>**

Submitted on 18 Oct 2021

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# The Role of Macrophages During Mammalian Tissue Remodeling and Regeneration Under Infectious and Non-Infectious Conditions

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equally to this work

### Specialty section:

This article was submitted to  
Inflammation,  
a section of the journal  
Frontiers in Immunology

**Received:** 11 May 2021

**Accepted:** 22 June 2021

**Published:** 14 July 2021

### Citation:

Bohau C, Johansen MD,  
Jorgensen C, Kremer L,  
Ipseiz N and Djouad F (2021)  
The Role of Macrophages During  
Mammalian Tissue Remodeling and  
Regeneration Under Infectious and  
Non-Infectious Conditions.  
*Front. Immunol.* 12:707856.  
doi: 10.3389/fimmu.2021.707856

Several infectious pathologies in humans, such as tuberculosis or SARS-CoV-2, are responsible for tissue or lung damage, requiring regeneration. The regenerative capacity of adult mammals is limited to few organs. Critical injuries of non-regenerative organs trigger a repair process that leads to a definitive architectural and functional disruption, while superficial wounds result in scar formation. Tissue lesions in mammals, commonly studied under non-infectious conditions, trigger cell death at the site of the injury, as well as the production of danger signals favouring the massive recruitment of immune cells, particularly macrophages. Macrophages are also of paramount importance in infected injuries, characterized by the presence of pathogenic microorganisms, where they must respond to both infection and tissue damage. In this review, we compare the processes implicated in the tissue repair of non-infected *versus* infected injuries of two organs, the skeletal muscles and the lungs, focusing on the primary role of macrophages. We discuss also the negative impact of infection on the macrophage responses and the possible routes of investigation for new regenerative therapies to improve the recovery state as seen with COVID-19 patients.

**Keywords:** mammals, regeneration, repair, macrophages, infectious conditions, non-infectious conditions

## INTRODUCTION

Most mammals, such as mice and humans, possess limited regenerative capacities. Only a few rare tissues or organs such as muscle, lung epithelium and liver can regenerate in adult mammals after ablation or injury, leading to an integrated morphological and functional structure. For non-regenerative adult organs, while critical injuries usually lead to a definitive disruption of tissue architecture and functionality, superficial wounds are often followed by tissue remodelling and scar formation (1, 2). During the early stages of embryonic development, mammals develop an extraordinary regenerative potential, which is rapidly lost when reaching the adult stage. For

instance, E10 mouse embryos completely regenerate their forelimb bud after ablation (3), supporting the view of a regenerative capacity loss during development rather than an intrinsic mammalian deficiency. Therefore, it may be perceived that mammalian species possess the full capacity to regenerate entire parts of their body, as newts, but this potential is progressively lost during their development. Elucidation of the regeneration mechanisms related to embryos and adult mammals still requires extensive studies in order to propose and develop novel therapies aimed at restoring tissues and organs in humans.

Tissue lesions and their repair/regeneration process in mammals are commonly studied under so-called non-infectious conditions. Non-infected injuries include the generation of pathogen-free lesions, such as sterile amputation, burn, freezing, crushing or drug toxicity (4–6). In this context, many key mechanisms for the regeneration of tissues and organs have been identified, including cell death at the site of the injury as well as danger signals, favouring massive recruitment of the immune cells, including macrophages (M $\Phi$ ). In contrast, infected injuries are characterized by the presence of pathogenic microorganisms and include open wounds contaminated with external infectious agents or tissue/organ alterations caused by systemic or localized infections already present. Under these conditions, M $\Phi$  must respond to the two types of dangers related to infection and tissue damage.

While studies on regeneration are usually performed under non-sterile conditions, they do not reflect most of the natural situations and, therefore, fail to recapitulate all the complexities of the interactions encountered in wounds. Thus, to improve our knowledge and further develop protocols for the treatment of injuries in mammals, a comprehensive comparison of the processes implicated in the tissue repair of non-infected *versus* infected injuries requires additional investigations to identify critical pathways involved in tissue regeneration. In this review, we will mainly focus and compare the role of M $\Phi$  in regeneration of non-infected *versus* infected injured tissue in mammals. We will discuss the negative impact of infection on the M $\Phi$  responses, in turn altering the response and the fate of proliferating precursor cells. Considering the specificity of the processes involved in the regeneration and the broad spectrum of M $\Phi$  phenotypes in each regenerating organ, we will exclusively focus our review on two tissues, the skeletal muscles directly exposed to non-infected and infected open wounds and the lungs, which are continuously exposed to potential contaminated air.

## DEFINITION OF REGENERATION AND ROLE OF INFLAMMATION IN NON-INFECTED VERSUS INFECTED INJURIES

Regeneration is the process that leads to the restoration of a tissue or an organ following injury or amputation in terms of mass, structure and functions. In contrast, tissue repair, distinct from regeneration, is the most common mechanism occurring

after a major injury in adult mammals. It does not allow the tissue to recover its original architecture due to the formation of a fibrotic scar, resulting in the altered functionality and motility of the repaired tissue/organ.

Non-infected injuries are as diverse as the organs they can affect: burn, crush, cut, drug exposure. Despite their vast intrinsic nature, all injuries induce the same course of events that include wound closure, recruitment of immune cells and an acute inflammation phase, death of the damaged cells followed by resolution of the inflammation, cell de-differentiation and proliferation, disappearance of immune cells and formation of a novel tissue/organ (7). During the acute inflammation phase at the site of injury, necrosis leads to the rapid death of damaged cells and is characterised by the sudden rupture of the cell membrane and the release of danger molecules designated Damage-Associated Molecular Patterns (DAMPs) in the surrounding environment (8, 9). DAMPs are intracellular components, such as DNA, RNA, proteins or the vast group of alarmins like High Mobility Group Box 1 (HMGB1) (10), IL-1 $\alpha$  (11) and IL-33 (12, 13). The release of DAMPs triggers acute inflammation as well as the recruitment of immune cells to the site of injury.

Infected injuries are characterized by the presence of microbes or in many cases, opportunistic or pathogenic organisms. In addition to the traditional DAMPs released by the necrotic tissue, the presence of pathogens induces the recognition of Pathogen-Associated Molecular Patterns (PAMPs), ascribed as molecules located on the surface of the pathogens, which activate the immune response to the invading pathogen (14). PAMPs are a diverse group of signalling molecules that include lipopolysaccharide (LPS), single- and double-stranded viral RNA, flagellin and peptidoglycan, and are recognized by the Pattern Recognition Receptors (PRRs) located at the surface of nearby immune cells (15). The recognition of PAMPs activates pro-inflammatory pathways, ultimately leading to acute inflammation.

Although their mechanisms of action appear strictly different, inflammation in both non-infected and infected injuries appears to be induced by the same early pattern of immune cells recruitment. Indeed, within the first hours following injury, neutrophils enter the insulted site to immobilise, kill and phagocyte the pathogens or clear cellular debris (16–20). Neutrophils assist the recruitment of blood-derived monocytes *via* the secretion of the chemoattractant LL-37, cathepsin G, alpha defensin and azurocidin (21–23), which then differentiate into M $\Phi$ . After a few hours or a few days, B cells and T cells from the adaptive immune system enter the scene, providing a sustained systemic immunity until pathogen clearance is achieved (24). Injury and infection resolution is associated with a switch from a pro-inflammatory to anti-inflammatory/pro-resolving microenvironment and then, immune cells disappear progressively, either leaving the injured site or dying in the regenerating tissue (20, 25–27). Each of these steps is essential to ensure full tissue restoration by avoiding establishment of a chronic inflammation at the wound site that would block the subsequent regeneration process (28). While the role of the innate and adaptive immune response in resolving

inflammation and regeneration has been extensively described, we will mainly focus on the innate immune response, and more specifically on M $\Phi$ , in these processes.

## ROLE OF MACROPHAGES DURING INJURY

Monocyte-derived M $\Phi$  and tissue resident M $\Phi$  are innate immune cells present in all tissues during the entire life (29). M $\Phi$  are heterogenous and highly plastic cells (30). This plasticity allows them to adapt to their environment and to exert various functions within the tissues. At steady state, resident M $\Phi$  patrol within the tissues to maintain homeostasis by clearing dead cells, promoting cellular communication and phagocytosing invading microorganisms. In mice, tissue resident M $\Phi$  have a pre-natal origin (yolk sac- and foetal liver-derived) and are believed to mostly maintain themselves by self-proliferation (31). Their function, localisation, origin and phenotypic traits are dependent on the expression of specific transcription factors. Many review articles have summarised the current knowledge of tissue resident M $\Phi$  development and function (32–35). In the event of an injury or during pathogen invasion, tissue resident M $\Phi$  are activated and assist the recruitment of neutrophils (36–38) and monocyte-derived M $\Phi$  (36, 39). The infiltrating M $\Phi$  can be roughly classified into two bulk populations: the pro-inflammatory M $\Phi$ , recruited within two days following the initial insult, and the anti-inflammatory M $\Phi$ , appearing usually from day three. Based on their secretome profile, M $\Phi$  were initially classified as “M1” and “M2”, albeit it is now clear that their diversity is much more complex than originally suspected, further segregating into additional subpopulations (40, 41). Appearing first at the site of injury, the pro-inflammatory M $\Phi$  help at eliminating dead neutrophils, phagocytosed pathogens or dying cells from the injured area (33). In contrast, anti-inflammatory M $\Phi$ , emerging essentially during the second wave of M $\Phi$  recruitment, are considered as pro-resolving and are essential for the recruitment of new progenitor cells and for the resolution of the inflammation (42). The anti-inflammatory M $\Phi$  are either derived from the pro-inflammatory M $\Phi$  pool, which undergo a phenotypic switch (43) notably after phagocytosis of the dead neutrophils (25, 44) or are directly recruited from blood monocytes (45). M $\Phi$  are key players at every step of tissue injury resolution. Not only critical for controlling inflammation, they also intervene during parenchymal and mesenchymal repair processes as well as in fibrosis (46). Through the secretion of various factors [Transforming Growth factor beta (TGF- $\beta$ ), Platelet-derived growth factor (PDGF), Vascular endothelial growth factor (VEGF), Tumour necrosis factor (TNF), Interleukin 1 (IL-1) and matrix metalloproteinases (MMPs)], M $\Phi$  promote angiogenesis, recruit fibroblasts and keratinocytes and participate to the remodelling of the extracellular matrix. The elimination of murine M $\Phi$ , consecutive of the injection of lipochlodronate, negatively impacts wound healing and collagen deposition, translating into the loss of tissue

functionality. The temporal depletion of M $\Phi$  during the pro-inflammatory phase or during the resolution phase of inflammation has a differential impact on tissue restoration, thus inferring that M $\Phi$  subtypes play different roles during this process. Time and spatial regulation of M $\Phi$  accumulation and polarization is equally important during pathogen infection (47). Strong evidence indicates that the clearance of pathogens colonizing the injured area requires M $\Phi$  which are essential to the healing process (48, 49) although many important questions remain unaddressed. For instance, it is not known whether the pre-established pathogen-induced inflammation detrimentally impacts the speed and efficiency of tissue repair after tissue injury. Additionally, it remains also to be established whether the cumulative presence of DAMPs and PAMPs affects resolution of the injury in an organ-dependent manner.

## SKELETAL MUSCLE REGENERATION

Skeletal muscles which are composed of myofibers, connective tissue, nerves, blood, lymph vessels and immune cells with tissue resident M $\Phi$ , represent approximately 40% of the body mass in humans. This organ can fully regenerate after minor injury (50, 51). However, severe injuries such as mechanical shock, burn and deep laceration can lead to incomplete healing, scar formation and fibrosis, resulting in a long-lasting or permanent loss of function.

Muscle repair is a complex process. Damaged myofibers and endothelial cells first undergo a necrosis/degeneration stage, characterized by the release of DAMPs and triggering acute inflammation. Then, the quiescent muscle stem cells adopt an activated state, proliferate and differentiate, providing precursors cells, which will ultimately lead to mature muscle fibers (5).

Muscle stem cells or satellite cells play an important role in tissue restoration after muscle injury. These cells, expressing in resting states various specific markers including the paired homeobox factors Pax3 and Pax7, reside in specialized local environment between the basal lamina and the myofiber sarcolemma (52). When muscle damage is induced, these quiescent cells rapidly transit to an activated state characterized by the expression of markers such as the myogenic regulatory factors MYF5, MYOD, MYOGENIN, MRF4 to regenerate the injured tissue (53). After their activation, satellite cells proliferate. While one part of the proliferating cells differentiates into myoblasts to regenerate the damaged muscle, another part of the cells reconstitutes the pool of quiescent satellite cells. The newly formed myoblasts can then fuse with the pre-existing myoblasts in the tissues or fuse with each other through the expression of several factors, such as transforming growth factor beta (TGF $\beta$ ) to repair damaged muscle fibers (54–56). This complex mechanism involving cell migration, recognition of the ongoing events and cell adhesion is not fully understood (54, 55). This cascade of events, relies on immune cell response and more particularly on the M $\Phi$  response. Indeed, muscle resident M $\Phi$  are mostly located in the perimysium (connective tissue surrounding muscle fascicles) and epimysium (fascia surrounding the muscle)

and are estimated to be at a ratio of one MΦ per five muscle fibers. However, both the origin and role of the muscle resident MΦ in development and tissue regeneration remain poorly described (57–60).

Currently, most studies concentrate on the resolution of injury under non-infectious conditions, while most open injuries occur under non-sterile conditions and exposed to microbes, eventually leading to complicated clinical manifestations and diseases (61). Thus, understanding the mechanisms regulating infected *versus* non-infected skeletal muscle injury regeneration are of particular importance to pinpoint the key elements necessary for restoration of functional tissues/organs (Figure 1).

## Non-Infected Skeletal Muscle Injury

Regeneration of skeletal muscle in mice is usually studied after injury of the Tibialis anterior, *Triceps brachii*, Gastrocnemius and Soleus muscles (4, 5). Muscles are usually injured either by freezing or following injection of chemicals [barium chloride (BaCl<sub>2</sub>)] or toxins from snake venom [notexin (NTX) and cardiotoxin (CTX)] (6). CTX offers the best regeneration outcome, based on histological analyses (6). However, the use of CTX to measure the wide array of tissue repair and regeneration processes need to be carefully considered within the context of the mechanisms required at the cellular level.

MΦ are present and essential in every single step required for the regeneration process since their depletion inhibits tissue restoration (43, 62–65). This has been shown by depleting macrophages *via* different pharmacological or genetic approaches, including (i) lipochlodronate injection, (ii) the use of transgenic mice with the CD11b promoter directing the expression of a diphtheria toxin receptor (43) or (iii) the use of CCL2- and CCR2-knockout mice (66, 67).

Upon injury, resident MΦ do not phagocytose the dying cells, but rapidly respond to DAMPs and promote the recruitment of other leukocytes, such as neutrophils and monocytes, notably *via* the secretion of CCL2 and CXCL1 (68, 69). Within several hours following injury, neutrophils followed by Ly6C<sup>high</sup> F4/80<sup>low</sup> monocyte/MΦ enter the injured site. These pro-inflammatory MΦ clear the dead cells, promote the recruitment of satellite cells and myogenic precursor cell proliferation *via* secretion of IL-6, TNF, G-CSF and IL-1β, while simultaneously blocking their differentiation (70–74). From 48 hrs after injury, the pro-inflammatory Ly6C<sup>high</sup> F4/80<sup>low</sup> monocytes/MΦ progressively transition to “pro-resolving” Ly6C<sup>low</sup> F4/80<sup>high</sup> MΦ, producing high levels of insulin-like growth factor-1 (IGF-1), IL-10 and TGFβ-1, dampening the inflammatory response and favouring tissue repair (75–78). The phenotype skewing of infiltrating MΦ is, at least partially, due to phagocytosis of debris, which activates the AMPKα1 and C/EBPβ pathway and results in the expression of typical anti-inflammatory genes (78, 79). This phenotypic switch is also dependent on Treg-induced Interferon gamma (IFN-γ) reduction (80). In parallel, from 1 day post injury, Lin<sup>-</sup> Integrin-α7<sup>-</sup> Sca1<sup>+</sup> PDGFR-α<sup>+</sup> fibro/adipogenic progenitors (FAP) and non-myogenic mesenchymal cells, are recruited to the injured site to support myogenesis (81). Although essential, FAP expansion is transient and must be rapidly reduced under

normal conditions of regeneration. It can become persistent in degenerative conditions, such as chronic lesions and muscular dystrophies. Inflammatory MΦ participate in the programmed elimination of these progenitors by induction of apoptosis mediated by TNF (82). The interaction between cell progenitors and inflammatory cells in the damaged muscle influences the course of the regeneration process. However, the macrophage phenotype can also be influenced by the extracellular environment. An infectious environment, described in the following section, can modulate the response of these cells and impair regeneration of muscle tissues.

## Infected Skeletal Muscle Injury

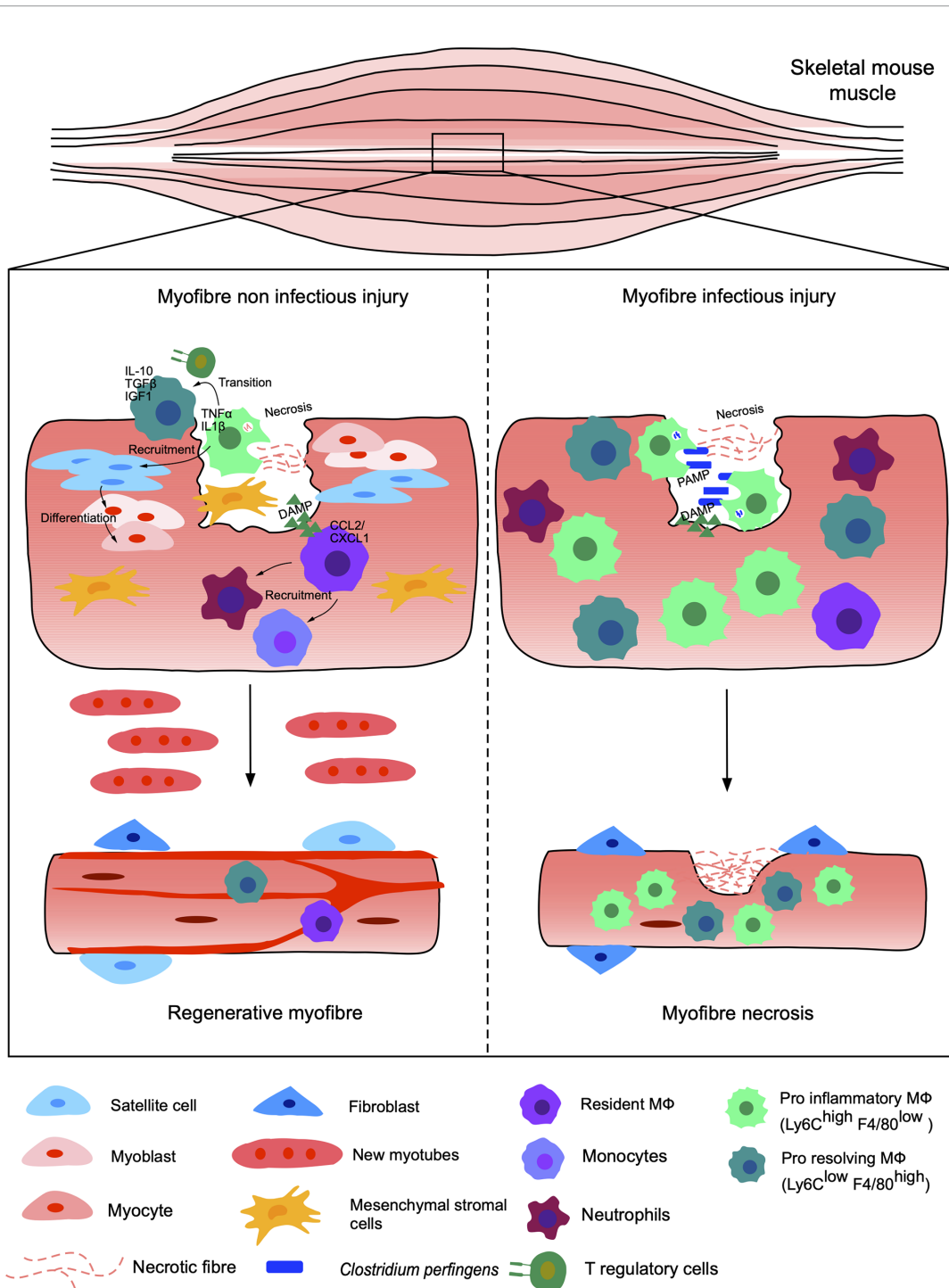
Muscle repair of an infected injury has received little attention, but studies agree that the presence of bacteria or parasites can substantially delay muscle regeneration, often resulting in a loss of the muscle mass and overall mobility and function (83).

Muscle infection by the Gram-positive anaerobic bacteria, *Clostridium perfringens* is one of the major causes of gas gangrene development, also called clostridial myonecrosis. Patients with peripheral vascular disease and type I diabetes are more prone to gas gangrene, however the common sources are traumatic lesion and deep surgery. Fatal if left untreated, gas gangrene is estimated to affect at least 1000 patients in the USA every year, but the disease burden in less developed countries remains unknown (84, 85). A mouse model of gas gangrene, consisting of intramuscular injection of *C. perfringens*, results in increased inflammation, dysregulated recruitment and maintenance of both pro- and anti-inflammatory MΦ with deficient muscle regeneration, compared to non-infected acute muscle injury (61).

Skeletal muscle can also be infected by the parasite *Toxoplasma gondii*, which by itself induces chronic inflammation and long-term muscle damage, myositis and cachexia, characterized by 20% body mass loss and elevated TNF, IL-1 and IL-6 (86, 87). A comparison between non-infected injured and *T. gondii*-infected injured muscles revealed that *T. gondii* led to the accumulation of pro-inflammatory MΦ after injury and impaired regeneration (86). The lack of pro-inflammatory to pro-resolving MΦ switch is likely resulting from a dysregulation of T cells since Tregs have been shown to be required for M1 to M2 transition (86). Single cell RNA sequencing (scRNA-seq) confirmed striking differences in the transcriptomic profiles of MΦ recruited after injury in infected *versus* non-infected mice, with a prevalence of pro-inflammatory phenotypes in the infected injured mice (88). However, many aspects of skeletal muscle repair during *T. gondii* infection remain to be understood, requiring further investigations.

## LUNG REGENERATION

The lung is an essential physiological mammalian structure responsible for gas exchange. It is a highly dynamic micro-environment which plays a critical role in cellular respiration and in mounting an immunological response to both infectious agents such as bacteria and viruses, and non-infectious agents such as environmental pollutants. Accordingly, the lung



**FIGURE 1** | Non-infected versus infected injuries of the murine skeletal muscle. Injury of muscle myofibers under sterile conditions, such as freezing, chemical injections or exposure to toxins, leads to necrosis of the myofibers and endothelial cells responsible for the release of DAMPs. Resident MΦ respond to DAMPs and recruit neutrophils and other monocyte-derived MΦ by releasing CCL2/CXCL1. The pro-inflammatory Ly6Chi F4/80 low MΦ, TNFα and IL-1β positive, eliminate dead cells and recruit satellite stem cells as well as myogenic precursors secreting pro-inflammatory cytokines. The pro-inflammatory MΦ are then gradually replaced by anti-inflammatory MΦ, known as pro-resolving Ly6Clow F4/80 high secreting IGF1, IL10 and TGFβ. The switch of MΦ subpopulations is induced in part by the phagocytosis of debris by pro-inflammatory MΦ, which activate the AMPK and C/EBPβ pathways, but also via the presence of T regulatory cells. Finally, stromal mesenchymal cells (FAP) are recruited and support myogenesis. The satellite cells generate myoblasts, differentiating into myocytes giving new myofibers and functional regenerated tissue. This same injury under infectious conditions, for example in the presence of *Clostridium perfringens*, leads to a significant recruitment of pro-inflammatory MΦ. The pro- and anti-inflammatory balance is dysregulated and the inflammation becomes excessive and persistent. Thus, the tissue does not regenerate and becomes necrotic, losing its functional properties.

possesses a high propensity to regenerate through widespread proliferation and differentiation of progenitor cells upon injury. Epithelial insults and/or respiratory infections can lead to the disruption of gas exchange at the alveoli, destroying alveolar epithelial type 1 (AT1) and type 2 (AT2) populations, which in extreme cases can lead to acute respiratory distress syndrome (ARDS).

The lung airway is a complex architecture composed of a large diversity of cells with dedicated functions, depending on where they stand in the lungs (89, 90). The epithelium of the trachea and bronchioles consists mainly of basal cells, club cells, goblet cells and ciliated cells (91). Basal cells in humans are distributed in the trachea to the terminal bronchioles and are mainly found in the trachea of mice. The renewal rate of these cells in physiological conditions is low, but after injury, they can differentiate into secretory cells, goblets and multiciliated cells (92–95). Club cells, which are abundant in the murine bronchioles can also differentiate into ciliated cells after injury. Goblet cells are found within the respiratory and intestinal epithelial lining, and are responsible for mucin production, commonly characterized by MUC5AC and MUC5B production. The final structure of the bronchial tree, the alveoli, comprises two types of epithelial cells: type I alveolar (AT1) and type II alveolar (AT2) cells (96). AT2 cells make up only 5% of the alveolar surface, but these can differentiate into AT1 after injury to maintain the integrity of the epithelium (89, 97). In addition, once differentiated, these cells are versatile and can return, at least partially, to a precursor/undifferentiated phenotype. At steady state, all these cells are in a quiescent state, which has made their roles and identification very challenging (89, 98–100). Importantly, these cells can undergo proliferation and differentiation in response to various stimuli or injuries (101). However, the type and extent of the injury as well as the regenerative capacity of lungs is highly dependent on the nature of the injury (102–104). As such, careful considerations are needed with regard to the choice of the model used. M $\Phi$  represent crucial cells for the pulmonary function and particularly in the response to lung injury. A recent study underscored the importance of M $\Phi$  in the lung epithelium regeneration *via* an IL-33/ST2 mechanism (105). The physiological role of M $\Phi$  in lung regeneration is still poorly understood and is accentuated by an ongoing debate on the origin, function and phenotypic traits of the different pulmonary M $\Phi$  subtypes.

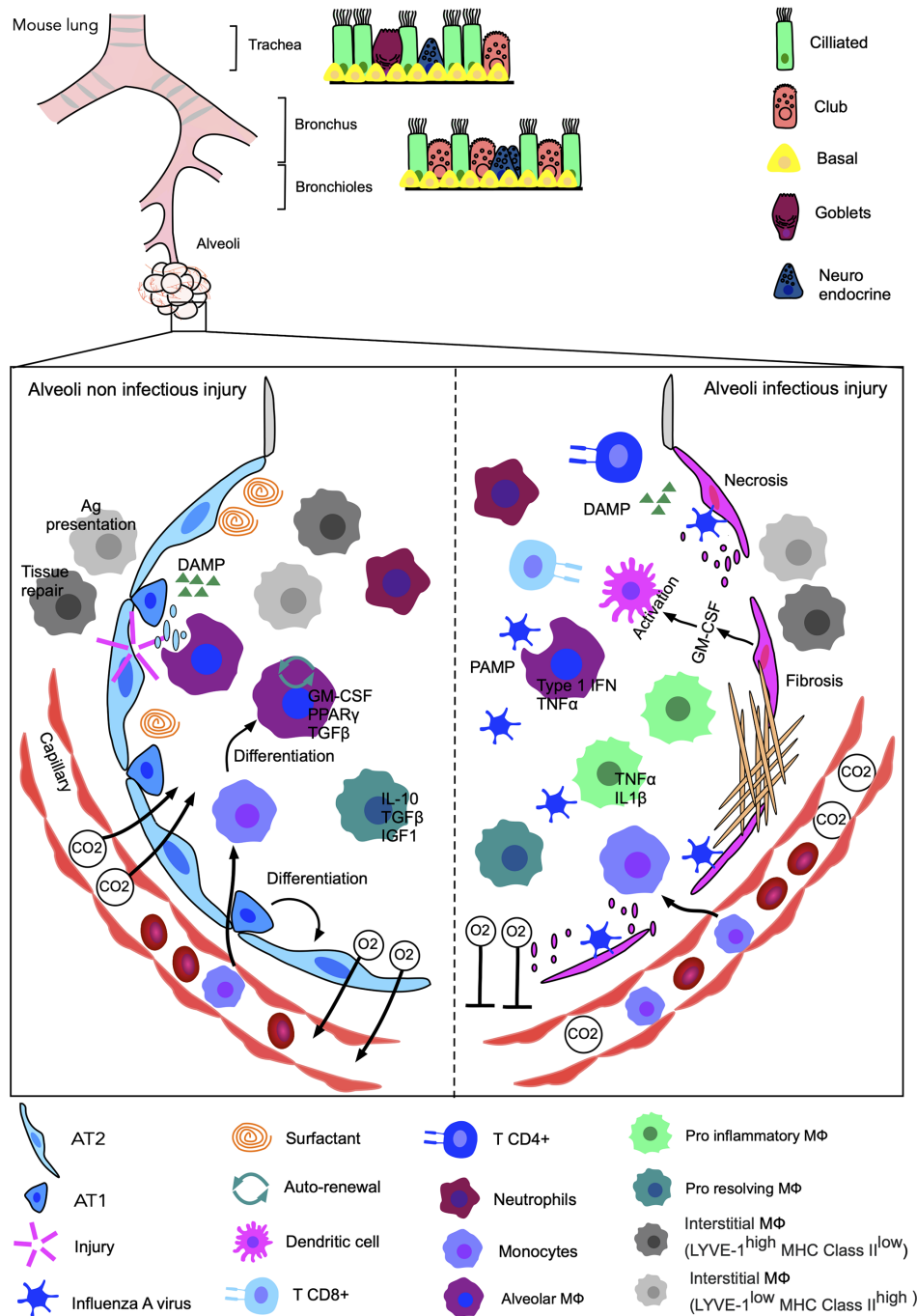
At steady state, lung tissues harbour two types of resident M $\Phi$ : alveolar and interstitial (106). The alveolar M $\Phi$ , located in the lumen of the alveoli, live in a strategic place because they are in direct contact with the inhaled air and, therefore, represent the first line of defense against invading particles or microbes. They trigger the immune response to dangers while preventing excessive responses and tissue damage. This M $\Phi$  population also regulates the surfactant homeostasis, which is critical for gas exchange (107). Originated mainly from fetal monocytes, they adopt their phenotype shortly after birth and are dependent on the GM-CSF/PPAR- $\gamma$  (108, 109) pathway as well as their own production of TGF- $\beta$  (110). The pulmonary environment, at steady state, gives them an anti-inflammatory phenotype.

Interstitial M $\Phi$ s are located between the pulmonary epithelium and the capillaries, predominantly within the alveolar interstitium, the submucosa and the perivascular adventitia. These cells assist alveolar M $\Phi$  to protect the tissue against infections. Two distinct subsets of interstitial M $\Phi$  have recently been identified in murine lungs, including LYVE-1<sup>low</sup> MHC Class II<sup>high</sup> involved in antigen presentation, and LYVE-1<sup>high</sup> MHC Class II<sup>low</sup> specializing in tissue repair (111, 112). However, the origin of the interstitial M $\Phi$  is complex, as this population are thought to have a mixed origin, which makes their phenotypic characterization challenging. Mostly derived from the bone marrow, a small proportion of interstitial M $\Phi$  has been shown to originate from the yolk sac (113, 114), but this requires further investigations.

Survival and renewal of the resident lung M $\Phi$  depend on both the type and the size of injury encountered. While alveolar M $\Phi$  proliferate slowly to renew themselves at steady state in a manner dependent on M-CSF and GM-CSF (115), severe injury promotes their disappearance. To repopulate lung tissues, these cells can either proliferate locally or be replaced by monocyte-derived M $\Phi$ , which, over time, take up the alveolar M $\Phi$  characteristic. Interstitial M $\Phi$  can also spread near the injured site *via* differentiation of blood, local or splenic monocytes into interstitial lung M $\Phi$ . Survival of monocyte-derived M $\Phi$  recruited following injury varies also depending on the nature of the injury (116–118).

## Non-Infected Lung Injury

Various animal models have been developed in the laboratory to mimic the conditions of non-infectious lung injury in human: ventilator-induced injury (119), acid aspiration (120), contusion (121–123), bleomycin injection (124), exposition to SO<sub>2</sub> (125), Cl<sub>2</sub> (126) and cigarette smoke (127, 128) (**Figure 2**). The role of M $\Phi$  in each of these models has been investigated by focusing predominantly on alveolar M $\Phi$ . Mechanical ventilation-induced injury activates alveolar M $\Phi$  and transient depletion of these cells using clodronate improves pulmonary elastance, while reducing oedema and tissue permeability (129, 130). Acid-induced injury triggers the rapid recruitment of neutrophils and blood-monocyte-derived M $\Phi$  and the release of microparticles within the bronchoalveolar lavage fluid (BALF). These microparticles seem to induce a pro-inflammatory response in alveolar epithelial cell line MLE-12, but are safely removed by resident alveolar M $\Phi$  in a non-inflammatory MerTK-dependent manner (131). Initial *in vitro* work performed with human alveolar M $\Phi$  identified their positive role on Type 2 alveolar epithelial cell proliferation *via* the release of PDGF, IGF-1 and FGF, following incubation with silica (132). A recent study identified their direct influence on epithelial cell proliferation following bleomycin-induced injury in mice in a Wnt-dependent pathway (133), concurring with previous study highlighting the importance of Ly6C<sup>hi</sup> monocytes and M $\Phi$  in the development and resolution of fibrosis after bleomycin-induced injury (134). Increased numbers of circulating, interstitial and alveolar M $\Phi$  are found in the lungs following partial pneumonectomy and CCR2<sup>+</sup> monocytes are



**FIGURE 2 |** Non-infected versus infected injuries of the murine lungs. The release of DAMPs linked to a sterile induced-injury (ventilator-induced, acid aspiration, contusion, bleomycin injection, resection) in the pulmonary alveolus triggers an immune response consisting primarily of neutrophils and MΦ, resulting in regeneration of the pulmonary epithelium. Alveolar MΦ (GM-CSF, PPAR-γ and TGF-β), the first barrier to danger, phagocytose debris and dead cells. They prevent excessive inflammation, the formation of lesions and regulate surfactant. They can self-renew or be substituted by monocyte-derived MΦ. The two types of interstitial MΦ, located in part between the pulmonary epithelium and blood capillaries, enter the alveoli and help the alveolar MΦ to respond to dangers. LYVE-1<sup>low</sup> MHC Class II<sup>high</sup> MΦ are responsible for antigen presentation while LYVE-1<sup>high</sup> MHC Class II<sup>low</sup> help tissue repair. Upon tissue restoration, exchanges of O<sub>2</sub> and CO<sub>2</sub> through the capillaries return to normal. Injury in infectious conditions, for example caused by infection with Influenza A virus in mice, may impair the ability to regenerate. Alveolar MΦ phagocytose debris, dead cells and the infectious agent. Alveolar MΦ initially anti-inflammatory, adopt an inflammatory phenotype with the release of IFN-γ and TNF-α leading to the production of GM-CSF by epithelial cells, in turn activating dendritic cells (DC). Three weeks after infection of MΦ, neutrophils and CD4<sup>+</sup>, CD8<sup>+</sup> T cells are still present. Excessive inflammation with the persistent presence of pro-inflammatory MΦ can eventually lead to extensive cell necrosis and the formation of non-functioning fibrous scar tissue. As a result, oxygen is no longer properly transferred to the blood capillaries and breathing difficulties may occur.



essential for lung regeneration (135). Mice have also the capacity to adapt to recurrent oxidative toxicant exposure such as Cl<sub>2</sub> and this adaptation seems to be dependent on alveolar MΦ through the production of PGE<sub>2</sub> and TGFβ (136). The balance between pro-inflammatory and anti-inflammatory MΦ is essential to ensure meaningful control of inflammation and tissue repair, although the exact role of the different MΦ subsets in the development and resolution of fibrosis is still poorly understood (137). However, the importance of the first pro-inflammatory phase should not be disregarded, as evidence recurrently emphasizes its importance for the initiation of the later pro-resolving phase (138).

## Infected Lung Injury

Most lung injuries following bacterial, fungal, parasitic or viral infection result in a loss of tissue elastance and integrity, often requiring extensive regeneration following elimination of the pathogen (139, 140). However, tissue regeneration can fail, precluding full pulmonary recovery in some patients. Tissue recovery and injury resolution can be very challenging and is highly dependent on the nature of the infectious agents (Figure 2).

## INFLUENZA VIRUSES

Influenza viruses are a family of RNA viruses infecting epithelial cells present in the upper and lower respiratory tract. The infected cells often die *via* apoptosis, leading to extensive infection and epithelial injury. Although most individuals recover well after infection, some patients experience long-term consequences, characterized by alveolar hypersensitivity (alveolitis), acute respiratory distress syndrome (ARDS) and fibrosis (141, 142). Murine models of influenza infection revealed that the inflammatory status in BALF can persist even after the infection is cleared. Importantly, MΦ, neutrophils, CD4<sup>+</sup> and CD8<sup>+</sup> T cells are present at least three weeks after infection, even after influenza virus is no longer present. Furthermore, alveolitis was observed up to 60 days after infection. In addition, influenza virus not only induces cellular stress but affects also the lungs at the transcriptomic and epigenetic levels, leading to long-term lung changes as a consequence of infection (143). Resident alveolar MΦ are the first immune cells to react to viral infection due to their close proximity to the site of infection. Alveolar MΦ actively phagocytose the viral particles as well as the dead and apoptotic cells and produce type I IFN, which are essential for the control of viral infection (144–147). The activated alveolar MΦ also release TNF, an important factor inducing GM-CSF production from epithelial cells, which in turn activates CD103<sup>+</sup> DC and induced AT2 epithelial cell proliferation, required for the regeneration process (148, 149). Following influenza infection, monocyte-derived MΦ are recruited to the lungs where they persist and over time, acquire hallmarks of tissue resident alveolar MΦ where they participate in the replenishment of the alveolar MΦ pool following resolution of acute infection. Interestingly, the monocyte-derived MΦ transcriptomic

profiles remain altered for several weeks after influenza infection, while tissue resident alveolar MΦ are barely affected and, therefore, considered as “terminally sedated” (118, 150, 151). Given the importance of MΦ on epithelial cell proliferation and differentiation, it is reasonable to assume that the effectiveness of lung tissue regeneration is dependent on the phenotype of both tissue resident and newly recruited monocyte-derived alveolar MΦ.

## TUBERCULOSIS

Tuberculosis (TB), caused by the pathogenic bacteria *Mycobacterium tuberculosis*, is a global health concern and consistently one of the top ten causes of death worldwide ([https://www.who.int/tb/publications/global\\_report/en/](https://www.who.int/tb/publications/global_report/en/)). Half of the patients with TB infection present with lung dysfunction, even after chemotherapy or microbiological healing to clearance (152, 153). While the pulmonary epithelium is able to regenerate after injury in some rare cases, this potential is lost in TB patients (152). When the permissive environment for regeneration is altered, a significant deposition of collagen occurs, leading to fibrosis. One of the main causes of this lesion and fibrosis is the formation of structures called granulomas (152). Granulomatous lesions are considered as the hallmark of pulmonary TB and consist of a complex immune structure linking innate and adaptive immunity (154, 155). Following aerosol inhalation, *M. tuberculosis* is rapidly phagocytosed by alveolar MΦ, at which point the bacilli can utilise this host immune cell as an immunoprivileged niche. Neighbouring immune cells are recruited to the infection site, whereby the granuloma is formed. This structure is initiated by MΦ at the center, consolidated by the recruitment of other immune cells such as neutrophils, dendritic cells or B and T lymphocytes grouping together at the periphery of the granuloma (154–156). The protective or deleterious role of this structure has not yet been clearly defined. While some granulomas appear to control the infection and completely constrain the mycobacteria for many years, others overflow and eventually rupture, releasing the pathogen into the extracellular environment. These granulomas not only promote the spread and dissemination of the bacilli throughout the body and in the environment through the sputum but also generate cavities and irreversible lung lesions (157). Thus, the granuloma represents a major determinant for the disease outcome, formation of lesions and ultimately tissue restoration where MΦ play a central role. Pro-inflammatory MΦ are likely to promote granuloma formation and exerting a bactericidal activity *in vitro*, whereas anti-inflammatory MΦ inhibit these effects (158–161). The role and polarization of MΦ in granulomas in the presence of *M. tuberculosis* requires further attention, however studying the role of these structures remains complex due to the important cellular heterogeneity existing between individuals. In addition, murine models, although very useful for studying this pathology, incompletely reproduce the mechanisms associated with human granulomatous infiltrations, therefore limiting

studies devoted to regeneration of the pulmonary epithelium in TB (162).

## SARS-COV-2

SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), is responsible for >180 million infections and 3.8 million deaths worldwide since its emergence in late 2019. Clinical manifestation is variable, ranging from asymptomatic or mild disease with moderate respiratory distress, to severe and life-threatening disease resulting in ARDS, acute lung injury and the need for mechanical ventilation, which in some cases results in death. Patients with moderate and severe COVID-19 have reported extended recovery periods and relapsing symptoms, but the underlying mechanisms remain unknown. Most current research has concentrated on understanding SARS-CoV-2 pathogenesis and developing effective vaccines and therapeutics to prevent or combat the disease. Unfortunately, there is still a limited understanding of the long-term effects following COVID-19 recovery.

Excessive inflammatory responses are a critical feature of severe COVID-19 and postulated to contribute to patient's decline and death. The significant influx of inflammatory cells within alveoli leads to interstitial pneumonia, obstructing efficient gas exchange. Furthermore, ARDS is a known contributing factor to pulmonary fibrosis and is directly correlated with increased tissue resistance and substantial deterioration in the lung function. Recently, several representative animal models for SARS-CoV-2 pathogenesis have been identified, which recapitulate critical aspects of disease pathogenesis including extensive lung inflammation, severe lung damage and pulmonary fibrosis as well as significant pulmonary decline (163). This has been further demonstrated in COVID-19 mouse models, whereby significant changes to pulmonary function have been demonstrated to occur only during the latter stages of disease progression, coinciding with increased lung inflammatory infiltration and extensive interstitial inflammation (164). However, retrospective studies showed that AT2 epithelial cells

were Ki67<sup>+</sup>, demonstrating that these cells were actively replicating following SARS-CoV-2 infection, suggesting that there is at least some degree of alveolar regeneration following COVID-19 resolution (165). Whether the extensive COVID-19 lung damage is able to regress over time, resulting in the restoration of the pulmonary lung function remains unknown.

## CONCLUSION

Understanding the processes associated with regeneration in mammals to improve regenerative capacities in humans, is one of the greatest challenges of the 21st century. Indeed, most degenerative diseases, accentuated with aging of the population, do not have therapies. Several major infectious diseases in humans, such as TB or SARS-CoV-2, are also responsible for tissue or lung damage, requiring regeneration. Restoration of tissues/organs through regenerative mechanisms, and not by repair, offers the functionality of the original structure to be regained. As a consequence, there is increasing interest in elucidating these mechanisms, which will be of high medical value. Numerous studies have already identified key mechanisms to understand the crucial role of the immune cells, such as MΦ, in regeneration. However, the vast majority of these studies have been carried out under non-infectious conditions, which do not necessarily recapitulate the complexity of injuries encountered in humans. Therefore, the implementation of studies reproducing systemic and local infectious pathologies associated with injuries are particularly warranted. In the long term, it is anticipated that such studies may lead to the discovery of new regenerative therapies and/or improve the recovery state as seen with COVID-19 patients.

## AUTHOR CONTRIBUTIONS

CB, NI, and FD propose the structure of the review. CB, MJ, CJ, LK, NI, and FD wrote the review. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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