Macrophages in the pancreas: Villains by circumstances, not necessarily by actions

Andrea F. Cruz¹ | Rokhsareh Rohban² | Farzad Esni¹³⁴

Introduction: Mounting evidence suggest that macrophages play crucial roles in disease and tissue regeneration. However, despite much efforts during the past decade, our knowledge about the extent of macrophages’ contribution to adult pancreatic regeneration after injury or during pancreatic disease progression is still limited. Nevertheless, it is generally accepted that some macrophage features that normally would contribute to healing and regeneration may be detrimental in pancreatic cancer. Altogether, the current literature contains conflicting reports on whether macrophages act as friends or foe in these conditions.

Methods and Results: In this review, we briefly review the origins of tissue resident and infiltrating macrophages and the importance of cellular crosstalking between macrophages and other resident cells in tissue regeneration. The primary objective of this review is to summarize our knowledge of the distinct roles of tissue resident and infiltrating macrophages, the impact of M1 and M2 macrophage phenotypes, and emerging evidence on macrophage crosstalking in pancreatic injury, regeneration, and disease.

Abstract

Correspondence
Farzad Esni, Department of Surgery, John G. Rangos Research Center, University of Pittsburgh, One Children’s Hospital Drive, Rangos Floor 6, Room 6123, Pittsburgh, PA 15224. Email: farzad.esni@chp.edu

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Abbreviations: ADAM17, disintegrin and metalloproteinase domain-containing protein 17; ADAMTS1, disintegrin and metalloproteinase with thrombospondin motifs 1; Akt, v-akt murine thymoma viral oncogene; BMP-2, bone morphogenetic protein 2; CCR2, C-C motif chemokine receptor 2; CREB, cAMP response element-binding protein; CSC, cancer stem cell; CSF1, colony stimulating factor 1; CUX1, cut like homeobox gene; CXCL1, C-X-C motif ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; DAMP, damage-associated molecular pattern; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FoxO1, forkhead box O1 gene; HSC, hematopoietic stem cell; IAPP, islet amyloid polypeptide; ICAM-1, intercellular adhesion molecule; IFN-γ, interferon-γ; IGF-1, insulin-like growth factor; IKK2/β, inhibitor of nuclear factor kappa B kinase subunit β; IL, interleukin; ISG15, IFN-stimulated factor 15; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIP-1α, macrophage inflammatory protein-1α; MIP-1β, macrophage inflammatory protein-1β; NLRP3, NOD-like receptor, pyrin domain-containing protein 3; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; PAMP, pathogen-associated molecular pattern; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PGE₂, prostaglandin E₂; pro-NGF, pro-nerve growth factor; PPAR-γ, peroxisome proliferator-activated receptor γ; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; REG4, regenerating islet-derived protein 4; Socs3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.
Conclusion: Macrophages are involved with various stages of pancreatic cancer development, pancreatitis, and diabetes. Elucidating their role in these conditions will aid the development of targeted therapeutic treatments.

KEYWORDS
diabetes, monocytes/macrophages, pancreatic cancer, pancreatitis, regeneration

1 | INTRODUCTION

There are multiple subpopulations of macrophages with distinct phenotypes dependent on the anatomical location and microenvironment stimuli. The term “macrophages” has been used to define a population of cells descended from a mononuclear lineage specialized for the identification, phagocytosis, and destruction of harmful biological agents, such as bacteria. However, growing evidence suggests that cellular crosstalk between macrophages and surrounding tissue resident cells is an important aspect of tissue regeneration. On the other hand, impaired macrophage function, either due to inherent defects or abnormal stimuli would instead contribute to disease progression. Here, we review an increasing body of literature that describe the involvement of macrophages during normal vs disease conditions.

2 | MACROPHAGE ORIGINS

Generally, there are three main populations of macrophages: yolk sac-derived tissue resident macrophages, fetal liver-derived tissue resident macrophages, and bone marrow–derived infiltrating macrophages (Figure 1). Mounting evidence indicates that tissue resident macrophages and infiltrating macrophages arise from three different waves of successive hematopoiesis that occur throughout development and adulthood. Tissue resident macrophages reside in the tissue and arise from the embryonic precursors generated through the first two

![Figure 1](image-url)  
**Figure 1** Fetal hematopoiesis. There are three waves of successive hematopoiesis that occur throughout development and adulthood: primitive, transient definitive, and definitive
waves of successive hematopoiesis originating in the extraembryonic yolk, whereas infiltrating macrophages arise from common myeloid progenitor cells generated during the third wave of hematopoiesis in the bone marrow. Briefly, the first wave is primitive hematopoiesis and it arises from the extraembryonic yolk sac and generates yolk sac progenitors that later become primitive macrophages, erythroblasts, and megakaryocytes. The next wave is the transient definitive wave that produces erythromyeloid precursors that remain locally and become yolk sac macrophages or migrate to the fetal liver, upon establishment of fetal blood circulation, and differentiate into other cell lineages, such as monocytes. The third wave is definitive hematopoiesis. Immature hematopoietic stem cells (HSCs) emerge from the aorta-gonad-mesonephros and not only migrate to the fetal liver to mature into fetal HSCs, but also seed the fetal bone marrow to eventually generate adult HSCs. The HSCs eventually produce discrete intermediate progenitors, like common myeloid progenitors that further differentiate into monocytes (Figure 1). As such, HSCs from the definitive wave are precursors to infiltrating macrophages; however, the identity of tissue resident macrophage precursors is still unclear. The current theories regarding the origins of tissue resident macrophages has been extensively discussed elsewhere.

Tissues are able to replenish their population of resident macrophages through low-level proliferation during steady-state, but this can be increased with bone marrow–derived circulating monocytes that differentiate into macrophages during pathologies. Several studies have shown that macrophage accumulation in tissue after injury is due to the recruitment of circulating monocytes, rather than the expansion of resident macrophages. Circulating monocytes are categorized into two groups based on expression of the Ly6C marker. Ly6C+ monocytes directly originate from the bone marrow progenitors, whereas Ly6C− monocytes are derived from the Ly6C+ monocytes. The two types of blood circulating monocytes also have different functions. Ly6C− monocytes patrol the vasculature to remove damaged endothelial cells. On the other hand, Ly6C+ monocytes in the vasculature sense tissue damage, infiltrate the injury site, and differentiate into macrophages. These infiltrating macrophages become polarized (or activated) in response to signals associated with pathogens or present in injured tissue. In fact, infiltrating macrophages exist across a dynamic M1-M2 polarization spectrum with an array of intermediate phenotypes in between. Stimulation from macrophage colony stimulating factor 1, interferon-γ (IFN-γ), and lipopolysaccharide (LPS) induces monocyte differentiation into M1-like (classic) macrophages, whereas other factors such as interleukin-4 (IL-4), and IL-13 induces monocyte differentiation into M2-like (alternatively activated) macrophages. M1 cells are implicated in initiating and sustaining inflammation through production of high levels of proinflammatory cytokines, reactive nitrogen and oxygen intermediates, while the more

![FIGURE 2](image-url)  
Tissue regeneration. Upon injury, monocyte-derived macrophages are recruited to the injury site and stimulated to adopt a M1 phenotype. M1 macrophages are involved with clearing necrotic cells and tissue debris from the site, and inducing cytotoxic processes, initiate the inflammatory response and secrete pro-inflammatory cytokines (e.g. TNF-a, IL-1b, and IL-6). During the later stages of inflammation, there is a switch from the proinflammatory M1 to the prorepair M2 phenotype. M2 macrophages promote tissue repair through the secretion of proangiogenic and growth factors (e.g. IL-10, TNF-a, IL-1b, and IL-6) and stimulation of fibroblast deposition of granulation tissue. The macrophages predominantly involved with the initial inflammation response are monocyte-derived macrophages, whereas macrophages involved in inflammation resolution and tissue repair are tissue resident macrophages in origin.
heterogeneous M2 cells are characterized by alternative arginine metabolism, exhibit a different chemokine expression profile and are associated with resolution or smoldering chronic inflammation.\(^{32,34}\) In addition to many immune-related cytokines, macrophages also produce numerous effector molecules such as platelet-derived growth factor (PDGF), hepatocyte growth factor, fibroblast growth factor, transforming growth factor (TGF), and Wnt ligands.\(^{35}\) While macrophages can broadly be described as having an M1 or an M2 phenotype, it is important to keep in mind that these segregations were defined in vitro, under well-defined stimuli and may not necessarily represent what happens in vivo. Several studies have shown the fate and phenotype of monocytes and macrophages are not as easily shaped by external stimuli as once believed. In addition to the Ly6C marker, monocytes can be further distinguished apart with the expression of surface receptors C-C motif chemokine receptor 2 (CCR2) and C-X3-C motif chemokine receptor 1 (CX\(_3\)CR1). Rodent studies have shown that CCR\(_2^+\)CX\(_3\)CR1\(^+\)Ly6C\(^\text{hi}\) and CCR\(_2^+\)CX\(_3\)CR1\(^++\)Ly6C\(^\text{lo}\) monocytes, upon appropriate stimulation, more readily and specifically differentiate into M1 and M2 macrophages, respectively.\(^{36-39}\) Furthermore, macrophages may display the same M1 or M2 phenotype, but exhibit different expression profiles with respect for regenerative factors such as Wnt ligands or growth factors.\(^{40}\)

Altogether, the current literature highlights the necessity of a revision in how we define different macrophage polarization phenotypes, at least in studies exploring the regenerative properties of macrophages.

3 | MACROPHAGES AND TISSUE REGENERATION

Tissue regeneration is defined as the process in which damaged or diseased tissue is renewed and regained or replaced, respectively. There are several types of tissue injury that can occur, such as pathogen entry, oxidative stress, or mechanical damage.\(^{41,42}\) On the other hand, some tissues like the gut have constant low levels of inflammation to maintain intestinal homeostasis.\(^{43}\) Regardless of the type of insult, cell death induces the release of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which activate a number of receptors and release cytokines and chemokines to induce an inflammatory response and leukocyte recruitment to the site of injury.\(^{41,42,44}\) The initiated tissue regeneration process can be categorized into three different stages: inflammation, proliferation, and restoration/remodeling. A successful tissue regeneration process relies on a complex interaction between cells that provide necessary regenerative signals and cells that are receptive to those signals. Several studies have shown how macrophages provide and orchestrate the cues necessary for regeneration after injury.\(^{22,35,45-55}\) In general, infiltrating monocyte-derived macrophages are more involved with the early inflammatory response, from clearing necrotic cells and tissue debris from the site, inducing cytotoxic processes, and promoting inflammation. On the other hand, tissue resident macrophages hold a greater role during inflammation resolution and tissue repair by producing proangiogenic and growth factors and stimulating fibroblast deposition of granulation tissue.\(^{9,41,42}\) Throughout tissue regeneration, there is a general pattern of monocyte-derived macrophages infiltrating the injury site, adopting a proinflammatory M1 phenotype in the early stages, and shifting to an anti-inflammatory, pro-repair M2 phenotype in the later stages\(^{56,57}\) (Figure 2).

The role of M1 and M2 macrophages in tissue regeneration of liver, skeletal muscle, kidney, and nerves are reviewed in depth elsewhere.\(^{56}\)

The sequential occurrence of M1 and M2 macrophage phenotypes is crucial for normal tissue regeneration;\(^{57}\) however, the mechanism underlying the phenotypic switch is unclear. One theory is that the microenvironment of some tissues, like the central nervous system, liver, skeletal muscle, heart, and pancreas, produce temporally dynamic and transient signals that induce in situ M1 to M2 macrophage phenotype conversion. An in situ conversion would explain why infiltrating macrophages are seen to possess both proinflammatory and anti-inflammatory/prorepair roles.\(^{22,58-64}\) Signals that induce an in situ conversion can be an increase/decrease in specific factors, activation of a signaling pathway, or crosstalk between macrophages and other cells. To begin with, a reduction in DAMPs, PAMPs, and apoptotic neutrophils has been shown to induce the switch in macrophage phenotype from proinflammatory to anti-inflammatory.\(^{41}\) In addition, during skeletal muscle regeneration, the phagocytosis of cellular debris and the expression of secretory leukocyte peptidase inhibitor and peroxisome proliferator-activated receptor γ (PPAR-γ) promote conversion of inflammatory CX\(_3\)CR1\(^{hi}\)/Ly6C\(^+\) macrophages into anti-inflammatory CX\(_3\)CR1\(^{hi}\)/Ly6C\(^{−}\) macrophages. CX\(_3\)CR1\(^{hi}\)/Ly6C\(^{−}\) macrophages promote myogenic differentiation and myofiber growth and protection of myotube differentiation, which is crucial for proper fiber membrane repair.\(^{25}\) Moreover, in the kidney, the Wnt/β-catenin signaling pathway via Wnt3a-induced upregulation and activation of signal transducer and activator of transcription 3 (STAT3) has been shown to induce M2 macrophage polarization.\(^{55}\) Finally, there is evidence of crosstalk playing a role in the phenotypic switch in macrophages.
during tissue regeneration. In the heart, the switch from inflammatory to anti-inflammatory macrophages is mediated by bone marrow–derived mesenchymal stromal cells via IL-10 secretion.\(^{66,67}\) However, an alternative theory is that there is a sequential recruitment of macrophages and expression of specific cell surface receptors at the injury site. A study on myocardial infarction in mice showed that the expansion of circulating Ly6C\(^\text{hi}\) monocytes and expression of receptor CCR2 led to the migration of proinflammatory Ly6C\(^\text{hi}\) monocytes to the injury site. Later, expression of receptor CX\(_3\)CR1 led to the preferential recruitment of circulating Ly6C\(^\text{lo}\) monocytes to the site. Anti-inflammatory Ly6C\(^\text{lo}\) monocytes express vascular endothelial growth factor (VEGF) and begin granulation tissue formation. Therefore, it is the expansion of circulating monocytes and specific CCR2 or CX\(_3\)CR1 receptor expression that drives a preferential recruitment and phenotype of infiltrating macrophages, respectively.\(^{47}\)

All in all, macrophages play numerous and crucial roles during tissue regeneration. Upon injury, monocyte-derived macrophages infiltrate the site and the predominant phenotype is M1, which secrete proinflammatory factors to activate various signaling pathways. At some point, the dominant macrophage phenotype switches to M2, which are anti-inflammatory and reparatory. There is a dispute over the mechanism behind the phenotypic switch; it could either be driven by an in situ conversion of M1 to M2 or a selective, sequential recruitment of macrophages. The monocyte-derived macrophage populations are part of the initial inflammatory response, whereas tissue resident macrophages appear to be more involved with the resolution of inflammation and tissue repair.

4 | MACROPHAGES CROSS TALK DURING TISSUE REGENERATION

Cellular crosstalk describes how one or more components of a signaling pathway affects another signaling pathway either directly or indirectly to produce a specific biological response.\(^{68}\) Several studies have shown that macrophages crosstalk with endothelial cells, smooth muscle cells, mesenchymal stem cells, and stellate cells to support different aspects of tissue regeneration, such as macrophage recruitment, macrophage polarization, cell proliferation, and angiogenesis. For example, macrophages express Wnt ligands and respond to Wnt signaling to promote endothelial cell proliferation and migration, which is important for angiogenesis.\(^{69}\) In particular, proinflammatory factors IFN-\(\gamma\) and LPS upregulate Wnt5a expression in macrophages.\(^{70}\) Wnt5a is then able to regulate angiogenesis at multiple levels, which in turn can directly induce the expression of additional proangiogenic cytokines such as IL-6, IL-8, and IL-1\(\beta\).\(^{71-74}\) Wnt5a also indirectly induces the proliferation and migration of endothelial cells and increase in Tie-2 expression in endothelial cells and macrophages.\(^{69,75}\) Macrophages are then further stimulated by angiopoietin 2 to become proangiogenic.\(^{76}\) In addition, Wnt5a upregulates CCL2 expression in endothelial cells to indirectly recruit more macrophages.\(^{77}\) Moreover, the crosstalk between macrophages and smooth muscle cells promotes angiogenesis during atherogenesis. Coculture of smooth muscle cells and macrophages lead to an increase in tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), IL-6, IL-1\(\beta\), and toll-like receptor 2 (TLR2) levels, which altogether increases secretion of angiogenic factors VEGF and IL-8 likely through TLR signaling pathways.\(^{78}\) Another study found that transforming growth factor-\(\beta\) (TGF-\(\beta\)) can also stimulate VEGF production and angiogenesis via the TGF-\(\beta\) signaling pathway.\(^{79}\) Furthermore, the crosstalk between macrophages and mesenchymal stem cells is crucial for bone healing.\(^{80-82}\) Macrophages release chemokines (CCL2, stromal cell-derived factor 1, C-X-C motif ligand 8 [CXCL8]), proinflammatory cytokines (TNF-\(\alpha\), IL-1\(\beta\), IL-6), and osteoinductive factors (oncostatin M, bone morphogenetic protein 2, prostaglandin E2 [PGE2]) which are received by mesenchymal cells. In response to these signals, mesenchymal cells direct osteoprogenitor differentiation into osteoblasts, and release immunosuppressive signals, like CCL2, VEGF-A, PGE-2, and nitric oxide (NO), that regulate macrophage recruitment and activity.\(^{82,83}\) In addition, the crosstalk between macrophages and hepatic stellate cells, a liver-specific pericyte that behaves like mesenchymal stem cells, is important for macrophage polarization and progression of liver repair.\(^{84-88}\) Following liver injury, injured parenchymal cells release PAMPs and/or DAMPs, which bind to TLR4 receptors on hepatic stellate cells or other pericytes. Hepatic stellate cells secrete chemotactants like macrophage migration inhibitory factor, CXCL1, CCL2, IL-6, and IL-8, to recruit neutrophils and monocytes to the site.\(^{89-95}\) Monocyte-derived M1 macrophages and neutrophils secrete amphiregulin and IL-17a, respectively, and these two proteins convert TGF-\(\beta\) to its active form so it can activate hepatic stellate cells and pericytes.\(^{96-100}\) Over time the number of activated pericytes and activated TGF-\(\beta\) levels increase. Increasing levels of TGF-\(\beta\) stimulate a M1 to M2 polarization shift via Akt/SNAIL and Akt/FoxO1 signaling pathways, and secretion of MMP-7 by scar-associated macrophages to promote differentiation of hepatocyte-produced pro-NGF into nerve growth factor (NGF). NGF binds to p75 NGF receptor on activated pericytes and induces apoptosis and fibrosis.\(^{101-107}\) Furthermore, macrophages crosstalk with satellite cells to regulate the myogenesis process.\(^{108}\) Not only do
macrophages secrete proinflammatory cytokines, such as IL-6, TNF-α, and PGE-2, but also the enzyme ADAMTS1, which induces satellite cell activation and proliferation and promotes muscle regeneration. Moreover, anti-inflammatory macrophages secrete cytokines, such as IL-4 and insulin-like growth factor 1, that induces myoblast differentiation and myofiber growth.

To sum up, there is increasing evidence that crosstalk between macrophages and other resident cells help drive tissue regeneration.

5 | MACROPHAGES IN THE REGENERATING PANCREAS

The origins and phenotypes of resident macrophages differ within the intrapancreatic microenvironment. One study describes a single population of resident macrophages residing in the islets of Langerhans that arose from definitive hematopoiesis, remained locally in the islets since birth, proliferate in situ slowly, and display the M1 phenotype. However, another study found two separate subsets of resident macrophages, using surface markers CD11c and F4/80, residing within the islets. CD11c− [R1] and CD11c+ [R2] resident macrophages reside in the peri- and intraislets, respectively, and are not derived from circulating monocytes. There are two populations of resident macrophages in the interacinar stroma, which are distinguished apart by CD206 (mannose receptor) and CD301 (CLEC10A) expression. The CD206/CD301+ resident macrophages arise from primitive hematopoiesis, concentrate around the pancreatic ducts, and display an M2 phenotype. On the other hand, the CD206/CD301− resident macrophages arise from definitive hematopoiesis, replenished by circulating monocytes, and display an M2 phenotype (Figure 3).

Since fetal macrophages are thought to contribute to pancreatic islet morphogenesis and remodeling during the fetal and neonatal stages, it is also possible that macrophages play a role in adult pancreatic regeneration. In fact, there is emerging evidence showing that macrophages crosstalk with resident cells via release of factors like IL-1β, epidermal growth factor (EGF), TGF-β1, and Wnt3a to promote β-cell proliferation and pancreas regeneration.

To begin with, islet macrophages release low levels of IL-1β, which enhances β-cell insulin secretion especially during periods of acute stress. In addition, macrophage crosstalk with β-cells assist in β-cell proliferation and regeneration following pancreatic injury. During the inflammation resolution phase, M2 macrophages release EGF and TGF-β1 and these signals are received by β-cells. EGF acts on epidermal growth factor receptor (EGFR) to inhibit SMAD2 nuclear translocation, thereby inhibiting TGF-β signaling. TGF-β1 acts on TGF-β receptor to upregulate SMAD7, which not only causes nuclear exclusion of cell cycle regulator p27 but also increases cell cycle activators cyclin D1 and cyclin D2. Altogether, this promotes β-cell proliferation. Moreover, in a diabetic phenotype mouse model, M2 macrophages release Wnt3a and this signal is received by receptors at the surface of β-cells. This leads to inhibition of glycogen synthase kinase 3 and subsequent β-catenin

![Diagram of proposed tissue resident macrophages in the pancreas: CD11c− [R1] peri-islet (orange), CD11c+ [R2] intraislet (green), CD206/CD301+ (blue), and CD206/CD301− (purple)]
translocation into the nucleus. There is also a marked increase in cyclin D2 in the nucleus. Altogether, the activation of the β-cell Wnt/β-catenin signaling pathway promotes β-cell replication. Moreover, in a mouse model with VEGF-A overexpression-induced β-cell loss, macrophage crosstalk with islet endothelial cells was important for β-cell proliferation. These reports indicate M2 macrophages crosstalk with multiple cell types in islets is important to β-cell regeneration following pancreatic injury (Figure 4). Furthermore, the origins of M2 macrophages responsible for β-cell proliferation have been identified as resident tissue macrophages. In fact, both the peri- and intraslets resident macrophages are found to promote β-cell proliferation.

6 | MACROPHAGES IN PANCREATIC DISEASE

6.1 | Diabetes

There is much evidence showing that prolonged macrophage activation causes β-cell death during type 1 and type 2 diabetes mellitus via the release of cytokines and nutrients, respectively. The onset of type 1 diabetes is marked by the infiltration of macrophages and T cells in the islets of Langerhans. In type 1 diabetes, macrophage secretion of cytokines IL-1β and/or TNF-α + IFN-γ activates nuclear factor kappa B (NF-κB) and STAT1. NF-κB activation then leads to NO production and chemokines as well as endoplasmic reticulum (ER) calcium production. ER stress and mitochondrial death signals subsequently induce β-cell death.

On the other hand, β-cell death in type 2 diabetes is caused by chronic elevation of glucose and free fatty acid levels and crosstalk with islet M1 macrophages. The free fatty acids force β cells to produce islet amyloid polypeptide (IAPP). The release of IAPP and adenosine triphosphate from β cells signals for the recruitment of bone marrow-derived monocytes and M1 macrophage accumulation to the islets. The elevated levels of glucose lead to activation of the NLRP3-dependent inflammasomes and processing and production of proinflammatory factor IL-1β in M1 macrophages. M1 macrophages also release TNF-α and the increased levels of both TNF-α and IL-1β crosstalk with β cells and cause β-cell dysfunction and eventual cell death. β-cell death releases more chemokines and cytokines, thereby creating a feedback loop that continues to drive inflammation and the β-cell failure that is characteristic of type 2 diabetes.

Although there is significant evidence that shows macrophages cause β-cell death during type 1 and type 2 diabetes, there is evidence that suggests that macrophages are also involved with pancreas and β-cell regeneration.

6.2 | Pancreatitis

In the healthy pancreas, acinar cells and ductal cells are responsible for the production of digestive enzymes and transportation of enzymes to the gut, respectively. During acute pancreatitis, there is the premature activation of trypsinogen in acinar cells, leading to autodigestion of the pancreas, stimulation of M1 macrophages, and release of proinflammatory factors. Proinflammatory factors TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein 1 can recruit neutrophils and more monocytes to the pancreas and increase the release of proinflammatory mediators. More importantly, the release of cytokines TNF-α and RANTES by macrophages stimulates the activation of NF-κB in acinar cells to induce acinar cell transdifferentiation into a duct-like progenitor cell types, which is termed acinar-to-ductal metaplasia (ADM). Notch receptors and EGFR have also been shown to induce ADM in acinar cells. M2 macrophages are recruited to help the cells revert back to acinar cells and initiate tissue remodeling and repair. Ultimately, ADM decreases the production of digestive enzymes, mitigates the inflammatory response, and sets the stage for tissue repair. Recurrent pancreatic injury can eventually lead to the development of chronic pancreatitis, which is characterized by chronic inflammation, irreversible fibrosis, acinar cell atrophy and contorted ducts. Unlike acute pancreatitis, most macrophages in chronic pancreatitis display a M2 phenotype. The infiltrating macrophages crosstalk with and activate nearby pancreatic stellate cells (PSCs) via the TGF-β/PDGF signaling pathway. PSCs are periacinar stromal cells, which are present in a quiescent state in healthy pancreas. PSCs are activated during initial phases of pancreatic injury and play a key role in

![FIGURE 4 M2 macrophages crosstalk with β cells to promote β-cell proliferation and insulin secretion. EGF, epidermal growth factor; IL-1β, interleukin-1β; TGF-β1, transforming growth factor-β1](image-url)
pancreatitis and pancreatic cancer as the predominant source of collagen in the fibrotic pancreas. Activated PSCs release IL-4 and IL-13, which promotes M2 macrophage polarization. In fact, inhibition of IL-4 and IL-13 in ex vivo human tissue and mice has been shown to lead to a decrease in M2 macrophages levels and fibrosis progression. Most notably, chronic pancreatitis is strongly associated with the development of pancreatic ductal adenocarcinoma (PDAC).

To sum up, there is a heterogenous population of macrophages in the pancreas that differ in origin and function. Recent studies show that macrophages cross-talk with other cells present in the pancreas to promote β-cell proliferation and pancreatic regeneration following injury. M1 macrophages play a dominate role in resolving acute pancreatitis and M2 macrophages play a dominate role in the chronic pancreatitis and β-cell proliferation.

### 6.3 Pancreatic cancer

Patients with pancreatic cancer have a poor prognosis and a survival rate of about 6% within 5 years of initial diagnosis. The most common type of pancreatic cancer is PDAC. The late detection and aggressive nature of PDAC makes it notoriously difficult to treat, therefore, understanding the drivers of PDAC initiation, progression, and metastasis is imperative to developing therapy treatments. Nearly 95% of all pancreatic cancers have one of three different proto-oncogene mutations of Kras within the pancreatic acinar cells. Therefore, the general steps toward the development of PDAC is as follows: acquirement of a Kras mutation in an acinar cell, ADM, formation of pancreatic intraepithelial neoplasia (PanIN) lesions or other lesions, progression from lesion to PDAC, and continued promotion of tumor growth and metastasis. Interestingly, macrophages have been shown to play a role at each of these steps toward PDAC. Inflammatory macrophages promote the formation of precursor PanIN lesions or other lesions by crosstalk with acinar cells carrying a Kras mutation to induce inappropriate activation of signaling pathways that bring on ADM, and secreting factors that promote tissue remodeling. Alternatively activated macrophages drive the development of PanIN lesions to PDAC. In addition, alternatively activated tumor-associated macrophages (TAMs) promote further tumor growth and PDAC metastasis. We do acknowledge that there is still an ongoing debate on which cells contribute to the pancreatic cancer, and while other cell types such as duct cell cannot be ruled out, the current review focuses on acinar origin of the PDAC.

To begin with, inflammatory M1 macrophages are stimulated by KrasG12D-acinar cells to release factors that cause inappropriate activation of signaling pathways, such as the NF-κB, Notch, EGFR/mitogen-activated protein kinase (MAPK), Wnt/β-catenin, and STAT3/suppressor of cytokine signaling 3 (Socs3), to stimulate ADM. Acinar cells with the KrasG12D mutation upregulate ICAM-1 expression and a fraction of it is shed as a soluble form (sICAM-1), which acts as a chemoattractant and recruits M1 macrophages. The M1 macrophage interacts with the KrasG12D-acinar cell and secretes MMPs, like MMP-9, to degrade the extracellular matrix and promoting tissue remodeling. M1 macrophages also secrete inflammatory cytokines, such as TNF, that induce activation of the NF-κB signaling pathway to drive ADM in acinar cells. The KrasG12D mutation stimulates production of activator protein 1 (AP1), which induces IL-1α overexpression. IL-1α activates downstream inhibitor of nuclear factor kappa B kinase subunit β (IKK2/β), which then activates NF-κB. NF-κB promotes transcription of IL-1α and p62, and these two factors act on IKK2/β to establish an autoregulatory feedback loop for constitutive activation of the NF-κB signaling pathway. In addition, there is crosstalk between the NF-κB and Notch signaling pathways in KrasG12D-acinar cells. IKK2 from the NF-κB pathway synergizes with basal Notch to transcribe Notch target genes, one being a suppressor of anti-inflammatory transcription factor PPAR-γ. As such, this helps to maintain the inflammatory response initiated by KrasG12D-acinar cells. Moreover, the KrasG12D mutation activates the MAPK signaling pathway. Kras upregulates EGFR expression and enhances EGFR activity via EGFR ligand sheddase, ADAM17. An example of crosstalk between TAM and the epithelium is the stimulation of EGFR expression in neoplastic epithelium by macrophages and stimulation of macrophages to secrete EGFR ligands by KrasG12D-acinar cells. Some ligands bind to EGFR on KrasG12D-acinar cells and activate the MAPK signaling pathway and repress acinar-specific transcription factors, whereas other ligands stimulate stromal fibroblasts to produce collagen. Interestingly, low levels of Wnt signaling in cell lines with Kras mutations crosstalk with the MAPK signaling pathway to also promote ADM and PanIN formation. Furthermore, myeloid cell secretion of IL-6 induces the activation of the STAT3/Socs3 signaling pathway in KrasG12D-acinar cells. The signaling pathway is continuously activated in a feed-forward response loop. STAT3 signaling has also been shown to help KrasG12D-acinar cells maintain a proliferative, dedifferentiated state and contribute to inflammation. IL-6 is not the only pathway that promotes STAT3 activation. It was recently reported that extracellular high mobility group box 1, either passively released by damaged/dying neoplastic cells, or actively secreted by TAMs stimulates...
prolactin expression by macrophages. The macrophage-derived prolactin binds to its cognate receptor on PanIN cells, where it maintains focal adhesion kinase 1 and STAT3 activity. In addition, prolactin may promote fibrosis through PRLR-expressing resident macrophages.  

In addition, Stat3 signaling controls MMP-7 expression, which regulates tumor size and metastasis, in KrasG12D-acinar cells. Ultimately, the KrasG12D mutation continuously promotes crosstalking with macrophages that secrete factors that activate signaling pathways in acinar cells that not only induce ADM but also maintains the dedifferentiated cellular state. In addition, the KrasG12D mutation sustains, rather than directly causes, cell proliferation, thereby allowing for the formation of intraepithelial neoplastic lesions (PanINs) or other lesions (Figure 5).

Next, the role of macrophages during the progression from PanIN lesion to PDAC is still largely unknown. However, a recent study shows that the inflammatory M1-like macrophages switch to tumor-promoting, alternatively activated M2-like macrophages at ADM/PanIN lesions (Figure 6). In particular, IL-13, which is likely produced by PSCs, binds to receptor IL-13-Rα1 on inflammatory macrophages to initiate the polarization switch towards an alternatively active macrophage. Alternatively activated macrophages then secrete factors such as CCL2 and IL-1ra to drive fibrogenesis and PanIN lesion growth.

Lastly, circulating monocytes and macrophages are recruited to the stromal compartment of the tumor microenvironment (TME), henceforth known as TAMs, where they secrete factors to alter the TME and drive

**FIGURE 5** Schematic of proposed macrophage crosstalk and subsequent signaling cascades initiated by the Kras mutation (Kras*) in an acinar cell to induce acinar-to-ductal metaplasia (ADM). The Kras* acinar cell recruits M1 macrophages through the release of chemoattractants (blue circles). The macrophage subsequently releases proinflammatory cytokines (purple triangles) that activate various signaling pathways, such as nuclear factor kappa B (NF-κB), Notch, mitogen-activated protein kinase (MAPK), Wnt/β-catenin, and STAT3/Socs3, in acinar cells. The activation of these signaling pathways leads to the transcription of target genes that ultimately suppress acinar-specific transcription factors and/or anti-inflammatory transcription factors, thereby inducing ADM. The NF-κB and Notch signaling pathways and the MAPK and Wnt/β-catenin signaling pathways also participate in crosstalk. Macrophages also secrete extracellular matrix (ECM) degradation enzymes, which promotes tissue remodeling. The combined actions of irreversible ADM, continuous macrophage secretion of inflammatory cytokines and ECM degradation enzymes, and sustained cell proliferation is permissive for precursor intraepithelial neoplastic lesions (PanINs) or other lesions formation. Socs3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3.
**PDAC progression and metastasis.** The stroma is comprised of many different cell types, but this review will only focus on TAMs. TAMs found in PDAC can be either resident macrophages or monocyte-derived macrophages in origin. Resident-derived TAMs undergo in situ proliferation and are responsible for the fibrotic response and tumor progression, whereas monocyte-derived TAMs help with antigen presentation and immune response.

All tumors have M1-like and M2-like TAMs, but the amount of each phenotype changes over the course of tumorigenesis. During the beginning stages of PDAC, M1-like macrophages are found in abundance at sites of chronic inflammation and tumors. As tumor invasion and vascularization begins, the macrophages switch to the M2-like phenotype (Figure 6). Most TAMs have a M2-like phenotype and their presence in PDAC is associated with poor outcomes. The mechanism behind TAM polarization to an M2-like phenotype is still unclear, but there is growing evidence that the activation of signaling pathways via crosstalk can induce repolarization. In cell lines, cancer cells secrete regenerating islet-derived protein 4 (REG4). REG4 activates the EGFR/AKT/cAMP response element-binding protein signaling pathway and this may, in part, induce M2 polarization. In addition, in cell lines, tumor and other stromal cells secrete TGF-β, which induces homeobox transcription factor CUX1 and the NF-κB signaling pathway via acetylation, thereby repressing NF-κB-regulated proinflammatory cytokines and antagonizing TAM M1-like phenotype. Furthermore, crosstalk between pancreatic tumor cells and macrophages via exosomal miRNA is thought to also induce M2 polarization. The hypoxic microenvironment of solid tumors promotes pancreatic tumor cells to release miR-301a-3p-rich exosomes. These exosomes activates the phosphatase and tensin homolog/PI3Kγ pathway to induce M2 macrophage polarization. Crosstalk with cancer stem cells (CSCs) have also been shown to induce an M2-like phenotype in macrophages via Nodal/Activin A and TGF-β1 secretion and activation of STAT3 signaling. Ultimately, the M2-like TAMs are responsible for promoting PDAC tumorigenesis and metastasis.}

**FIGURE 6** Diagram of the appearance of macrophages during the development and progression of pancreatic ductal adenocarcinoma (PDAC). Inflammatory M1 macrophages are stimulated by acinar cells carrying a Kras mutation (Kras*) to release factors that activate various signaling pathways to induce acinar-to-ductal metaplasia (ADM). Inflammatory macrophages undergo repolarization and become alternatively activated M2 macrophages. Without Kras*, M2 macrophages would assist with the redifferentiation of acinar cells and initiate tissue remodeling and repair. However, with Kras*, factors secreted by the M2 macrophages drive PanIN growth and progression instead. Ultimately, PDAC develops and the tumor-associated macrophages (TAMs) in the tumor microenvironment (TME) promote tumor growth, progression, and metastases of PDAC. M1-like TAMs are observed in the beginning stages of PDAC and are involved with inflammation. On the other hand, M2-like TAMs are in greater abundance during the later stages of PDAC and reinforce tumor growth, invasion, vascularization, and metastasis.
In particular, crosstalk between macrophages and CSCs enhances tumorigenesis. For example, reduction in the number of infiltrating macrophages resulted in a significant decline of CSCs. In addition to controlling the number of CSCs, TAM can also increase the tumor-initiating capacity of CSCs through STAT3 signaling pathway. In vitro primary human pancreatic cancer spheres show CSCs secrete IFN-β and, in turn, stimulates TAMs to secrete IFN-stimulated factor 15 (ISG15). ISG15 is shown to enhance CSC self-renewal and tumorigenic properties. Moreover, polarized TAMs are also shown to secrete antimicrobial peptide human cathelicidin 18/LL-37, which binds to CSC receptors and enhance their stemness and tumorigenic properties. Finally, binding of CD47, which is expressed by CSCs, to SIRPα on macrophages leads to prevention of CSCs phagocytosis by macrophages. Altogether, TAM-mediated paracrine signaling promotes the stem-like features of CSCs, thereby enhancing tumor progression, metastasis, and chemoresistance in PDAC. Interestingly, there is also evidence that liver macrophages play a role in promoting pancreatic cancer-related illnesses, such as cachexia (wasting syndrome). In PDAC patients, there is an increase in peripheral blood mononuclear cells. It is hypothesized that the monocytes infiltrate the liver, triggering activation of liver parenchymal cells, and inducing the release of proinflammatory cytokines, like TNF-α, IL-6, and IL-8. In turn, this activates NF-κB and STAT3 transcription factors and hepatocytes for additional release of proinflammatory cytokines.

In summary, the Kras mutation and inflammation activates additional signaling pathways that not only induces ADM, but also prevents redifferentiation back to acinar cells and subsequently leads to the formation of precursor PanIN lesions. In the ADM/PanIN lesions, macrophages undergo a phenotypic switch from inflammatory to alternatively activated. The alternatively activated macrophages continue to drive the progression from PanIN lesion to PDAC. M2-like TAMs continue to drive tumor growth, progression, and metastases of PDAC via activation of various molecular signaling pathways. Notably, there is emerging evidence that shows crosstalk between macrophages and CSCs in the TME play a role in supporting tumorigenesis and metastasis of PDAC. Given the involvement of macrophages in general, and M2 macrophages in particular in various stages of PDAC development, targeted therapeutic treatments aiming to reduce the number of M2 subtype either through inhibition of recruitment, specific ablation or conversion to M1 phenotype has shown promising results in numerous clinical trials.

7 | CONCLUSION

Macrophages are indispensable not only for fighting harmful biological agents but also for healing and tissue regeneration. In that regard, M1 and M2 phenotypes play separate, yet equally important roles. Macrophages are like good Samaritans, always ready to help, but sometimes they unwillingly help the wrong side. In other words, they are villains by circumstances, not necessarily by actions.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Andrea F. Cruz http://orcid.org/0000-0001-9353-9942
Rokhsareh Rohban http://orcid.org/0000-0003-3922-4952
Farzad Esni http://orcid.org/0000-0002-0342-6862

REFERENCES

1. Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science. 2010;330(6005):841-845. https://doi.org/10.1126/science.1194637
2. Gautier EL, Shay T, Miller J, et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nature Immunol. 2012;13(11):1118-1128. https://doi.org/10.1038/ni.2419
3. Hoefl G, Wang Y, Greter M, et al. Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac-derived macrophages. J Exp Med. 2012;209(6):1167-1181. https://doi.org/10.1084/jem.20120340
4. Schulz C, Perdiguerog E, Chorro L, et al. A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science. 2012;336(6077):86-90. https://doi.org/10.1126/science.1219179
5. Guilliams M, De Kleer I, Henri S, et al. Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. J Exp Med. 2013;210(10):1977-1992. https://doi.org/10.1084/jem.20131199
6. Yona S, Kim KW, Wolf Y, et al. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity. 2013;38(1):79-91. https://doi.org/10.1016/j.immuni.2012.12.001
7. Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. Immunity. 2014;41(1):21-35. https://doi.org/10.1016/j.immuni.2014.06.013 PubMed PMID: 25035951.
8. Gomez Perdiguer E, Klapproth K, Schulz C, et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature*. 2015;518(7540):547-551. https://doi.org/10.1038/nature13989

9. Epelman S, Lavine KJ, Beaudin AE, et al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. *Immunity*. 2014;40(1):91-104. https://doi.org/10.1016/j.immuni.2013.11.019

10. Theret M, Mounier R, Rossi F. The origins and non-canonical functions of macrophages in development and regeneration. *Development*. 2019;146(9):dev156000. https://doi.org/10.1242/dev.156000

11. Ginhoux F, Guillemis M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity*. 2016;44(3):439-449. https://doi.org/10.1016/j.immuni.2016.02.024

12. Orkin SH, Zon LI. Hematopoiesis: an evolving paradigm for stem cell biology. *Cell*. 2008;132(4):631-644. https://doi.org/10.1016/j.cell.2008.01.025

13. Palis J, Yoder MC. Yolk-sac hematopoiesis: the first blood cells of mouse and man. *Exp Hematol*. 2001;29(8):927-936. https://doi.org/10.1016/S0301-472X(01)00669-5

14. Wicksteed B, Brissova M, Yan W, et al. Conditional gene targeting in mouse pancreatic β-cells: analysis of ectopic Cre transgene expression in the brain. *Diabetes*. 2010;59(12):3090-3098. https://doi.org/10.2337/db10-0624

15. Hoeffel G, Ginhoux F. Ontogeny of tissue-resident macrophages. *Front Immunol*. 2015;6(486):486. https://doi.org/10.3389/fimmu.2015.00486

16. Bertrand JY, Jalil A, Klaine M, Jung S, Cuman A, Godin I. Three pathways to mature macrophages in the early mouse yolk sac. *Blood*. 2005;106(9):3004-3011. https://doi.org/10.1182/blood-2005-02-0461

17. Akashi K, Traver D, Miyamoto T, Weissman IL. A clonogenic common myeloid progenitor that gives rise to all myeloid lineages. *Nature*. 2000;404(6774):193-197. https://doi.org/10.1038/3504599

18. Hashimoto D, Chow A, Noizat C, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. *Immunity*. 2013;38(4):792-804. https://doi.org/10.1016/j.immuni.2013.04.004

19. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol*. 2005;5(12):953-964. https://doi.org/10.1038/nri1733

20. Jenkins SJ, Ruckerl D, Cook PC, et al. Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. *Science*. 2011;332:1284-1288. https://doi.org/10.1126/science.1204351

21. Amano SU, Cohen JL, Vangala P, et al. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. *Cell Metab*. 2014;19(1):162-171. https://doi.org/10.1016/j.cmet.2013.11.017

22. Arnold L, Henry A, Poron F, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into anti-inflammatory macrophages to support myogenesis. *J Exp Med*. 2007;204(5):1057-1069. https://doi.org/10.1084/jem.20070075

23. van Rooijen N, Hendriks E. Liposomes for specific depletion of macrophages from organs and tissues. In: Weissig V, ed. Liposomes: Methods and Protocols, Volume 1: Pharmaceutical Nanocarriers. Totowa, NJ: Humana Press; 2010:189-203.

24. Bryer SC, Fantuzzi G, Van Rooijen N, Koh TJ. Urokinase-type plasminogen activator plays essential roles in macrophage chemotaxis and skeletal muscle regeneration. *J Immunol*. 2008;180(2):1179-1188. https://doi.org/10.4049/jimmunol.180.2.1179

25. Willenborg S, Lucas T, van Loo G, et al. CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair. *Blood*. 2012;120(3):613-625. https://doi.org/10.1182/blood-2012-01-403386

26. McCulloch DK, Koerker DJ, Kahn SE, Bonner-Weir S, Palmer JP. Correlations of In Vivo β-Cell Function Tests With β-Cell Mass and Pancreatic Insulin Content in Streptozocin-Administered Baboons. *Diabetes*. 1991;40(6):673-679. https://doi.org/10.2337/db04.60.6.673

27. Geissmann F, Jung S, Litman DR. Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity*. 2003;19(1):71-82. https://doi.org/10.1016/S1074-7613(03)00174-2

28. Carlin Leo M, Stamatatos Efstathiou G, Auffray C, et al. Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell*. 2013;153(2):362-375. https://doi.org/10.1016/j.cell.2013.03.010

29. Jakubzick C, Gautier Emmanuel L, Gubbins Sophie L, et al. Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. *Immunity*. 2013;39(3):599-610. https://doi.org/10.1016/j.immuni.2013.08.007

30. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122(3):787-795. https://doi.org/10.1172/JCI59643

31. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol*. 2009;27(1):451-483. https://doi.org/10.1146/annurev.immunol.021908.132532

32. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122(3):787-795. https://doi.org/10.1172/JCI59643

33. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity*. 2010;32(5):593-604. https://doi.org/10.1016/j.immuni.2010.05.007

34. Brown BN, Ratner BD, Goodman SB, Amar S, Badylak SF. Macrophage polarization: an opportunity for improved outcomes in biomaterials and regenerative medicine. *Biomaterials*. 2012;33(15):3792-3802. https://doi.org/10.1016/j.biomaterials.2012.02.034

35. Stetfater JA 3rd, Ren S, Lang RA, Duffield JS. Metchnikoff's policemen: macrophages in development, homeostasis and regeneration. *Trends Mol Med*. 2011;17(12):743-752. https://doi.org/10.1016/j.molmed.2011.07.009

36. Varol C, Landsman L, Fogg DK, et al. Monocytes give rise to mucosal, but not splenic, conventional dendritic cells. *J Exp Med*. 2007;204(1):171-180. https://doi.org/10.1084/jem.20061011

37. Yrlid U, Jenkins CD, MacPherson GG. Relationships between distinct blood monocyte subsets and migrating intestinal lymph dendritic cells in vivo under steady-state conditions.
38. Sunderkötter C, Nikolic T, Dillon MJ, et al. Subpopulations of mouse blood monocytes differ in maturation stage and inflammatory response. *J Immunol*. 2004;172(7):4410-4417. https://doi.org/10.4049/jimmunol.172.7.4410
39. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. *Nat Rev Immunol*. 2011;11(11):762-774. https://doi.org/10.1038/nri3070
40. Hoeffel G, Wang Y, Greter M, et al. Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac-derived macrophages. *J Exp Med*. 2012;209(6):1167-1181. https://doi.org/10.1084/jem.20120340
41. Lech M, Anders H-J. Macrophages and fibrosis: how resident and infiltrating mononuclear phagocytes orchestrate all phases of tissue injury and repair. *Biochim Biophys Acta*. 2013;1832(7):989-997. https://doi.org/10.1016/j.bbadis.2012.12.001
42. Wynn T. Cellular and molecular mechanisms of fibrosis. *J Pathol*. 2008;214(2):199-210. https://doi.org/10.1002/path.2277
43. MacDonald TT, Monteleone I, Fantini MC, Monteleone G. Regulation of homeostasis and inflammation in the intestine. *Gastroenterology*. 2011;140(6):1768-1775. https://doi.org/10.1053/j.gastro.2011.02.047
44. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol*. 2005;15(11):599-607. https://doi.org/10.1016/j.tcb.2005.09.002
45. Pull SL, Doherty JM, Mills JC, Gordon JI, Stappenbeck TS. Regulation of homeostasis and inflammation in the intestine. *Gastroenterology*. 2011;140(6):1768-1775. https://doi.org/10.1053/j.gastro.2011.02.047
46. Pn Loke, Gallagher I, Nair MG, et al. Alternative activation is an innate response to injury that requires CD4+ T cells to be sustained during chronic infection. *J Immunol*. 2007;179(6):3926-3936. https://doi.org/10.4049/jimmunol.179.6.3926
47. Nahrendorf M, Swirski FK, Aiakwa E, et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. *J Exp Med*. 2007;204(12):3037-3047. https://doi.org/10.1084/jem.20070885
48. Lucas T, Waisman A, Ranjan R, et al. Differential roles of macrophages in diverse phases of skin repair. *J Immunol*. 2010;184(7):3964-3977. https://doi.org/10.4049/jimmunol.0903356
49. Stefater JA 3rd, Lewkowich I, Rao S, et al. Regulation of angiogenesis by a non-canonical Wnt-Fli1 pathway in myeloid cells. *Nature*. 2011;474(7352):511-515. https://doi.org/10.1038/nature10085
50. Boultet L, Govaere O, Bird TG, et al. Macrophage-derived Wnt opposes Notch signaling to specify hepatic progenitor cell fate in chronic liver disease. *Nature Med*. 2012;18(4):572-579. https://doi.org/10.1038/nm.2667
51. Stefater JA 3rd, Rao S, Bezold K, et al. Macrophage Wnt-Calcineurin-Fli1 signaling regulates mouse wound angiogenesis and repair. *Blood*. 2013;121(13):2574-2578. https://doi.org/10.1182/blood-2012-06-434621
52. Bird TG, Lu W-Y, Boultet L, et al. Bone marrow injection stimulates hepatic ductular reactions in the absence of injury via macrophage-mediated TWEAK signaling. *Proc Natl Acad Sci U S A*. 2013;110(16):6542-6547. https://doi.org/10.1073/pnas.1302168110
53. Godwin JW, Pinto AR, Rosenthal NA. Macrophages are required for adult salamander limb regeneration. *Proc Natl Acad Sci U S A*. 2013;110(23):9415-9420. https://doi.org/10.1073/pnas.1300290110
54. Aurora AB, Porrello ER, Tan W, et al. Macrophages are required for neonatal heart regeneration. *J Clin Invest*. 2014;124(3):1382-1392. https://doi.org/10.1172/JCI72181
55. Criscimanna A, Coudriet GM, Gittes GK, Pipanelli JD, Esnf F. Activated macrophages create lineage-specific microenvironments for pancreatic acinar- and β-cell regeneration in mice. *Gastroenterology*. 2014;147(5):1106-1118.e11. https://doi.org/10.1053/j.gastro.2014.08.008
56. Chazaud B. Macrophages: supportive cells for tissue repair and regeneration. *Immunobiology*. 2014;219(3):172-178. https://doi.org/10.1016/j.imbio.2013.09.001
57. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity*. 2016;44(3):450-462. https://doi.org/10.1016/j.immuni.2016.02.015
58. Zigmond E, Samia-Grinberg S, Pasmanik-Chor M, et al. Infiltrating monocyte-derived macrophages and resident Kupffer cells display different ontogeny and functions in acute liver injury. *J Immunol*. 2014;193(1):344-353. https://doi.org/10.4049/jimmunol.1400574
59. Miron VE, Boyd A, Zhao J-W, et al. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nat Neurosci*. 2013;16(9):1211-1218. https://doi.org/10.1038/nn.3469
60. Dal-Secco D, Wang J, Zeng Z, et al. A dynamic spectrum of monocytes arising from the in situ reprogramming of CCR2+ monocytes at a site of sterile injury. *J Exp Med*. 2015;212:447-456. https://doi.org/10.1084/jem.20141539
61. Ramachandran P, Pellicoro A, Vernon MA, et al. Differential Ly6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. *Proc Natl Acad Sci U S A*. 2012;109(46):E3186-E3195. https://doi.org/10.1073/pnas.1119964109
62. Duffield JS, Forbes SJ, Constandinou CM, et al. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J Clin Invest*. 2005;115(1):56-65. https://doi.org/10.1172/JCI22675
63. Van Gassen N, Van Overmeire E, Leuckx G, et al. Macrophage dynamics are regulated by local macrophage proliferation and monocyte recruitment in injured pancreas. *Eur J Immunol*. 2015;45(5):1482-1493. https://doi.org/10.1002/eji.201445013
64. Lin S-L, Li B, Rao S, et al. Macrophage Wnt7b is critical for kidney repair and regeneration. *Proc Natl Acad Sci U S A*. 2010;107(9):4194-4199. https://doi.org/10.1073/pnas.0912283107
65. Feng Y, Ren J, Gui Y, et al. Wnt/β-catenin–promoted macrophage alternative activation contributes to kidney fibrosis. *J Am Soc Nephrol*. 2018;29(1):182-193. https://doi.org/10.1681/asn.2017040391
66. Dayan V, Yannarelli G, Billia F, et al. Mesenchymal stromal cells mediate a switch to alternatively activated monocytes/macrophages after acute myocardial infarction. *Basic Res Cardiol*. 2011;106(6):1299-1310. https://doi.org/10.1007/s00395-011-0221-9
67. Ben-Mordechai T, Holbova R, Landa-Rouben N, et al. Macrophage subpopulations are essential for infarct repair with...
and without stem cell therapy. J Am Coll Cardiol. 2013;62(20):1890-1901. https://doi.org/10.1016/j.jacc.2013.07.057

68. Vert G, Chory J. Crosstalk in cellular signaling: background noise or the real thing? Dev Cell. 2011;21(6):985-991. https://doi.org/10.1016/j.devcel.2011.11.006

69. Newman AC, Hughes CCW. Macrophages and angiogenesis: a role for Wnt signaling. Vasc Cell. 2012;4(1):13. https://doi.org/10.1186/2045-824X-4-13

70. Pereira C, Schauer DJ, Bachli EB, Kurrer MO, Schoedon G. Wnt5A/CaMKII signaling contributes to the inflammatory response of macrophages and is a target for the anti-inflammatory action of activated protein C and interleukin-10. Arterioscler Thromb Vasc Biol. 2008;28(3):504-510. https://doi.org/10.1161/ATVBAHA.107.157438

71. Campbell IL, Abraham CR, Masliah E, et al. Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. Proc Natl Acad Sci U S A. 1993;90(21):10061-10065. https://doi.org/10.1073/pnas.90.21.10061

72. Fan Y, Ye J, Shen F, et al. Interleukin 6 stimulates circulating blood-derived endothelial progenitor cell angiogenesis in vitro. J Cereb Blood Flow Metab. 2008;28(1):90-98. https://doi.org/10.1038/sj.jcbf.9600509

73. Li A, Dubey S, Varney ML, Dave BJ, Singh RK. IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinase production and regulated angiogenesis. J Immunol. 2005;170(6):3369-3376. https://doi.org/10.4049/jimmunol.170.6.3369

74. Rosell A, Araî K, Lok J, et al. Interleukin-6 augments angiogenic responses of murine endothelial progenitor cells in vitro. J Cereb Blood Flow Metab. 2009;29(5):933-943. https://doi.org/10.1038/sj.jcbf.9600509

75. Mascarcañón TNH, Agalliu D, Vorontchikhina M, et al. Wnt5A signaling induces proliferation and survival of endothelial cells in vitro and expression of MMP-1 and Tie-2. Mol Biol Cell. 2006;17(12):5163-5172. https://doi.org/10.1091/mbc.e06-04-0320

76. Coffelt SB, Tal AO, Scholz A, et al. Angiopoietin-2 regulates gene expression in TIE2-expressing monocytes and augments their proangiogenic functions. Cancer Res. 2010;70(13):5270-5280. https://doi.org/10.1158/0008-5472.Can-10-0012

77. Kim J, Kim J, Kim DW, et al. Wnt5A induces endothelial inflammation via β-catenin-independent signaling. J Immunol. 2010;185(2):1274-1282. https://doi.org/10.4049/jimmunol.20100181

78. Butoi E, Gan AM, Tucureanu MM, et al. Cross-talk between macrophages and smooth muscle cells impairs collagen and metalloproteinase synthesis and promotes angiogenesis. Biochim Biophys Acta. 2016;1863(7 part A):1568-1578. https://doi.org/10.1016/j.bbamacr.2016.04.001

79. Jeon S-H, Chae B-C, Kim H-A, et al. Mechanisms underlying TGF-β1-induced expression of VEGF and Flk-1 in mouse macrophages and their implications for angiogenesis. J Leukoc Biol. 2007;81(2):557-566. https://doi.org/10.1189/jlb.0806517

80. Chang MK, Raggett L-J, Alexander KA, et al. Osseal tissue macrophages are intercalated throughout human and mouse bone lining tissues and regulate osteoblast function in vitro and in vivo. J Immunol. 2008;181(2):1232-1244. https://doi.org/10.4049/jimmunol.181.2.1232

81. Vi L, Baht GS, Whetstone H, et al. Macrophages promote osteoblastic differentiation in vivo: implications in fracture repair and bone homeostasis. J Bone Miner Res. 2015;30(6):1090-1102. https://doi.org/10.1002/jbmr.2422

82. Pajarinen J, Lin T, Gibon E, et al. Mesenchymal stem cell-macrophage crosstalk and bone healing. Biomaterials. 2019;196:80-89. https://doi.org/10.1016/j.biomaterials.2017.12.025

83. Stefanowski J, Lang A, Rauch A, et al. Spatial distribution of macrophages during callus formation and maturation reveals close crosstalk between macrophages and newly forming vessels. Front Immunol. 2019;10:2588. https://doi.org/10.3389/fimmu.2019.02588

84. da Silva Meirelles L, Bellagamba BC, Camassola M, Nardi NB. Mesenchymal stem cells and their relationship to pericytes. Front Bioeng. 2016;21:130-156. https://doi.org/10.2741/4380

85. Kordes C, Sawitzka I, Götz S, Häussinger D. Hepatic stellate cells support hematopoiesis and are liver-resident mesenchymal stem cells. Cell Physiol Biochem. 2013;31(2-3):290-304. https://doi.org/10.1159/000343368

86. Kordes C, Sawitzka I, Götz S, Herebian D, Häussinger D. Hepatic stellate cells contribute to progenitor cells and liver regeneration. J Clin Invest. 2014;124(12):5503-5515. https://doi.org/10.1172/jci74119

87. Crisan M, Yap S, Castella L, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell. 2008;3(3):301-313. https://doi.org/10.1016/j.stem.2008.07.003

88. da Silva Meirelles L, Marson RF, Solari MIG, Nardi NB. Are liver pericytes just precursors of myofibroblasts in hepatic diseases? Insights from the crosstalk between perivascular and inflammatory cells in liver injury and repair. Cells. 2020;9(1):188. https://doi.org/10.3390/cells9010188

89. Baffy G. Kupffer cells in non-alcoholic fatty liver disease: the emerging view. J Hepatol. 2009;51(1):212-223. https://doi.org/10.1016/j.jhep.2009.03.008

90. Paik Y-H, Schwabe RF, Bataller R, Russo MP, Jobin C, Brenner DA. Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells. Hepatology. 2003;37(5):1043-1055. https://doi.org/10.1053/jhep.2003.30182

91. Qin CC, Liu YN, Hu Y, Yang Y, Chen Z. Macrophage inflammation protein-2 as mediator of inflammation in acute liver injury. World J Gastroenterol. 2017;23(17):3043-3052. https://doi.org/10.3748/wjg.v23.i17.3043

92. Mollica Poeta V, Massara M, Capucciatti A, Bonecchi R. Chemokines and chemokine receptors: new targets for cancer immunotherapy. Front Immunol. 2019;10:379. https://doi.org/10.3389/fimmu.2019.00379

93. Jordi DL. Endothelial signalling events during leukocyte transmigration. FEBS J. 2006;273(19):4408-4415. https://doi.org/10.1111/j.1742-4658.2006.05440.x

94. Paik YH, Lee KS, Lee HJ, et al. Hepatic stellate cells primed with cytokines upregulate inflammation in response to peptidoglycan or lipoteichoic acid. Lab Invest. 2006;86(7):676-686. https://doi.org/10.1038/labinvest.3700422

95. Stark K, Eckart A, Haidari S, et al. Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and ‘instruct’ them with pattern-recognition and motility programs. Nature Immunol. 2013;14(1):41-51. https://doi.org/10.1038/ni.2477

96. Tan Z, Qian X, Jiang R, et al. IL-17A plays a critical role in the pathogenesis of liver fibrosis through hepatic stellate cell
activation. *J Immunol*. 2013;191(4):1835-1844. https://doi.org/10.4049/jimmunol.1203013

97. Karlmark KR, Weiskirchen R, Zimmermann HW, et al. Hepatic recruitment of the inflammatory Gr1+ monocyte subset upon liver injury promotes hepatic fibrosis. *Hepatology*. 2009;50(1):261-274. https://doi.org/10.1002/hep.22950

98. Perugorria MJ, Latasa MU, Nicou A, et al. The epidermal growth factor receptor ligand amphiregulin participates in the development of mouse liver fibrosis. *Hepatology*. 2008;48(4):1251-1261. https://doi.org/10.1002/hep.22437

99. Minutti CM, Modak RV, Macdonald F, et al. A macrophage-percycte axis directs tissue restoration via amphiregulin-induced transforming growth factor beta activation. *Immunity*. 2019;50(3):645-654.e6. https://doi.org/10.1016/j.immuni.2019.01.008

100. Meng C, Liu G, Hu M, Zhou M, Zhang S, Xu Y. Amphiregulin may be a new biomarker of classically activated macrophages. *Biochem Biophys Res Commun*. 2015;466(3):393-399. https://doi.org/10.1016/j.bbrc.2015.09.037

101. Kendall TJ, Henndige S, Aucott RL, et al. p75 neurotrophin receptor signaling regulates hepatic myofibroblast proliferation and apoptosis in recovery from rodent liver fibrosis. *Hepatology*. 2009;49(5):901-910. https://doi.org/10.1002/hep.22701

102. Oakley F, Trimm N, Constandinou CM, et al. Hepatocytes express nerve growth factor during liver injury: evidence for paracrine regulation of hepatic stellate cell apoptosis. *Am J Pathol*. 2003;163(5):1849-1858. https://doi.org/10.1016/S0002-9440(10)63544-4

103. Trimm N, Morgan S, Evans M, et al. Hepatic stellate cells express the low affinity nerve growth factor receptor p75 and undergo apoptosis in response to nerve growth factor stimulation. *Am J Pathol*. 2000;156(4):1235-1243. https://doi.org/10.1016/S0002-9440(10)64994-2

104. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. *Science*. 2017;356(6342):1026-1030. https://doi.org/10.1126/science.aam7928

105. Dong D, Shi W, Yi SJ, Chen H, Groffen J, Heisterkamp N. TGF-β signaling plays a critical role in promoting alternative macrophage activation. *BMC Immunol*. 2012;13:31. https://doi.org/10.1186/1471-2472-13-31

106. Zhang F, Wang H, Wang X, et al. TGF-β induces M2-like macrophage polarization via SNAIL-mediated suppression of a pro-inflammatory phenotype. *Oncotarget*. 2016;7(32):52294-52306. https://doi.org/10.18632/oncotarget.10561

107. Liu F, Qiu H, Xue M, et al. MSC-secreted TGF-β regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. *Stem Cell Res Ther*. 2019;10(1):345. https://doi.org/10.1186/s13287-019-1447-y

108. Dort J, Fabre P, Molina T, Dumont NA. Macrophages are key regulators of stem cells during skeletal muscle regeneration and diseases. *Stem Cells Int*. 2019;2019:4761427. https://doi.org/10.1155/2019/4761427

109. Krafts KP. Tissue repair: the hidden drama. *Organogenesis*. 2010;6(4):225-233. https://doi.org/10.4161/org.6.4.12555

110. Calderon B, Carrero JA, Ferris ST, et al. The pancreas anatomy and properties of resident macrophages. *J Exp Med*. 2015;212(10):1497-1512. https://doi.org/10.1084/jem.20150496

111. Ying W, Lee YS, Dong Y, et al. Expansion of islet-resident macrophages leads to inflammation affecting β cell proliferation and function in obesity. *Cell Metab*. 2019;29(2):457-474. https://doi.org/10.1016/j.cmet.2018.12.003

112. Homo-Delarche F, Drexhage HA. Immune cells, pancreas development, regeneration and type 1 diabetes. *Trends Immunol*. 2004;25(5):222-229. https://doi.org/10.1016/j.it.2004.02.012

113. Geutskens SB, Otonkoski T, Pulikkinen MA, Drexhage HA, Leenen PJ. Macrophages in the murine pancreas and their involvement in fetal endocrine development in vitro. *J Leukoc Biol*. 2005;78(4):845-852. https://doi.org/10.1189/jlb.1004624

114. Banaei-Bouchareb L, Peuchmaur M, Czernichow P, Polak M. A transient microenvironment loaded mainly with macrophages in the early developing human pancreas. *J Endocrinol*. 2006;188(3):467-480. https://doi.org/10.1677/joe.1.06225

115. Aamodt KI, Powers AC. Signals in the pancreatic islet microenvironment influence β-cell proliferation. *Diabetes Obes Metab*. 2017;19(suppl 1):124-136. https://doi.org/10.1111/dom.13031

116. Tanabe K, Amo-Shinoki K, Hatanaka M, Tanizawa Y. Interorgan crosstalk contributing to β-cell dysfunction. *J Diabetes Res*. 2017;2017:3605178. https://doi.org/10.1155/2017/3605178

117. Denroche HC, Nackiewicz D, Verchere CB. When beta cells talk back. *Diabetologia*. 2018;61(1):39-42. https://doi.org/10.1007/s00125-017-4443-8

118. Van Gassen N, Staels W, Van Overmeire E, et al. Concise review: macrophages: versatile gatekeepers during pancreatic β-cell development, injury, and regeneration. *Stem Cells Transl Med*. 2015;4(6):555-563. https://doi.org/10.5966/scm.2014-0272

119. Hajmrlc C, Smith N, Spigelman AF, et al. Interleukin-1 signaling contributes to acute islet compensation. *JCI Insight*. 2016;1(4):e86055. https://doi.org/10.1172/jci.insight.86055

120. Xiao X, Gaffar I, Guo P, et al. M2 macrophages promote beta-cell proliferation by up-regulation of SMAD7. *Proc Natl Acad Sci U S A*. 2014;111(13):E1211-E1220. https://doi.org/10.1073/pnas.1321347111

121. Suzuki T, Dai P, Hatakeyama T, et al. TGF-β signaling regulates pancreatic β-cell proliferation through control of cell cycle regulator p27 expression. *Acta Histochem Cytochem*. 2013;46(2):51-58. https://doi.org/10.1267/ahc.12035

122. Cao X, Han Z-B, Zhao H, Liu Q. Transplantation of mesenchymal stem cells recruits trophic macrophages to induce pancreatic beta cell regeneration in diabetic mice. *Int J Biochem Cell Biol*. 2014;53:372-379. https://doi.org/10.1016/j.biocel.2014.06.003

123. Brissova M, Aamodt K, Brahmachary P, et al. Islet microenvironment, modulated by vascular endothelial growth factor-a signaling, promotes β cell regeneration. *Cell Metab*. 2014;19(3):498-511. https://doi.org/10.1016/j.cmet.2014.02.001

124. Jun H-S, Yoon C-S, Zbytnuik L, van Rooijen N, Yoon J-W. The role of macrophages in T cell-mediated autoimmune diabetes in nonobese diabetic mice. *J Exp Med*. 1999;189(2):347-358. https://doi.org/10.1084/jem.189.2.347

125. Calderon B, Suri A, Unanue ER. In CD4+ T-cell-induced diabetes, macrophages are the final effector cells that mediate β-cell killing: studies from an acute model. *Am J Pathol*. 2006;169(6):2137-2147. https://doi.org/10.2353/ajpath.2006.060639

126. Willcox A, Richardson SI, Bone AJ, Foulis AK, Morgan NG. Analysis of islet inflammation in human type 1 diabetes. *Clin Exp Immunol*. 2009;155(2):173-181. https://doi.org/10.1111/j.1365-2249.2008.03860.x
127. Eizirik DL, Mandrup-Poulsen T. A choice of death—the signal-transduction of immune-mediated beta-cell apoptosis. Diabetologia. 2001;44(12):2115-2133. https://doi.org/10.1007/s001250100021

128. Darville MI, Eizirik DL. Regulation by cytokines of the inducible nitric oxide synthase promoter in insulin-producing cells. Diabetologia. 1998;41(9):1101-1108. https://doi.org/10.1007/s001250100136

129. Cnop M, Welsh N, Jonas J-C, Jörns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic β-cell death in type 1 and type 2 diabetes: many differences, few similarities. Diabetes. 2005;54(suppl 2):S97-S107. https://doi.org/10.2337/diabetes.54.suppl_2_S97

130. Gea-Sorli S, Closa D. Role of macrophages in the progression of acute pancreatitis. World J Gastrointest Pharmacol Ther. 2010;1(5):107-111. https://doi.org/10.4292/wjgpt.v1.i5.107

131. Liou G-Y, Döppler H, Neeb L, et al. Macrophage-secreted cytokines drive pancreatic acinar-to-duodenal metaplasia through NF-xB and MMPs. J Cell Biol. 2013;202(3):563-577. https://doi.org/10.1083/jcb.201301001

132. Huang H, Liu Y, Daniuk J, et al. Activation of nuclear factor-xb in acinar cells increases the severity of pancreatitis in mice. Gastroenterology. 2013;144(1):202-210. https://doi.org/10.1053/j.gastro.2012.09.059

133. Miyamoto Y, Maitra A, Ghosh B, et al. Notch mediates TGF-α-induced changes in epithelial differentiation during pancreatic tumorigenesis. Cancer Cell. 2003;3(6):565-576. https://doi.org/10.1016/S1535-6108(03)00140-5

134. Sawey ET, Johnson JA, Crawford HC. Matrix metalloproteinase 7 controls pancreatic acinar cell transdifferentiation by activating the Notch signaling pathway. Proc Natl Acad Sci U S A. 2007;104(49):19327-19332. https://doi.org/10.1073/pnas.0705953104

135. Meyers N, Gérard C, Lemaigre FP, Jacquemin P. Differential impact of the ERBB receptors EGFR and ERBB2 on the initiation of precursor lesions of pancreatic ductal adenocarcinoma. Sci Rep. 2020;10(1):5241. https://doi.org/10.1038/s41598-020-62106-8

136. Zhang Y, Yan W, Mathew E, et al. Epithelial-mesenchymal cell crosstalk regulates acinar cell plasticity and pancreatic remodeling in mice. eLife. 2017;6:e27388. https://doi.org/10.7554/eLife.27388

137. Halbrook CJ, Wen H-J, Ruggeri JM, et al. Mitogen-activated protein kinase kinase activity maintains acinar-to-duodenal metaplasia and is required for organ regeneration in pancreatitis. Cell Mol Gastroenterology Hepatol. 2017;3(1):99-118. https://doi.org/10.1016/j.jcmgh.2016.09.009

138. Strobel O, Dor Y, Alsinà J, et al. In vivo lineage tracing defines the role of acinar-to-duodenal transdifferentiation in inflammatory ductal metaplasia. Gastroenterology. 2007;133(6):1999-2009. https://doi.org/10.1053/j.gastro.2007.09.009 Epub 2007/09/14 PubMed PMID: 18054571.

139. Houbracken I, de Waede E, Lardon J, et al. Lineage tracing evidence for transdifferentiation of acinar to duct cells and plasticity of human pancreas. Gastroenterology. 2011;141(2):731-741. https://doi.org/10.1053/j.gastro.2011.04.050

140. Klöppel G. Chronic pancreatitis, pseudotumors and other tumor-like lesions. Mod Pathol. 2007;20(1):S113-S131. https://doi.org/10.1038/modpathol.3800690

141. Xue J, Sharma V, Hsieh MH, et al. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun. 2015;6:7158. https://doi.org/10.1038/ncomms11858

142. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252-1261. https://doi.org/10.1053/j.gastro.2013.01.068

143. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73-85. https://doi.org/10.1016/S0140-6736(16)30141-0

144. Orth M, Metzger P, Gerum S, et al. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol. 2019;14(1):141. https://doi.org/10.1186/s13014-019-1345-6

145. Storz P. The crosstalk between acinar cells with Kras mutations and M1-polarized macrophages leads to initiation of pancreatic precancerous lesions. Oncoimmunology. 2015;4(6): e1008794. https://doi.org/10.1080/2162402X.2015.1008794

146. Morris JP, Wang SC, Hrebok M, KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma. Nat Rev Cancer. 2010;10(10):683-695. https://doi.org/10.1038/nrc2899

147. Waters AM, Der CJ. KRAS: the critical driver and therapeutic target for pancreatic cancer. Cold Spring Harb Perspect Med. 2018;8(9):a031435. https://doi.org/10.1101/cshperspect.a031435

148. Storz P. Acinar cell plasticity and development of pancreatic ductal adenocarcinoma. Nat Rev Gastroenterol Hepatol. 2017;14(5):296-304. https://doi.org/10.1038/nrgastro.2017.12

149. Ling J, Kang Y, Zhao R, et al. KrasG12D-induced IKKβ/β-NF-xB activation by IL-1x and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(1):105-120. https://doi.org/10.1016/j.ccr.2011.12.006

150. Maniati E, Bossard M, Cook N, et al. Crosstalk between the canonical NF-xB and Notch signaling pathways inhibits Ppary expression and promotes pancreatic cancer progression in mice. J Clin Invest. 2011;121(12):4685-4699. https://doi.org/10.1172/JCI45797

151. Ardito Christine M, Grüner Barbara M, Takeuchi Kenneth K, et al. EGF receptor is required for KRAS-induced pancreatic tumorigenesis. Cancer Cell. 2012;22(3):304-317. https://doi.org/10.1016/j.ccr.2012.07.024

152. Bishehsari F, Zhang L, Barlass U, et al. KRAS mutation and epithelial-macrophage interplay in pancreatic neoplastic transformation. Int J Cancer. 2018;143(8):1994-2007. https://doi.org/10.1002/ijc.31592

153. Colinsson EA, Trejo CL, Silva JM, et al. A central role for RAR-→MEK→ERK signaling in the genesis of pancreatic ductal adenocarcinoma. Cancer Discov. 2012;2(8):685-693. https://doi.org/10.1158/2159-8290.CD-11-0347

154. Zhang Y, Velez-Delgado A, Mathew E, et al. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut. 2017;66(1):124-136. https://doi.org/10.1136/gutjnl-2016-312078

155. Lesina M, Kurkowski MU, Ludes K, et al. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell. 2011;19(4):456-469. https://doi.org/10.1016/j.ccr.2011.03.009
156. Tandon M, Corduff GM, Criscimanna A, et al. Prolactin promotes fibrosis and pancreatic cancer progression. Cancer Res. 2019;79:5316-5327. https://doi.org/10.1158/0008-5472.CAN-18-3064

157. Fukuda A, Wang SC, Morris JPt, et al. Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. Cancer Cell. 2011;19(4):441-455. https://doi.org/10.1016/j.ccr.2011.03.002

158. Liu J, Akanuma N, Liu C, et al. TGF-β1 promotes acinar to ductal metaplasia of human pancreatic acinar cells. Sci Rep. 2016;6:30904. https://doi.org/10.1038/srep30904

159. Liou G-Y, Basta L, Fleming A, et al. The presence of interleukin-13 at pancreatic ADM/PanIN lesions alters macrophage populations and mediates pancreatic tumorigenesis. Cell Rep. 2017;19(7):1322-1333. https://doi.org/10.1016/j.celrep.2017.04.052

160. Zhu Y, Herndon JM, Sojka DK, et al. Tissue-resident macrophages in pancreatic ductal adenocarcinoma originate from embryonic hematopoiesis and promote tumor progression. Immunity. 2017;47(2):323-338. https://doi.org/10.1016/j.immuni.2017.07.014

161. Zhang Y, Crawford HC, Pasca di Magliano M. Epithelial-stromal interactions in pancreatic cancer. Annu Rev Physiol. 2019;81:211-233. https://doi.org/10.1146/annurev-physiol-020518-114515

162. Helm O, Held-Feindt J, Schäfer H, Sebens S. M1 and M2: there is no “good” and “bad”—how macrophages promote malignancy-associated features in tumorigenesis. Oncoimmunology. 2014;3(7):e946818. https://doi.org/10.4161/onci.21642011.2014946818

163. Farajzadeh Valilou S, Keshavarz L. Mielgo A, Schmid MC. Impact of tumour associated macrophages in pancreatic cancer. BMB Rep. 2013;46(3):131-138. https://doi.org/10.5483/bmbrep.2013.46.3.036

164. Cui R, Yue W, Lattime EC, Stein MN, Xu Q, Tan X-L. Targeting tumor-associated macrophages to combat pancreatic cancer. Oncotarget. 2016;7(31):50735-50754. https://doi.org/10.18611/ oncrtarget.9383

165. Kurahara H, Shinchii H, Mataki Y, et al. Significance of M2-polarized tumor-associated macrophage in pancreatic cancer. J Surg Res. 2011;167(2):e211-e219. https://doi.org/10.1016/j. jss.2009.05.026

166. Ino Y, Yamazaki-Itoh R, Shimada K, et al. Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer. Br J Cancer. 2013;108(4):914-923. https://doi.org/10.1038/bjc.2013.32

167. Ma X, Wu D, Zhou S, et al. The pancreatic cancer secreted REG4 promotes macrophage polarization to M2 through EGFR/AKT/CREB pathway. Oncol Rep. 2016;35(1):189-196. https://doi.org/10.3892/or.2015.4357

168. Kühnemuth B, Mühlberg L, Schipper M, et al. CUX1 modulates polarization of tumor-associated macrophages by antagonizing NF-κB signaling. Oncogene. 2015;34(2):177-187. https://doi.org/10.1038/onc.2013.530

169. Wang X, Luo G, Zhang K, et al. Hypoxic tumor-derived exosomal miR-301a mediates M2 macrophage polarization via PTEN/P13Kγ to promote pancreatic cancer metastasis. Cancer Res. 2018;78(16):4586-4598. https://doi.org/10.1158/0008-5472.Can-17-3841

170. Mitchem JB, Brennan DJ, Knolhoff BL, et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res. 2013;73(3):1128-1141. https://doi.org/10.1158/0008-5472.Can-12-2731

171. Sainz B, Alcala S, Garcia E, et al. Microenvironmental HcAP-18/LL-37 promotes pancreatic ductal adenocarcinoma by activating its cancer stem cell compartment. Gut. 2015;64(12):1921-1935. https://doi.org/10.1136/gutjnl-2014-308935

172. Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA, Vonderheide RH. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. Cancer Res. 2007;67(19):9518-9527. https://doi.org/10.1158/0008-5472.CAN-07-0175

173. Li X, Liu R, Su X, et al. Harnessing tumor-associated macrophages as aids for cancer immunotherapy. Mol Cancer. 2019;18(1):177. https://doi.org/10.1186/s12943-019-1102-3

174. Hu H, Jiao F, Han T, Wang L-W. Functional significance of macrophages in pancreatic cancer biology. Tumor Biol. 2015;36(12):9119-9126. https://doi.org/10.1007/s13277-015-4127-2

175. Habtezion A, Edderkaoui M, Pandol SJ. Macrophages and pancreatic ductal adenocarcinoma. Cancer Lett. 2016;381(1):211-216. https://doi.org/10.1016/j.canlet.2015.11.049

176. Padoan A, Plebani M, Basso D. Inflammation and pancreatic cancer: focus on metabolism, cytokines, and immunity. Int J Mol Sci. 2019;20(3):676. https://doi.org/10.3390/ijms20030676

177. Thomas D, Radhakrishnan P. Tumor-stromal crosstalk in pancreatic cancer and tissue fibrosis. Mol Cancer. 2019;18(1):14. https://doi.org/10.1186/s12943-018-0927-5

178. Mutguc AC, Besikcioglu HE, Wang S, Friess H, Ceyhan GO, Demir IE. Insulin/IGF-driven cancer cell-stroma crosstalk as a novel therapeutic target in pancreatic cancer. Mol Cancer. 2018;17(1):66. https://doi.org/10.1186/s12943-018-0860-0

179. Zhan H-X, Zhou B, Cheng Y-G, et al. Crosstalk between stromal cells and cancer cells in pancreatic cancer: new insights into stromal biology. Cancer Lett. 2017;392:83-93. https://doi.org/10.1016/j.canlet.2017.01.041

180. Sainz B, Carron E, Vallespinós M, Machado HL. Cancer stem cells and macrophages: implications in tumor biology and therapeutic strategies. Mediators Inflammat. 2016;2016:9012369. https://doi.org/10.1155/2016/9012369

181. Mittem JB, Brennan DJ, Knolhoff BL, et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res. 2013;73(3):1128-1141. https://doi.org/10.1158/0008-5472.CAN-12-2731

182. Cioffi M, Trabulo S, Hidalgo M, et al. Inhibition of CD47 effectively targets pancreatic cancer stem cells via dual mechanisms. Clin Cancer Res. 2015;21(10):2325-2337. https://doi.org/10.1158/1078-0432.CCR-14-1399

183. Martignoni ME, Kunze P, Hildebrandt W, et al. Role of mononuclear cells and inflammatory cytokines in pancreatic
cancer-related cachexia. Clin Cancer Res. 2005;11(16):5802-5808. https://doi.org/10.1158/1078-0432.Ccr-05-0185

186. McMillan DC, Scott HR, Watson WS, Preston T, Milroy R, McArdle CS. Longitudinal study of body cell mass depletion and the inflammatory response in cancer patients. Nutr Cancer. 1998;31(2):101-105. https://doi.org/10.1080/01635589809514687

187. O’Riordain MG, Falconer JS, Maingay J, Fearon KC, Ross JA. Peripheral blood cells from weight-losing cancer patients control the hepatic acute phase response by a primarily interleukin-6 dependent mechanism. Int J Oncol. 1999;15(4):823-827. https://doi.org/10.3892/ijo.15.4.823

188. Moldawer LL, Rogy MA, Lowry SF. The role of cytokines in cancer cachexia. J Parenter Enter Nutr. 1992;16(6S):43S-49S. https://doi.org/10.1177/014860719201600602

189. Martignoni M, Dimitriu C, Bachmann J, et al. Liver macrophages contribute to pancreatic cancer-related cachexia. Oncol Rep. 2009;21:363-369. https://doi.org/10.3892/or_00000231

190. Watchorn TM, Dowidar N, Dejong CH, Waddell ID, Garden OJ, Ross JA. The cachectic mediator proteolysis inducing factor activates NF-kappaB and STAT3 in human Kupffer cells and monocytes. Int J Oncol. 2005;27(4):1105-1111.

191. Lankadasari MB, Mukhopadhyay P, Mohammed S, Harikumar KB. TAMing pancreatic cancer: combat with a double edged sword. Mol Cancer. 2019;18(1):48. https://doi.org/10.1186/s12943-019-0966-6

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