Macrophages and Wnts in Tissue Injury and Repair

Subjects: Immunology

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Macrophages, one of the body's most abundant populations of leukocytes, are mainly derived from the yolk sac during embryogenesis and are found in almost every tissue that plays an essential role during mammalian development. They are specialized phagocytes, large vacuolated cells with abundant cytoplasm containing lysosomal granules. Wnt signaling is a conserved pathway across species. It is involved in various essential tasks by regulating cell differentiation, proliferation, stem cell development, immune cell functions, and tissue repair. Evidence for the Wnt system's pivotal role is that aberrant alterations of this molecular pathway are involved in multiple human disorders and pathologies, such as congenital abnormalities, autoimmune diseases, and cancer. Wnt and macrophages in the most immunologically active lung, liver, intestine, kidney, heart, and skin are discussed.

injury repair Wnt

1. Introduction

Many researchers have focused on identifying and characterizing the different populations of macrophages that control the different stages of tissue repair, regeneration, and development in most organ systems [1]. Recent studies have suggested that various monocyte and macrophage populations play distinct and essential roles in chronic inflammation, tissue repair, regeneration, cancer, and fibrosis, as shown in **Figure 1**.

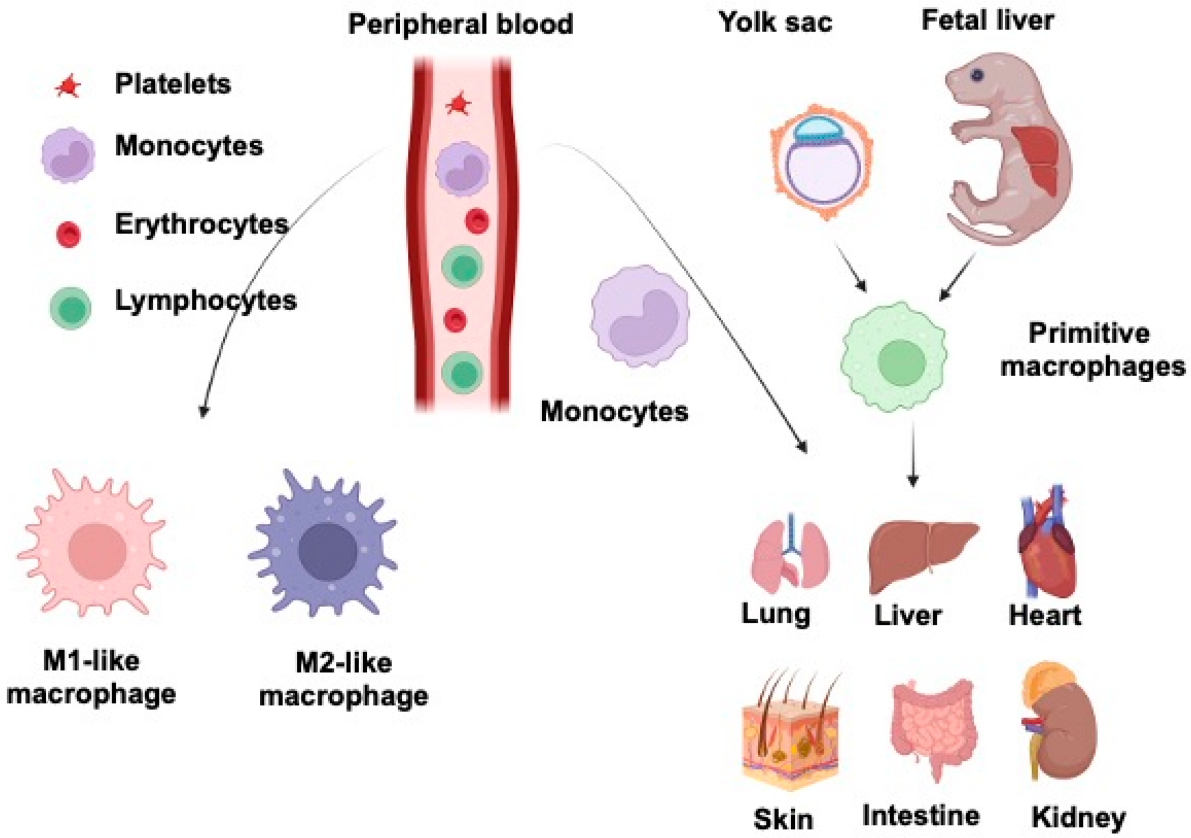

Figure 1. Macrophage development and functions in different organs. Tissue-resident macrophages are originated from the yolk sac/fetal liver and hematopoietic progenitors/circulating monocytes. Monocytes are further differentiated into M1-like and M2-like macrophages based on their expression markers upon a variety of stimuli. M2-like macrophages are known to be important for wound repair and also share similar features with TAMs. M1-like macrophages constitute the first line of defense against intracellular pathogens. Macrophages are sources of Wnt ligands and mediate Wnt ligand-mediated signaling for various immune responses for tissue inflammation and repair. This was created with Biorender.com.

2. Macrophages and Wnt Signaling in Lung Injury and Repair

At least two types of macrophage populations are located in the lung. Alveolar macrophages (AMs) are located at the interface between the lung mucosa and the external environment. [2][3][4]. They play the role of primary defense by directly sensing immunological stimuli such as inhaled particulate elements and bacteria [5]. Other macrophages, called interstitial macrophages (IMs), inhabit the lung interstitium between the alveoli and the capillaries [3][4]. They come in direct contact with the matrix and other pulmonary connective tissue components and can phagocytose particles and bacteria [6]. In other words, IMs can serve as a secondary defense against the invasion of particles and bacteria evading phagocytic activity by AMs. Furthermore, IMs, which have unique transcriptional features, can be distinguished from AMs by their distinct surface phenotype [6][7].

Once lung injury occurs, mechanisms for regeneration are initiated to restore the lung epithelium. Wnt signaling is known to be essential for lung regeneration [8]. β-catenin, the main component of the canonical Wnt signaling,

mediates pulmonary regeneration, acting as a transcription factor that stimulates the gene expression associated with epithelial regeneration and controlling the tight junctions of the epithelial cells in the lung. However, the investigation of the role of macrophage-derived Wnt ligands in the regeneration of lungs is in its infancy, and further studies are needed.

Lung macrophages are associated with interstitial lung diseases, such as idiopathic pulmonary fibrosis (IPF), which causes lung scarring for unknown reasons [9]. Hou and colleagues showed that Wnt/β-catenin signaling in M2 macrophages with significantly increased Wnt7a protein was activated, promoting differentiation of myofibroblasts by lung resident mesenchymal stem cells and exacerbating pulmonary fibrosis in mice [10]. In particular, they found that macrophages recruited into the fibrotic lungs of mice treated with bleomycin were mainly M2 macrophages. Wnt/β-catenin signaling activation in lung macrophages promoted fibrosis after bleomycin treatment [10][11][12]. Sennello et al. showed that lack of LRP5, the Wnt co-receptor, resulted in many fewer Siglec F^{low} AMs, a macrophage cell type that caused pulmonary fibrosis [12]. Given that Wnt/β-catenin signaling affects lung macrophages contributing to the development and persistence of pulmonary fibrosis, targeting macrophages with activated Wnt/β-catenin signaling could lead to new strategies to slow lung fibrosis.

The importance of the Wnt pathway in lung macrophages was observed in infection and inflammatory processes. For example, it was confirmed that Wnt1, Wnt6, and Wnt10a were induced in an inflammatory environment such as the lung of Mycobacterium tuberculosis-infected mice, and especially, Wnt6 was a novel factor inducing macrophage polarization with an M2-like phenotype [13]. In addition, Zhou and colleagues [14] investigated the effect of the Wnt signaling regulator Rspondin3 on resolving inflammatory injury. They found that lung endothelial cells release Rspondin3 in response to inflammatory damage, activating Wnt/β-catenin signaling in the lung IMs. The specific deletion of Rspondin3 in endothelial cells prevented the production of anti-inflammatory IMs in endotoxemic mice and caused a severe inflammatory injury.

3. Macrophages and Wnt Signaling in Liver Injury and Repair

Kupffer cells, also known as Kupffer–Borowicz cells, are the primary macrophages of the liver [15]. Kupffer cells are located in the liver sinusoid and are highly specialized for their phagocytic activity. They can sense danger-associated-molecular patterns (DAMPs) and pattern-associated-molecular patterns (PAMPs) via various receptors such as TLRs and Nod-like receptors (NLRs) [16].

Macrophages in the liver are one of the first responders to liver injury and are involved in modulating the fibrogenic response through several mechanisms. In addition, macrophages are closely related to the activated hepatic progenitor cells (HPCs) that occur parallel to fibrosis. Irvine and colleagues [17] investigated the role of Wnts derived from macrophages in chronic liver diseases (CLDs), especially concerning the HPC niche. Their results highlight that macrophage-derived Wnts have anti-fibrotic potential in CLDs and may be targeted for medical treatment. Carpino et al. [18] identified that the activated macrophages in pediatric nonalcoholic fatty liver disease (NAFLD) are closely associated with the HPC response through Wnt3a signaling. The study has shown that pro-

inflammatory macrophages are the predominant subset of pediatric NAFLD and the important role of macrophage polarization in the progression of pediatric NAFLD.

In response to liver injury, quiescent hepatic stellate cells (HSCs) undergo a distinctive morphological transformation into proliferative, contractile, and extracellular matrix protein-producing myofibroblasts, leading to liver fibrosis. Akcora and colleagues [19] investigated the association between canonical Wnt signaling in HSCs and liver fibrogenesis using β-catenin/CBP inhibitor ICG-001. Interestingly, ICG-001 remarkably decreased collagen accumulation and HSC activation and significantly inhibited macrophage infiltration, intrahepatic inflammation, and angiogenesis. Therefore, it is suggested that inhibiting the canonical Wnt pathway can ameliorate liver fibrosis in vivo. To clarify the role of macrophage-derived Wnt ligands in regulating hepatobiliary injury and repair, Jiang and colleagues [20] investigated the effect of macrophage-specific deletion of Wntless, a cargo protein critical for cellular Wnt secretion. This study showed that a shortage of Wnt secretion in macrophages caused more hepatic injury induced by 3,5-diethoxycarbonyl-1,4-dihydrocollidine because of damaged hepatocyte proliferation and increased M1 macrophages, which accelerate immune-mediated cell injury.

The correlation between the Wnt signaling and liver macrophages was also observed in infection and inflammatory processes. For example, the overexpression of liver kinase B1 mediated mycobacterial infection in macrophages via FOXO1/Wnt5a signaling was identified [21]. Furthermore, it was suggested that the expression of LRP1 in macrophages promoted hepatic inflammation by controlling Wnt signaling [22].

TAMs are a major element of the tumor microenvironment and play a central role in the progression of hepatocellular carcinoma. A study has also shown that cancer-cell-derived Wnt proteins stimulate M2-like polarization of TAMs through the canonical Wnt/β-catenin pathway, resulting in growth, migration, metastasis, and immune suppression of cancer in hepatocellular carcinoma [23]. Obesity can stimulate the risk of tumor formation, and steatosis in the liver often leads to carcinogenesis. To determine the mechanism by which steatosis promotes cancer formation, Debebe and colleagues [24] used various liver cancer models in order to investigate the role of obesity in cancer. They showed that a high-fat diet lipid accumulation could activate Wnt/β-catenin signals, and pharmacological inhibition or loss of these signals suppress the growth of tumor-initiating cells (TICs) in vitro and reduce the accumulation of TICs in vivo. Their data also confirmed that Wnt/β-catenin, caused by steatosis-induced macrophage infiltration, promotes tumor progenitor cell growth.

4. Macrophages and Wnt Signaling in Intestine Injury and Repair

Macrophages in the intestine have roles in tissue homeostasis and inflammation, especially in the resolution of inflammation [3][25][26]. In recent years, Wnt signaling has played an essential role in intestinal epithelial proliferation and differentiation, and the expression of Wnt ligands by macrophages has been studied [8].

Saha and colleagues [27] analyzed the role of macrophage-derived Wnts in intestinal repair and regeneration after radiation injury in mice. Using macrophage-specific deletion of the Porcupine gene to inhibit Wnt ligand release in

mice (*Csf1r.iCre-Porc*$^{flox/flox}$), they showed that macrophage-derived Wnts contained in extracellular vesicles (EV) are important to mediate radiation-induced gastrointestinal syndrome (RIGS). Treatment of Wnt-containing EVs by ultracentrifugation of cell-free supernatant from bone marrow macrophages or using a total exosome isolation kit on irradiated mice facilitated the recovery of the irradiated mice. Cosín-Roger and colleagues [28] investigated the macrophage phenotype that determines Wnt ligands, the effect of macrophage phenotype on epithelial activation of Wnt signaling, and its relevance to the Wnt signaling pathway in ulcerative colitis (UC). They showed that M2 macrophages, not M1, activated Wnt signaling via Wnt1, which reduces the differentiation of enterocytes. In addition, the number of CD206-positive-M2 macrophages in the mucosa of UC patients significantly increased and acted as a source of Wnt1, showing that excessive Wnt signaling in the intestinal epithelium was involved in the development of colorectal adenocarcinoma. Other researchers [29] found that signal transducer and activator of transcription 6 (STAT6) mediates M2 polarization and induces the expression of Wnt2b, Wnt7b, and Wnt10a in the mucosa of 2,4,6-trinitrobenzene sulfonic acid-treated mice. Furthermore, they suggested that the STAT6-dependent macrophage phenotype activates the Wnt signaling pathway, promoting mucosal repair.

In another study [30], the number of CD206-positive cells, anti-inflammatory M2 macrophages, was significantly higher in colorectal cancer, whereas pro-inflammatory M1 macrophages were remarkably lower. In particular, the authors of this study investigated whether gastrins synthesized by colon tumor cells affect a pattern of macrophage infiltration in colon cancer. Interestingly, these results suggested that the expression of Wnt ligands was decreased in macrophages differentiated in the presence of progestin; it inhibited the acquisition of the M2 polarization in human macrophages.

5. Macrophages and Wnt Signaling in Kidney Injury and Repair

Macrophages are well known to increase in the diseased kidney and play a central role in kidney damage, inflammation, and fibrosis [31][32]. They exhibit a distinct phenotype with functional properties in response to various stimuli of the local microenvironment during injury, inflammation, fibrosis, and repair [33][34].

Lin and colleagues [35] investigated whether the canonical Wnt signaling pathway was activated during injury and played an essential role in repair in the kidney using mice subjected to kidney-ischemia-reperfusion injury. Their data showed that the Wnt7b produced by macrophages stimulated kidney repair and regeneration. Thus, it was suggested that renal macrophages could establish a beneficial kidney repair and regeneration system. Although several studies have demonstrated that kidney mononuclear phagocytes (MPs) are required for post-injury healing, they were not designed to identify a subpopulation of kidney MPs defined by phenotype. In addition, it has yet to be revealed whether kidney-resident macrophage (KRM) could potentially play a therapeutic role after acute kidney injury (AKI). In 2019, Lever and colleagues [36] found evidence that KRMs generate and respond to Wnt ligands and activate canonical Wnt signaling. They concluded that the regenerative source of KRMs after AKI is primarily in situ renewal as opposed to the infiltration of macrophage precursors in the blood and that KRM triggers the MHCII phenotypic transformation during development and after injury. After kidney injury, KRM was also rich in the Wnt signaling pathway, demonstrating that the pathways essential for mouse and human kidney development are

activated. Their data showed that the mechanisms involved in kidney development in KRM might function after injury.

In recent years, many studies have investigated the role of Wnt/β-catenin in regulating macrophage activation and its contribution to renal fibrosis. Aberrant activation of the Wnt/β-catenin pathway is associated with renal fibrosis. Feng and colleagues demonstrated that Wnt3a enhanced M2 macrophage polarization induced by IL-4 or TGFβ1 caused STAT3 phosphorylation and nuclear translocation in vitro [37]. They also showed that β-catenin deletion of macrophages in the mice model attenuated fibrosis, macrophage accumulation, and M2 polarization observed in the kidney [38]. Thus, these results show that activation of Wnt/β-catenin signaling is essential to stimulate macrophage M2 polarization and promote macrophage proliferation during renal fibrosis. In another study, Feng et al. investigated how impaired regulation of the Wnt5a signaling in macrophages leads to renal fibrosis. In a mice model of kidney fibrosis, short hairpin RNA-mediated knockdown of Wnt5a expression reduced renal fibrosis and macrophage M2 polarization [39]. Their results showed that Wnt5a stimulates macrophage M2 polarization to promote renal fibrosis. Therefore, targeting Wnt signaling in macrophages may describe a new therapeutic strategy for protecting against renal fibrosis in patients with chronic kidney disease.

6. Macrophages and Wnt Signaling in Heart Injury and Repair

Macrophages and Wnt ligands are independently associated with cardiac development, reaction to cardiac injury, and repair [40]. Furthermore, Wnt signaling functions diversely in cardiovascular development and disease processes [41]. Monocytes and monocyte-derived macrophages are known to play important roles in the development of atherosclerosis and coronary heart disease, as well as in the immune response against cardiac ischemia [42][43].

After the heart is damaged, Wnt signaling is reactivated. There is increasing evidence that reactivation of the canonical Wnt signaling negatively affects infarct healing associated with cardiomyocyte death and cardiac fibrosis [42].

7. Macrophages and Wnt Signaling in Skin Injury and Repair

Macrophages are well known to play essential roles and coordinate in all stages of the skin wound healing process [44][45][46].

A skin injury can provide an ideal model for studying the role of the innate immune system between regeneration and fibrotic healing. Recently, the wound-induced hair neogenesis (WIHN) model, which can induce fibrotic scarring, was used to investigate the potential role of macrophages in determining healing fate by Gay and colleagues [47]. Their results showed that late wound macrophages phagocytosed the dermal Wnt inhibitor SFRP4 to establish sustained Wnt activity, leading to fibrosis. In addition, the phagocytosis of SFRP4 by macrophages in the human hidradenitis suppurativa was related to the recovery of fibrotic skin. These results revealed that

macrophages could change the fate of skin wound healing by regulating major signaling pathways via phagocytosis.

Macrophages are known to regulate developmental vascularization through non-canonical Wnt signaling and are associated with wound angiogenesis. Stefater III and colleagues [48] showed that wound macrophages use the Wnt-Flt1 signaling pathway via Flt1, a receptor for vascular endothelial growth factor A. Calcineurin is an important mediator in regulating wound response. Thus, they found that macrophages use Wnt-Calcineurin-Flt1 signaling to inhibit angiogenesis and slow repair.

To investigate the effect of perifollicular macrophage-derived Wnt on the activation of hair follicle stem cells (HF-SCs) and the induction of anagen (the active growth phase of hair follicles) in the hair cycle in mice, Castellana and colleagues [49] used and injected subcutaneously into mice a liposome containing IWP-2, a specific hydrophobic small molecule inhibitor of Wnt.

References

1. Varol, C.; Mildner, A.; Jung, S. Macrophages: Development and tissue specialization. Annu. Rev. Immunol. 2015, 33, 643–675.
2. Hussell, T.; Bell, T.J. Alveolar macrophages: Plasticity in a tissue-specific context. Nat. Rev. Immunol. 2014, 14, 81–93.
3. Mowat, A.M.; Scott, C.; Bain, C. Barrier-tissue macrophages: Functional adaptation to environmental challenges. Nat. Med. 2017, 23, 1258–1270.
4. Cheng, P.; Li, S.; Chen, H. Macrophages in Lung Injury, Repair, and Fibrosis. Cells 2021, 10, 436.
5. Puttur, F.; Gregory, L.G.; Lloyd, C.M. Airway macrophages as the guardians of tissue repair in the lung. Immunol. Cell Biol. 2019, 97, 246–257.
6. Liegeois, M.; Legrand, C.; Desmet, C.J.; Marichal, T.; Bureau, F. The interstitial macrophage: A long-neglected piece in the puzzle of lung immunity. Cell. Immunol. 2018, 330, 91–96.
7. Schyns, J.; Bureau, F.; Marichal, T. Lung Interstitial Macrophages: Past, Present, and Future. J. Immunol. Res. 2018, 2018, 5160794.
8. Cosin-Roger, J.; Ortiz-Masià, M.D.; Barrachina, M.D. Macrophages as an Emerging Source of Wnt Ligands: Relevance in Mucosal Integrity. Front. Immunol. 2019, 10, 2297.
9. Byrne, A.J.; Maher, T.M.; Lloyd, C.M. Pulmonary Macrophages: A New Therapeutic Pathway in Fibrosing Lung Disease? Trends Mol. Med. 2016, 22, 303–316.
10. Hou, J.; Shi, J.; Chen, L.; Lv, Z.; Chen, X.; Cao, H.; Xiang, Z.; Han, X. M2 macrophages promote myofibroblast differentiation of LR-MSCs and are associated with pulmonary fibrogenesis. Cell

Commun. Signal. 2018, 16, 89.

11. Cao, Z.; Lis, R.; Ginsberg, M.; Chavez, D.; Shido, K.; Rabbany, S.Y.; Fong, G.-H.; Sakmar, T.; Rafii, S.; Ding, B.-S. Targeting of the pulmonary capillary vascular niche promotes lung alveolar repair and ameliorates fibrosis. Nat. Med. 2016, 22, 154–162.
12. Sennello, J.A.; Misharin, A.V.; Flozak, A.S.; Berdnikovs, S.; Cheresh, P.; Varga, J.; Kamp, D.W.; Budinger, G.S.; Gottardi, C.J.; Lam, A.P. Lrp5/beta-Catenin Signaling Controls Lung Macrophage Differentiation and Inhibits Resolution of Fibrosis. Am. J. Respir. Cell Mol. Biol. 2017, 56, 191–201.
13. Schaale, K.; Brandenburg, J.; Kispert, A.; Leitges, M.; Ehlers, S.; Reiling, N. Wnt6 is expressed in granulomatous lesions of Mycobacterium tuberculosis-infected mice and is involved in macrophage differentiation and proliferation. J. Immunol. 2013, 191, 5182–5195.
14. Zhou, B.; Magana, L.; Hong, Z.; Huang, L.S.; Chakraborty, S.; Tsukasaki, Y.; Huang, C.; Wang, L.; Di, A.; Ganesh, B.; et al. The angiocrine Rspondin3 instructs interstitial macrophage transition via metabolic-epigenetic reprogramming and resolves inflammatory injury. Nat. Immunol. 2020, 21, 1430–1443.
15. Li, P.; He, K.; Li, J.; Liu, Z.; Gong, J. The role of Kupffer cells in hepatic diseases. Mol. Immunol. 2017, 85, 222–229.
16. Dou, L.; Shi, X.; He, X.; Gao, Y. Macrophage Phenotype and Function in Liver Disorder. Front. Immunol. 2019, 10, 3112.
17. Irvine, K.M.; Clouston, A.D.; Gadd, V.L.; Miller, G.C.; Wong, W.-Y.; Melino, M.; Maradana, M.R.; MacDonald, K.; Lang, R.A.; Sweet, M.J.; et al. Deletion of Wntless in myeloid cells exacerbates liver fibrosis and the ductular reaction in chronic liver injury. Fibrogenesis Tissue Repair 2015, 8, 19.
18. Carpino, G.; Nobili, V.; Renzi, A.; De Stefanis, C.; Stronati, L.; Franchitto, A.; Alisi, A.; Onori, P.; De Vito, R.; Alpini, G.; et al. Macrophage Activation in Pediatric Nonalcoholic Fatty Liver Disease (NAFLD) Correlates with Hepatic Progenitor Cell Response via Wnt3a Pathway. PLoS ONE 2016, 11, e0157246.
19. Akcora, B.O.; Storm, G.; Bansal, R. Inhibition of canonical WNT signaling pathway by beta-catenin/CBP inhibitor ICG-001 ameliorates liver fibrosis in vivo through suppression of stromal CXCL12. Biochim. Biophys. Acta Mol. Basis Dis. 2018, 1864, 804–818.
20. Jiang, A.; Okabe, H.; Popovic, B.; Preziosi, M.E.; Pradhan-Sundd, T.; Poddar, M.; Singh, S.; Bell, A.; England, S.G.; Nagarajan, S.; et al. Loss of Wnt Secretion by Macrophages Promotes Hepatobiliary Injury after Administration of 3,5-Diethoxycarbonyl-1, 4-Dihydrocollidine Diet. Am. J. Pathol. 2019, 189, 590–603.

21. Cui, J.; Li, M.; Liu, W.; Zhang, B.; Sun, B.; Niu, W.; Wang, Y. Liver kinase B1 overexpression controls mycobacterial infection in macrophages via FOXO1/Wnt5a signaling. J. Cell. Biochem. 2019, 120, 224–231.
22. Au, D.T.; Migliorini, M.; Strickland, D.K.; Muratoglu, S.C. Macrophage LRP1 Promotes Diet-Induced Hepatic Inflammation and Metabolic Dysfunction by Modulating Wnt Signaling. Mediat. Inflamm. 2018, 2018, 7902841.
23. Yang, Y.; Ye, Y.C.; Chen, Y.; Zhao, J.L.; Gao, C.C.; Han, H.; Liu, W.C.; Qin, H.Y. Crosstalk between hepatic tumor cells and macrophages via Wnt/beta-catenin signaling promotes M2-like macrophage polarization and reinforces tumor malignant behaviors. Cell Death Dis. 2018, 9, 793.
24. Debebe, A.; Medina, V.; Chen, C.Y.; Mahajan, I.M.; Jia, C.; Fu, D.; He, L.; Zeng, N.; Stiles, B.W.; Chen, C.L.; et al. Wnt/beta-catenin activation and macrophage induction during liver cancer development following steatosis. Oncogene 2017, 36, 6020–6029.
25. Na, Y.R.; Stakenborg, M.; Seok, S.H.; Matteoli, G. Macrophages in intestinal inflammation and resolution: A potential therapeutic target in IBD. Nat. Rev. Gastroenterol. Hepatol. 2019, 16, 531–543.
26. Ruder, B.; Becker, C. At the Forefront of the Mucosal Barrier: The Role of Macrophages in the Intestine. Cells 2020, 9, 2162.
27. Saha, S.; Aranda, E.; Hayakawa, Y.; Bhanja, P.; Atay, S.; Brodin, N.P.; Li, J.; Asfaha, S.; Liu, L.; Tailor, Y.; et al. Macrophage-derived extracellular vesicle-packaged WNTs rescue intestinal stem cells and enhance survival after radiation injury. Nat. Commun. 2016, 7, 13096.
28. Roger, J.C.; Ortiz-Masia, M.D.; Calatayud, S.; Hernandez, C.; Álvarez, A.; Hinojosa, J.; Esplugues, J.V.; Barrachina, M.D. M2 macrophages activate WNT signaling pathway in epithelial cells: Relevance in ulcerative colitis. PLoS ONE 2013, 8, e78128.
29. Cosín-Roger, J.; Ortiz-Masia, M.D.; Calatayud, S.; Hernandez, C.; Esplugues, J.V.; Barrachina, M.D. The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD. Mucosal Immunol. 2016, 9, 986–998.
30. Hernández, C.; Barrachina, M.D.; Cosín-Roger, J.; Ortiz-Masiá, D.; Álvarez; Terrádez, L.; Nicolau, M.J.; Alós, R.; Esplugues, J.V.; Calatayud, S. Progastrin represses the alternative activation of human macrophages and modulates their influence on colon cancer epithelial cells. PLoS ONE 2014, 9, e98458.
31. Cao, Q.; Harris, D.C.H.; Wang, Y. Macrophages in kidney injury, inflammation, and fibrosis. Physiology 2015, 30, 183–194.
32. Huen, S.C.; Cantley, L.G. Macrophages in Renal Injury and Repair. Annu. Rev. Physiol. 2017, 79, 449–469.

33. Chen, T.; Cao, Q.; Wang, Y.; Harris, D.C. M2 macrophages in kidney disease: Biology, therapies, and perspectives. Kidney Int. 2019, 95, 760–773.
34. Wen, Y.; Yan, H.-R.; Wang, B.; Liu, B.-C. Macrophage Heterogeneity in Kidney Injury and Fibrosis. Front. Immunol. 2021, 12, 681748.
35. Lin, S.-L.; Li, B.; Rao, S.; Yeo, E.-J.; Hudson, T.E.; Nowlin, B.T.; Pei, H.; Chen, L.; Zheng, J.J.; Carroll, T.J.; et al. Macrophage Wnt7b is critical for kidney repair and regeneration. Proc. Natl. Acad. Sci. USA 2010, 107, 4194–4199.
36. Lever, J.P.; Hull, T.D.; Boddu, R.; Pepin, M.; Black, L.M.; Adedoyin, O.O.; Yang, Z.; Traylor, A.M.; Jiang, Y.; Li, Z.; et al. Resident macrophages reprogram toward a developmental state after acute kidney injury. JCI Insight 2019, 4, e125503.
37. Feng, Y.; Ren, J.; Gui, Y.; Wei, W.; Shu, B.; Lu, Q.; Xue, X.; Sun, X.; He, W.; Yang, J.; et al. Wnt/beta-Catenin-Promoted Macrophage Alternative Activation Contributes to Kidney Fibrosis. J. Am. Soc. Nephrol. 2018, 29, 182–193.
38. Feng, Y.; Liang, Y.; Ren, J.; Dai, C. Canonical Wnt Signaling Promotes Macrophage Proliferation during Kidney Fibrosis. Kidney Dis. 2018, 4, 95–103.
39. Feng, Y.; Liang, Y.; Zhu, X.; Wang, M.; Gui, Y.; Lu, Q.; Gu, M.; Xue, X.; Sun, X.; He, W.; et al. The signaling protein Wnt5a promotes TGFbeta1-mediated macrophage polarization and kidney fibrosis by inducing the transcriptional regulators Yap/Taz. J. Biol. Chem. 2018, 293, 19290–19302.
40. Lafuse, W.P.; Wozniak, D.J.; Rajaram, M.V.S. Role of Cardiac Macrophages on Cardiac Inflammation, Fibrosis and Tissue Repair. Cells 2020, 10, 51.
41. Hermans, K.C.; Blankesteijn, W.M. Wnt Signaling in Cardiac Disease. Compr. Physiol. 2015, 5, 1183–1209.
42. Tao, H.; Yang, J.-J.; Shi, K.-H.; Li, J. Wnt signaling pathway in cardiac fibrosis: New insights and directions. Metabolism 2016, 65, 30–40.
43. Foulquier, S.; Daskalopoulos, E.P.; Lluri, G.; Hermans, K.C.M.; Deb, A.; Blankesteijn, W.M. WNT Signaling in Cardiac and Vascular Disease. Pharmacol. Rev. 2018, 70, 68–141.
44. Minutti, C.M.; Knipper, J.A.; Allen, J.E.; Zaiss, D.M.W. Tissue-specific contribution of macrophages to wound healing. Semin. Cell Dev. Biol. 2017, 61, 3–11.
45. Gieseck, R.L., 3rd; Wilson, M.S.; Wynn, T.A. Type 2 immunity in tissue repair and fibrosis. Nat. Rev. Immunol. 2018, 18, 62–76.
46. Malsin, E.S.; Kim, S.; Lam, A.P.; Gottardi, C.J. Macrophages as a Source and Recipient of Wnt Signals. Front. Immunol. 2019, 10, 1813.

47. Gay, D.; Ghinatti, G.; Guerrero-Juarez, C.F.; Ferrer, R.A.; Ferri, F.; Lim, C.H.; Murakami, S.; Gault, N.; Barroca, V.; Rombeau, I.; et al. Phagocytosis of Wnt inhibitor SFRP4 by late wound macrophages drives chronic Wnt activity for fibrotic skin healing. Sci. Adv. 2020, 6, eaay3704.
48. Stefater, J.A., 3rd; Rao, S.; Bezold, K.; Aplin, A.C.; Nicosia, R.F.; Pollard, J.W.; Ferrara, N.; Lang, R.A. Macrophage Wnt-Calcineurin-Flt1 signaling regulates mouse wound angiogenesis and repair. Blood 2013, 121, 2574–2578.
49. Castellana, D.; Paus, R.; Perez-Moreno, M. Macrophages contribute to the cyclic activation of adult hair follicle stem cells. PLoS Biol. 2014, 12, e1002002.