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Monitoring Macrophage Polarization in Infectious Disease, Lesson From SARS-CoV-2 Infection

Soraya Mezouar[1,2] | Jean-Louis Mege[1,3]

[1]Centre National de la Recherche Scientifique, Établissement Français du Sang, Anthropologie Bio-Culturelle, Droit, Éthique et Santé, Aix-Marseille University, Marseille, France | [2]Faculty of Medical and Paramedical Sciences, Aix-Marseille University, HIPE Human Lab, Marseille, France | [3]Department of Immunology, La Timone Hospital, Marseille, France

Correspondence: Jean-Louis Mege (jean-louis.mege@univ-amu.fr)

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ABSTRACT

The concept of macrophage polarization has been largely used in human diseases to define a typology of activation of myeloid cells reminiscent of lymphocyte functional subsets. In COVID-19, several studies have investigated myeloid compartment dysregulation and macrophage polarization as an indicator of disease prognosis and monitoring. SARS-CoV-2 induces an in vitro activation state in monocytes and macrophages that does not match the polarization categories in most studies. In COVID-19 patients, monocytes and macrophages are activated but they do not show a polarization profile. Therefore, the investigation of polarization under basic conditions was not relevant to assess monocyte and macrophage activation. The analysis of monocytes and macrophages with high-throughput methods has allowed the identification of new functional subsets in the context of COVID-19. This approach proposes an innovative stratification of myeloid cell activation. These new functional subsets of myeloid cells would be better biomarkers to assess the risk of complications in COVID-19, reserving the concept of polarization for pharmacological programme evaluation. This review reappraises the polarization of monocytes and macrophages in viral infections, particularly in COVID-19.

1 | Macrophage Polarization Concept

The concept of M1/M2 macrophage polarization was introduced by C. Mills in 2000 based on Th1/Th2 paradigm and experiments using IFNγ and LPS as agonists and macrophages from Th1- and Th2-type mouse strains [1]. Previously, S. Gordon described two activation states of macrophages, classical and alternative activation [2]. Finally, M1 was considered as the equivalent of classical activation and M2 as the equivalent of alternative activation, and M1 and M2 have been used extensively (Pubmed 1988 to 2023: 9288) (Figure 1). Hence, macrophages stimulated by LPS and/or IFNγ in which STAT1 was

Abbreviations: ACE, angiotensin converting enzyme; Ang, angiotensin; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; C/EBP, CCAAT-enhancer-binding protein; COMBAT, COVID-19 multi-omics blood atlas; COVID-19, coronavirus disease 2019; CTLA, cytotoxic T-lymphocyte-associated protein; DAMP, damage-associated molecular pattern; FABP4, fatty acid binding protein 4; FCN1, ficolin1; GAS, growth-arrest-specific; HLA, human leucocyte antigen; ICU, intensive care unit; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; IRF, IFN regulatory factors; LGMN, legumin; lncRNA, long noncoding RNA; LPS, lipopolysaccharide; LXR, liver X receptor; MDM, monocyte-derived macrophages; MERS-CoV, middle east respiratory syndrome coronavirus; MERTK, Mer tyrosine kinase; MHC, major histocompatibility complex; miRNA, microRNA; MMP, metalloproteinase; MRC1, mannose receptor C-type 1; NAMPT, nicotinamide phosphoribosyl transferase; NLRP, nod-like receptor family pyrin domain-containing protein; NOS, nitric oxide synthase; PAMP, pathogen-associated molecular pattern molecules; PBMC, peripheral blood mononuclear cells; PDL, programed death ligand; PMA, phorbol myristate acetate; PPAR, peroxisome proliferator-activated receptor; RNA, ribonucleic acid; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome coronavirus; scRNAseq, single cell RNA sequencing; SPP1, secreted phosphoprotein 1; STAT, signal transducer and activator of transcription; TCA, tricarboxylic acid; TGF, transforming growth factor; TGM2, transglutaminase 2; TLR, toll like receptor; TMPRSS2, transmembrane serine protease 2; TNF, tumour necrosis factor; WHO, world health organization.

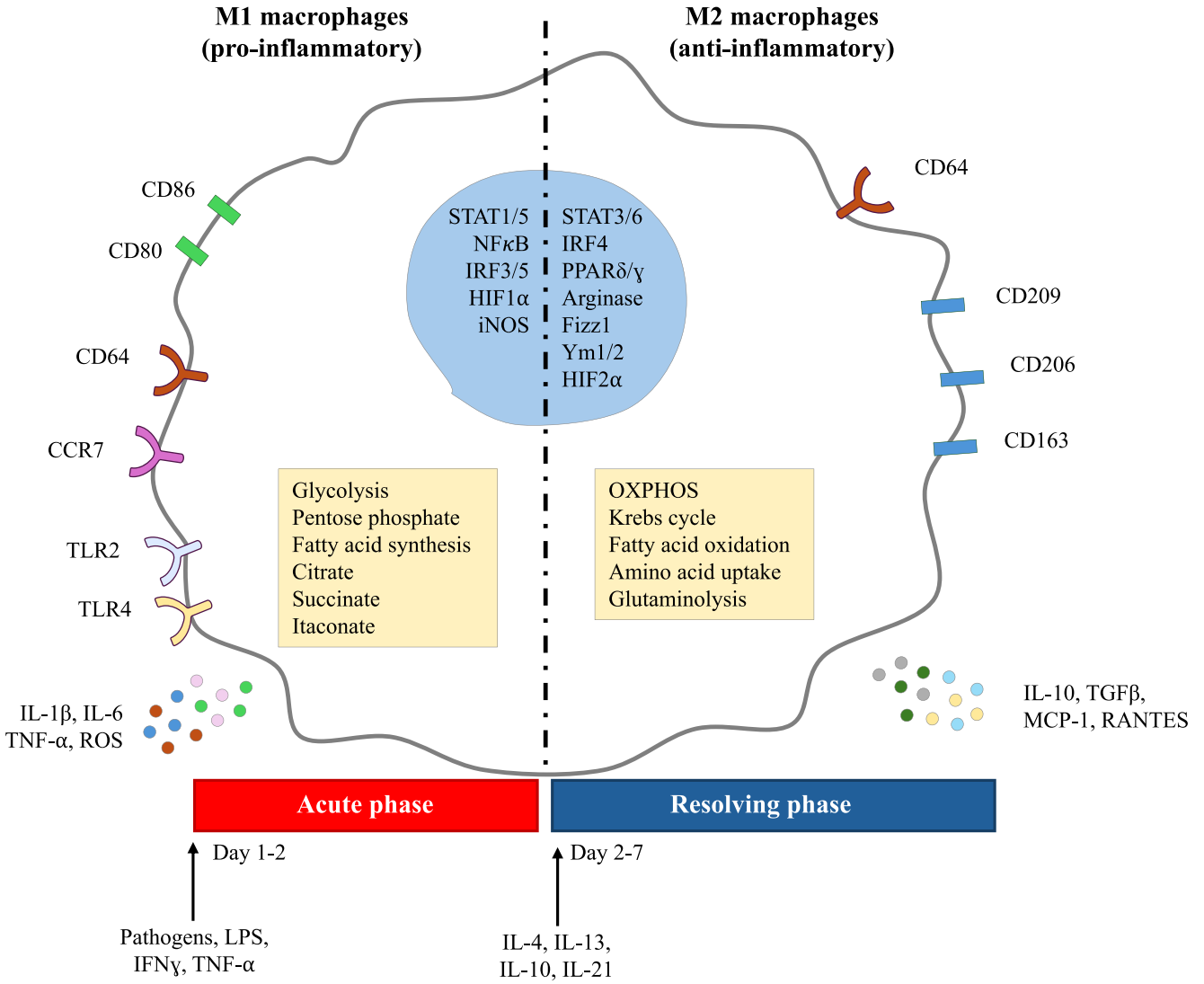

FIGURE 1 | M1 and M2 polarization profiles for macrophages. Schematic representation that illustrates the pro- and anti-inflammatory profiles of macrophages, referenced as M1 and M2. M1/M2 polarization profiles, during the acute and resolving phases, were summarised by surface markers, metabolism change and secreted cytokines following the interaction of macrophages with a large variety of stimuli. CCR, chemokine receptor; CD, clusters of differentiation; Fizz, found in inflammatory zone; HIF, hypoxia-inducible factor; IFN, interferon; IL, interleukin; IRF, interferon-regulatory factor; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; RANTES, regulated upon activation normal T expressed and secreted; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TGFB, tumour growth factor; TLR, Toll-like receptor; TNF, tumour necrosis factor.

activated and inflammatory cytokines and NOS products are overproduced, are considered as M1 macrophages; on the other side, macrophages stimulated by IL-4, in which STAT6 and arginase are activated are called M2 macrophages [3, 4]. But it has become evident that M2 macrophages are more heterogeneous than M1 macrophages. It is why they have been subdivided in four populations, from M2a to M2d. This approach enabled the introduction of IL-10 and TGFβ, known to play a critical role in normal and pathological regulation of immune responses [5, 6]. The way used to define the functional macrophage subsets reflects the state of the art of macrophage biology 20 years ago. Our knowledge of myeloid compartment has profoundly changed these latter years regarding macrophage ontogeny, activation/differentiation pathways and regulation mechanisms [7].

The regulation of macrophage activation and polarization is multifactorial and involves various molecules of macrophage signalling including the STAT family, PPARγ/LXR, CREB-C/EBP and IRFs. PPARγ, a regulator of lipid metabolism, is a key molecule whose signalling pathways are strongly associated to macrophage regulation. Induced by IL-4 and IL-13, PPARγ negatively regulates the expression of pro-inflammatory genes. In contrast, LXR, associated with retrograde cholesterol transport, suppresses inflammatory pathways and activates M2-promoting transcriptional factors such as MafB [8, 9]. C/EBPs represent also critical actors in macrophage activation. The C/EBPβ promotes TLR-mediated activation of arginase 1, a canonical component of M2-type signature whereas C/EBPρ promotes M1-type responses in macrophages [10]. Finally the IRF regulate type I IFNs and macrophage polarization: for instance,

IRF5 favours M1 polarization and IRF3 contribute to M2 activation [11].

More recently, the miRNA and lncRNA have emerged as major regulator of macrophage polarization. The M1 signature is associated with the expression of miR155, miR125b, miR9 and miR127 whereas M2 signature is associated with that of miR223 and miR124 [12, 13]. The M1- and M2-type macrophages exhibit distinct lncRNA profiles [14]. The M1/M2 stratification can be also analysed in the light of epigenetic regulation of macrophage activation. Hence, the epigenetic regulation of M2 macrophages involves histone methylation and acetylation, and IFNγ increases chromatin accessibility [15, 16]. The development these latter years of metabolomic approaches renewed our understanding of metabolism changes in macrophage activation. Hence, the proinflammatory M1 macrophages are dependent on glycolysis and pentose phosphate pathway. In contrast, immunoregulatory M2 macrophages engage TCA cycle and fatty acid oxidation and contribute to the metabolism of glutamine and arginase activity [17]. The inclusion of regulatory molecules in macrophage polarization signature increases the sensitivity of these biomarkers and may improve their use in homoeostasis and diseases.

2 | Macrophage Polarization in Respiratory Viral Infections

The respiratory infectious diseases have strong consequences via their acute severity and their sequelae, in both macrophage activation plays a critical role [18]. The measurement of macrophage activation/polarization in respiratory infectious diseases has been a source of extended literature and useful to stratify infected patients [19]. We tried to identify scientific publications in which the concept of macrophage polarization has been used to evaluate host response to viruses [20]. In a general point of view, the interaction of virus with macrophages elicits a pro-inflammatory response of M1 type whereas M2 phenotype is observed at late stages of infection [21]. We will illustrate the macrophage polarization in three examples of respiratory infections in which macrophages can be a target of virus and/or be involved in host defence and reparation.

2.1 | Respiratory Syncytial Virus

The RSV is a frequent aetiology of lower respiratory tract infections in children. The virus induces the expression of proinflammatory mediators and the recruitment of inflammatory cells in the lungs. M1-like macrophages are enriched in recruited monocytes and exacerbate airway inflammatory response; M2-like macrophages correspond to resident alveolar macrophages and contribute to repairing damaged lung tissues. The M1/M2 dichotomy is found during the kinetics of host response to RSV: M1 profile during the acute phase and M2 profile during the convalescence [22, 23]. RSV increases the risk of pneumococcal pneumonia. It stimulates the production of GAS-6 that interacts with its receptor Axl leading to the reprogramming of alveolar macrophages from M1 to M2 phenotype [24]. The virus is associated with the occurrence of asthma in adulthood. This is related to the ability of RSV to activate type 2 ILC resulting in alarmin and type 2 cytokine production and M2 shift in macrophages [25].

2.2 | Rhinovirus

Human rhinoviruses cause most virus-mediated exacerbations of asthma. This latter has been associated to reprogramming of immune response suggesting that macrophage polarization may affect host response to rhinoviruses. A. Nikonova et al. showed that M1-type MDM were more resistant to rhinovirus than M2-type or non-polarised MDMs. Rhinovirus infections were more severe in asthma patients than in healthy controls, but the authors did not find a shift of BAL cells towards a polarised status (M1 or M2) [26]. Experimentally, rhinovirus infection of MDM induced mainly the expression of M2-associated genes [27]. In murine model, rhinovirus response depends on macrophage activation [28]. In wild type mice, rhinovirus (RV-A1B strain) induced an enrichment with lung macrophages expressing M2-like markers. Based on IL-4 receptor invalidation, IL-13 appeared clearly involved in increased airway inflammation [29]. Lungs from mice sensitised with ovalbumin and challenged with rhinovirus exhibit an influx of inflammatory monocytes and exudatives macrophages. These latter were of M2-type, produced IL-13 and play a role in asthma exacerbation [30]. Except for virus-induced asthma exacerbation, myeloid cells exhibit hyperactivated phenotype that can be considered as M1-type profile.

2.3 | Influenza Virus

The seasonal respiratory epidemics of flu or pandemics like that of 1918 are due to influenza viruses belonging to *orthomyxoviridae*. The severity of influenza infection depends on strain diversity and host susceptibility source of an uncontrolled inflammatory response [31]. There is evidence that influenza virus productively infects myeloid cells and may affect their polarization status although convincing reports were scarce. HIN1, H3N2 and H9N2 influenza viruses stimulate M1-type polarization early and M2-type late after the infection [32]. Although H5N1 stimulates M1-type profile, the nature of modulated genes was distinct from M1-type profile stimulated by H1N1 [33]. The use of animal models revealed the role of macrophage reprogramming in infection outcome. Hence, the inactivation of NOS2 and IFNγ favour M2 reprogramming and improves outcome of influenza infection [34]. The infection with influenza virus is associated with a reduction of M2-type alveolar macrophages and a large recruitment of M1-type monocytes [35]. M2-type macrophages are more rapidly infected and killed by influenza virus than M1-type macrophages [36]. The transition from M1 state in murine alveolar macrophages to M2 state during pregnancy is associated with increased severity in response to H1N1 influenza infection [37]. In humans, monocytes from patients with severe influenza infection overexpress M1 markers and downmodulate M2 markers [38]. These results suggest that M1 and M2 programs of activation cannot predict the intensity of host response to influenza viruses.

These results show the limitations of macrophage polarization tool in respiratory infections and question the meaning of its use in a model of severe respiratory infection, the COVID-19.

3 | SARS-CoV-2 Infection and Macrophage Polarization

SARS-CoV-2 belongs to the family of coronaviruses, known to be pathogen for humans and animals, with SARS-CoV and MERS-CoV. SARS-CoV-2 was isolated in 2020 and responsible of COVID-19 outbreak that became a pandemic. Since the identification of initial strain, Wuhan-Hu1, in Wuhan (China), several variants have surged with epidemic waves: alpha/beta (2020–2021) and delta variants (2021–2022) are more transmissible and virulent than the reference strain and Omicron variant since 2022 are less virulent than the previous strains but exhibit multiple spike mutations associated with immune escape. COVID-19 [39, 40] lead to a tremendous number of contaminations (774 million cases) and deaths (7 million deaths) (WHO). The infection may be asymptomatic, acute leading to recovery or severe with acute respiratory distress syndrome, sepsis, neurological of cardiovascular complications in the presence of comorbidities (hypertension, diabetes, obesity) and elderly patients. The infection with SARS-CoV-2 may lead to long term neurological and cardiovascular complications that have a major impact on life quality [41, 42]. The outcome of SARS-CoV-2 infection will depend on the nature of immune response induced by the infection or the vaccination [43]. The innate and adaptive immune responses lead to antiviral immunity on one hand but the exacerbation of these two arms of immune response may be responsible of COVID-19 severity. Among the effectors of antiviral immunity, monocytes and macrophages play a complex role. They can recognise the viruses, mount an antiviral programme, and contribute to their elimination but their activation status may be critical for COVID-19 pathophysiology. We wondered if SARS-CoV-2 reprogrammates monocytes and macrophages towards M1 or M2 type and if myeloid cells from patients with COVID-19 are polarised.

3.1 | SARS-CoV-2 and Monocytes/Macrophages Polarization

SARS-CoV-2, initial Wuhan strain [44] and variants, alpha, beta, gamma, delta and omicron [45], can enter monocytes and MDM. There is a large consensus about the inability of SARS-CoV-2 to replicate in monocytes and MDM likely in relation with poor expression of SARS-CoV-2 receptors, ACE2 and TMPRSS2 [46–48]. This may be related to previous reports in which SARS-CoV-1 infection was abortive in myeloid cells whereas MERS-CoV replicated in monocytes and macrophages [49]. In addition, we found that Wuhan strain and delta variant did not replicate in macrophages from materno-foetal interface [50] SARS-CoV-2 replication would be, nevertheless, possible in tissue resident macrophages as in activated alveolar macrophages [51] and in murine models in which human lung is engrafted [52]. Taken together, these observations highlight the role of macrophages in SARS-CoV-2 tissue tropism.

Despite the lack of permissively of monocytes and MDMs for SARS-CoV2, the Wuhan strain stimulated cytokine release associating inflammatory (IL-6 and TNF) and immunoregulatory (IL-10 and TGFβ) cytokines (Figure 2). These results are not in favour of reprogramming of macrophage responses. The investigation of transcriptomic expression of M1 and M2 related genes emphasised the lack of polarization in resting monocytes and macrophages [44]. As Wuhan strain elicited an inflammatory non-polarised signature, we wondered if SARS-CoV-2 variants share this property. We found that all variants elicited macrophage activation but there was a tendency of increased expression of M1-related genes in response to beta variant (South Africa). This was confirmed by the measurement of cytokine release since IL-1β amount in response to beta variant was higher than that induced by other variants [45]. Hence, monocytes and MDMs are activated in response to SARS-CoV-2 in a non-polarised manner. This was emphasised using resident macrophages isolated from materno-foetal interface. Their interaction with SARS-CoV-2 organisms elicit an activation programme non-polarised consisting of inflammatory mediators and IL-10 [50]. As metabolic dysfunctions increase the risk of severe COVID-19, changes in metabolic status of macrophages may provide alternative approach of their role in SARS-CoV-2 susceptibility. It has been reported that SARS-CoV-2 increases glycolysis in macrophages, which reflects M1 polarization and favours viral replication and production of inflammatory cytokines [53]. The use of a M1/M2 signature based on cytokine imbalance showed limitations different types of myeloid cells, suggesting alternative approach of macrophage polarization.

The presence of IL-1β, rather associated with M1 polarization, in the signature of SARS-CoV-2-stimulated monocytes and macrophages deserves some comments (Figure 2). Among inflammatory cytokines released in response to SARS-CoV-2, IL-1β has been associated with the severity of COVID-19 and justified anti-cytokine treatment. It has been reported that inflammatory signature of SARS-CoV-2-stimulated myeloid cells exhibited an upregulation of IL-1 genes [54]. These findings suggest that SARS-CoV-2 engaged inflammasome in monocytes and the inhibition of virus life cycle with antiviral molecules blocked pyroptosis and IL-1β release [55]. Hence the interaction of human monocytes and lung macrophages in an humanised murine model with SARS-CoV-2 results in pyroptosis and caspase activation, gasdemin D cleavage and IL-1β production reflecting inflammasome activation [52, 55]. This activation pathway is likely critical since the inhibition of inflammasome reduces cell infiltration and enhances tissue recovery in humanised mice. There is some evidence that NLRP3 is activated in myeloid cells infected by SARS-CoV-2 in post-mortem tissue samples and PBMC [55]. It is evident that SARS-CoV-2 elicits pyroptosis pathway in myeloid cells, but this pathway was not considered as reflect of M1-type polarization. This observation suggests that a strong activation of monocytes and macrophages during SARS-CoV-2 infection does not mean that these cells are reprogrammated to M1 type profile.

The way to infect myeloid cells may affect their activation status. The role of virus receptors in macrophage activation and potential polarization has been reported in several reports. I. Pantazi et al. reported that SARS-CoV-2 S protein, known to

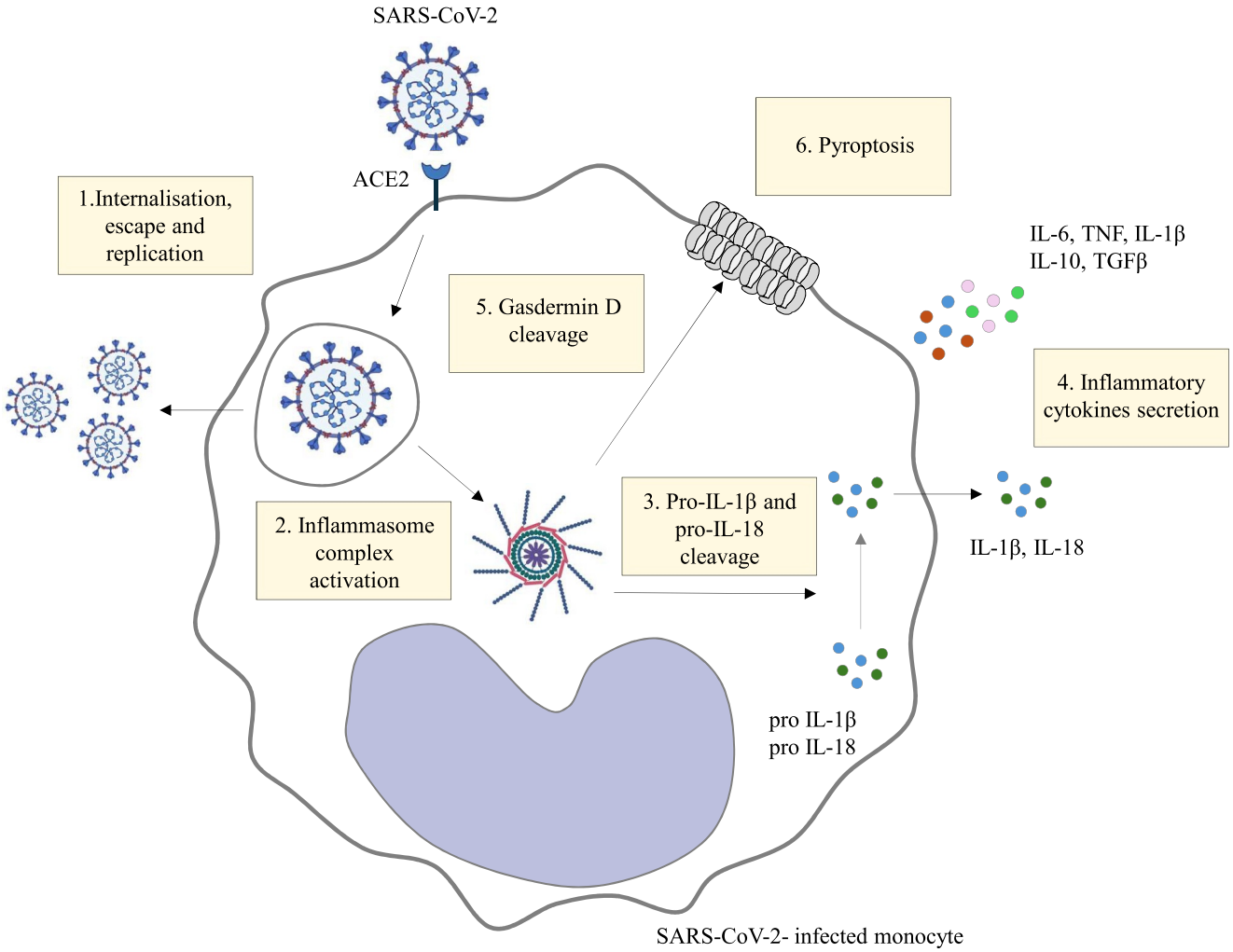

FIGURE 2 | Monocytes response to SARS-CoV-2 infection. 1. SARS-CoV-2 interaction with ACE2 receptor leads to internalisation, escapes degradation into the phagolysosome altogether leading to virus replication and virions release. 2. SARS-CoV-2 infection induces the activation of NLRP3 (NOD-like receptor family, pyrin domain containing 3) and AIM2 (absent in melanoma 2) that trigger the formation and the activation of the inflammasome complex. 3. Pro-inflammatory cytokines IL-1β and IL-18 were release after the cleavage of pro-IL-1β and pro-IL-18 by the activated inflammasome. 4. Inflammatory cytokines including pro- (interleukin [IL]-6, tumour necrosis factor [TNF], IL-1β) and anti- (IL-10, tumour growth factor [TGF]β) inflammatory cytokines were release by infected monocytes. 5 and 6. Pyroptosis was initiated by the cleavage and the insertion of Gasdermin D into the membrane. ACE2, angiotensin-converting enzyme 2; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGF, tumour growth factor; TNF, tumour necrosis factor.

bind ACE2 receptor, induced inflammatory mediators in PMA-differentiated THP-1 cell line, which can be mimicked by direct ACE2 binding [56]. This response needs to be related to the role of renin-Ang in macrophage activation: Ang II elicits inflammatory response whereas Ang (1–7) is rather suppressive; this latter is produced by monocytes and macrophages [57]. The use murine models in which ACE2 was overexpressed showed a decrease in M1-related genes and an increase in M2-related genes such as *Arg1* and *Ym1* whereas the reverse was observed when ACE2 expression was depressed [58]. The interaction of SARS-CoV-2 with human macrophages lead changes of ACE2 expression, which is debated and may explain part of monocyte response to virus. As spike protein of SARS-CoV-2 is decorated by glycans, lectins receptors may play a complementary role to ACE2 [59]. Q. Lu et al. reported the identification of 5 C-type lectins as glycan-dependent binding partner of S protein in myeloid cells. The lectin receptors favour the binding of SARS-CoV-2 in an ACE2 independent manner. They do not promote SARS-CoV-2 replication but elicit strong inflammatory response [60]. Hence, beta variant known to be less sensitive to neutralising antibodies and to exhibit increased affinity to ACE2, is likely the SARS-CoV-2 variant to elicit a M1-type macrophage response. The increased release of IL-1β may be related to SARS-CoV-2-stimulated NRLP3 inflammasome activation in THP-1 cells in the absence of SARS-CoV-2 replication [61]. At the opposite, omicron variant was the only to induce IL-10 overexpression, which likely decrease virus virulence in macrophages. The investigation of SARS-CoV-2 variants interaction with macrophages has been recently emphasised in a model of macrophages derived from induced pluripotent stem cells. The authors reported that delta variant induced a productive infection of macrophages and promoted their fusion whereas omicron variant infection was abortive with a defective fusogenicity. It is noteworthy that both variants

were unable to induce a M1-type inflammatory response [62]. Taken together, SARS-CoV-2 including Wuhan strain and various variants activate monocytes and macrophages but is unable to reprogrammate them into M1-type polarization.

3.2 | Monocytes/Macrophages Polarization Profile in COVID-19 Patients

The investigation of macrophages in patients is limited by the accessibility. If monocytes can be assessed in whole blood or after purification, the information about macrophages are scarce limited to alveolar fluid in patients with severe disease. For ethical reasons, tissue macrophages from patients with mild to moderate COVID-19 are rarely studied and monocytes will be the major source of information.

Quantitative and qualitative changes of myeloid cell compartment have reported in COVID-19 (Table 1). The variations in myeloid cell abundance have been associated with COVID-19 severity using several approaches from blood cell numeration to mass cytometry through flow cytometry. Initial reports showed a decrease in blood monocyte count, but the time course of the disease is a critical parameter [75, 76]. In parallel, monocytes are recruited monocytes in nasopharyngeal mucosa in response to chemokine overproduction [42]. Inflammatory circulating monocytes expressing HLA-DR and CD11c are found in mild COVID-19 patients [63]. E. Kvedaraite et al. reported an increase in intermediate monocyte number and a decrease in non-classical monocytes whereas classical monocytes remained unchanged. The measure of HLA-DR, CD86, CD141 and CCR2 enables a relation between phenotype and prognosis of COVID-19 [77]. The loss of non-classical monocytes and the appearance of $S100^{hi}HLA\text{-}DR^{low}$ are associated with severe disease [68]. The COMBAT consortium defined cell biomarkers of COVID-19 severity. The authors reported higher frequency of classical monocytes and fewer intermediate and non-classical monocytes in hospitalised COVID-19 patients with more severe disease. This increase in severity was associated with a shift of classical monocyte phenotype towards lower expression of HLA-DR, CD33 and CD11c [78]. Besides the down-modulation of HLA-DR that is reminiscent of polarization change of monocytes, the use of multi-omics methods revealed the appearance of populations with unusual phenotype

TABLE 1 | Population changes of alveolar macrophages and monocytes in COVID-19.

	Monocytes	Alveolar macrophages	References
Acute phase	• ↓ global monocyte population • ↑ intermediate, ↓ non-classical → classical	• No investigation	[44, 63]
Mild to moderate disease	• $CD169^{+}$ expressing CCL2 and IFNγ • $HLA\text{-}DR^{hi}$ $CD11c^{hi}$/$HLA\text{-}DR^{hi}CD83^{hi}$ • Antiviral IFN-signature • Mono_c2-CD14-HLABP1 and Mono_c3-CD14-VCAN monocytes sybtypes	• $FABP4^{+}$ alveolar macrophages	[64–67]
ARDS	• ↓ non-classical/↑ $S100^{hi}HLA\text{-}DR^{low}$ • ↑ classical, ↓ intermediate and non-classical • ↑ classical $HLA\text{-}DR^{low}CD33^{low}CD11c^{low}$ • Large vacuole: Monocyte maturation? • Classical cells: $CD141^{+}CD163^{+}$ in early phase and $HLA\text{-}DR^{low}CCR2^{low}VISTA^{low}$ in the late phase • Cells with RAGE ligands expression such as S100A12 and poorly HLA-DR • Inflammatory immature cells expressing S100A12, NRLP3, NAMPT and HLA-DR • Classical cells expressing type I IFN-genes • Mono_c1-CD14-CCL3 express CCL3, TNF, IL-1R	• $FCN1^{+}$ alveolar macrophages • M1-related macrophages • ↓ tissue-resident macrophages • Secretion of inflammatory cytokines • Depressed expression of HLA-DR • Inflammatory macrophages in exudative phase—M2-type macrophages in exudative and fibrotic phases • Fibrosis: • Macrophages accumulated in lung and contained SARS-CoV-2 RNA • CD163/LGMN subset exhibited similar a transcriptional signature like macrophages in idiopathic pulmonary fibrosis	[63, 65, 68–73]
Disease resolution	• Admission: High level of PD-L1 • Discharge: Shifted to $CD4^{+}CD11c^{+}HLA\text{-}DR^{+}$ cells and downregulation cell signalling molecules (pSTAT3)	• No investigation	[74]

Note: Identification of the proportion and the phenotype of alveolar macrophages and monocytes during the acute phase, mild/moderate disease, acute respiratory distress syndrome (ARDS) and disease resolution of coronavirus disease (COVID)-19.

including proliferating monocytes. Atypical population of monocytes with large vacuoles have been found in COVID-19 patients admitted to ICU. They exhibit staining for M1-specific cytokines and M2-associated IL-10 [79]. These findings question the place of myeloid cell maturation in activation status.

The dysregulation of lung resident macrophages may impact the evolution of pneumonia. The alveolar macrophages are considered as M2-related myeloid cells and are of embryonic origin; following aggression they can be replace by monocytes, which impact the activation status of alveolar environment. Inflammatory macrophages are present in lungs of critical patients with COVID-19 [69]. Lung biopsies reveal massive infiltration of monocytes, neutrophils and M1-related macrophages in patients with severe COVID-19 [80]. The number of lung tissue-resident alveolar macrophages is decreased in severe COVID-19, and patient alveolar macrophages express highly inflammatory cytokines with depressed expression of HLA-DR. This latter inflammatory response conjugated to SARS-CoV-2-elicited pyroptosis may account for depletion of alveolar macrophage pool [70]. The transcriptomic analysis of BAL fluid from patients with COVID-19 at the beginning of the pandemic showed an enrichment with proinflammatory cytokines and chemokines but anti-inflammatory genes such as *TGFB* were also increased. This type of profile does not correspond to a typology of macrophage polarization. Similar results were obtained with circulating mononuclear cells but the gene expression programs in BAL and blood are not superimposable [81].

The COVID-19 during pregnancy has increased the risk of severe evolution of the disease without leading to vertical transmission. The pregnancy is interesting for the question of macrophage polarization since these cells change their activation status during the three trimesters [82]. We investigated macrophages from the foeto-maternal interface from women infected during the three trimesters of pregnancy. Macrophages from second and third trimester exhibited an activated programme with M1-related genes and *TGFB*, that should be considered here as profibrotic than M2-related gene. Such profile cannot be classified as M1-type profile. The in vitro restimulation of macrophages with SARS-CoV-2 organisms was unable to induce a polarised phenotype [50]. The activation of monocytes and macrophages during COVID-19 reflects their interaction with tissue microenvironment. The coculture of SARS-CoV-2-infected epithelial cells and $CD14^{+}$ monocytes resulted in overexpression of inflammatory cytokines, IFN-stimulated genes and IL-10 but MHC-II was down-modulated [83]. The treatment of MDM with BAL fluid from patients infected with SARS-CoV-2 and early ARDS induced an IL-10-related polarization profile that associates the overexpression of CD163 and CD16 and depressed expression of CCL22. BAL fluid from late COVID-19 ARDS did not induce MDM polarization. There is a clear relationship between the phenotype of macrophages, the interacting cells and patient severity [84, 85].

These reports converge to show that circulating monocytes and tissue macrophages from COVID-19 patients exhibit an hyperactivation profile that does correspond to M1- or M2-type activation status but do not exclude that a certain degree of polarization was associated with disease history and that myeloid cells pass through several phenotypes.

3.3 | Relationship Between Macrophage Polarization and SARS-CoV-2 Response

The impact of macrophage polarization on coronavirus infection has been initiated with observations on SARS-CoV. Using $STAT1^{-/-}$ mice that are enriched with M2-type macrophages, the authors showed that the absence of STAT1 did not affect viral clearance but increased disease severity. In $STAT1^{-/-}/STAT6^{-/-}$mice, the pulmonary disease is prevented. Hence, polarization of macrophages towards M2 type is involved in severity of SARS-CoV infection [86]. In COVID-19, it was suspected that allergic diseases, prototype of M2 polarization-associated diseases, including asthma are a risk factor for disease severity but allergy was not associated with delayed clearance of SARS-CoV-2 [87]. Most of studies about macrophage polarization and COVID-19 used murine models. In alveolar macrophages from ACE2 transgenic mice, viral load was increased in M1-type differentiated cells as compared with M2-type cells. SARS-CoV-2 replicated in M1-type alveolar macrophages and was released as compared with M2-type alveolar macrophages. The authors suggested that the pH of M1-type alveolar macrophages was sufficient for viral escape whereas that of M2-type alveolar macrophages enabled mobilisation of acidic lysosomes that are deleterious for the viruses [51, 88]. An interesting mechanism based on ACE engagement with viral particles which increase endosomal pH and reprogrammate alveolar macrophages towards M2 profile. The ACE2 microparticles inhibit proinflammatory cytokine expression without affecting type I IFN production [89]. Similar results have been reported in humans. We showed that the viral load of M1-like and M0-like THP-1 cells was similar but viral load was decreased in M2-like THP-1 cells [44]. This finding suggests that type 2 macrophage polarization may be protective in SARS-CoV-2 infection. This finding may be related to the finding that patients with allergic asthma are poorly sensitive to SARS-CoV-2 and exhibit decreased expression of ACE2 and upregulation of IL-13, a Th2 cytokine known to depress the expression of ACE2 by bronchial epithelium [90]. Less clear-cut results were obtained with macrophages obtained from human pluripotent stem cells. The M1-type and M2-type macrophages share the ability to clear the virus if the load is moderate. M1-type macrophages induce more damage on lung cells via the production of inflammatory mediators in coculture models, which is not observed with M2-type macrophages [91]. As observed above, SARS-CoV-2 virus does not induce a polarization of myeloid cell activation, and their polarization poorly impacts their response to the virus.

4 | From Macrophage Polarization to Myeloid Population Changes in SARS-CoV-2 Infection

4.1 | Macrophage Polarization Limitations

The confrontation of macrophage polarization concept with infectious diseases reveals the limitation of polarization model and leads to propose another of macrophage investigation. In vivo, the agonists are not known, and the features of macrophage signature will define the type of macrophage polarization. Hence, when macrophages overexpress inflammatory

cytokines, they are of M1 type and when anti-inflammatory cytokines or cytokines associated with regeneration, they are of M2-type. In some paper, the overexpression of one marker of each activation category is sufficient to conclude to a polarised state of macrophages. Many researchers including us were aware that the model of macrophage suffers from dramatic limitations [92]. The first limitation of using M1/M2 dichotomy is the difficult to define a precise signature shared by scientific community, accounting for the discrepancies of conclusion about macrophage typology. The second limitation is the consequence of initial definition of macrophage polarization: M1 and M2 type correspond to LPS and IFNγ and IL-4 responses, respectively. However, a large variety of agonists can induce M1 and M2-type responses. We proposed to define macrophage activation diversity according to the type of agonist. This leads to an increased in functional states, which better reflect the diversity of macrophages responses to homoeostatic or pathologic conditions [93]. The third limitation is the consequence of changes in our view of macrophage ontogeny and plasticity with niche concept and the development of new tools [7, 94]. Hence, multiparametric flow cytometry and single cell scRNAseq have changed our definition of macrophage subsets with the emergence of new functional subsets. It is why we would like to introduce new macrophage subsets as alternative to macrophage polarization signature.

4.2 | Changes in Monocyte Populations

Monocytes contains three major subsets based on the expression of CD14 and CD16, classical, intermediate and non-classical monocytes [94, 95]. The exploration of monocyte compartment with mass cytometry and scRNAseq revealed that classical monocytes are also highly heterogenous and can be separated in several subclusters [63]. In COVID-19 course, non-classical $CD16^{+}$ monocytes are depressed in patients with severe disease whereas neutrophils are increased [71, 96]. Several studies summarised in the following section revealed the presence of new functional subsets of monocytes in the different clinical forms of COVID-19.

S. Chevrier et al. investigated 66 COVID-19 patients with mass cytometry. They identified a population of activated monocytes expressing CD169 only in patients with COVID-19. The $CD169^{+}$ monocytes express activation markers and pro-inflammatory cytokines (CCL2, IFNγ) and are enriched in patients with mild disease [64]. Hence, inflammatory monocytes may be protective. In contrast, study combining mass cytometry and scRNAseq showed severe COVID-19 patients are enriched in $CD14^{+}CD163^{+}$ classical monocytes in early phase of the disease and $HLA\text{-}DR^{low}CCR2^{low}$ $VISTA^{low}$ classical monocytes in the late phase. Patients with mild disease exhibited early activation of $HLA\text{-}DR^{hi}$ $CD11c^{hi}$/$HLA\text{-}DR^{hi}CD83^{hi}$ monocytes and a strong antiviral IFN-signature [93].

C.E. Burnett et al. investigated monocytes in COVID-19-patients with different trajectories using mass cytometry that targeted 30 protein markers and 14 phosphorylated signalling molecules. In patients who experienced disease resolution, monocytes expressing high level of PDL-1 at the time of the admission shifted to cells upregulating CD4, CD11c and HLA-DR and downregulation cell signalling molecules such pSTAT3 at time of discharge. Similar findings were obtained in non-classical monocytes from patients with ventilation at time of extubation [74].

S.T. Chen et al. provided a new stratification of monocytes using scRNAseq. They identified a cluster of classical monocytes expressing markedly RAGE ligands such as S100A12 and poorly HLA-DR, which was enriched in severe COVID-19 with end organ damage. Three clusters of inflammatory immature monocytes expressing S100A12, NRLP3 and NAMPT, an oxidative stress marker, which may be associated with disease severity according to the co-expression of HLA-DR. Finally, a cluster of classical monocytes expressing type I IFN-stimulated genes was found in COVID-19 patients including those with severe presentation [70]. This latter cluster questions the place of IFN-stimulated genes in polarization of myeloid cells.

X. Ren et al. found elevated expression of cytokines and inflammatory genes in COVID-19 patients at the severe progression stage. Three subtypes of monocytes were identified with enrichment with inflammatory mediators. The Mono_c1-CD14-CCL3 was associated with severe expression of COVID-19. In contrast, Mono_c2-CD14-HLABP1 and Mono_c3-CD14-VCAN subtypes were widely distributed independently of the prognosis. The authors found a unique pro-inflammatory signature that does not correspond to M1 signature and contains *TNF*, *CCL3*, *IL1B*, *CXCL8*, *IL6*, *TGFB*, *LTB* and *IFNG* genes. The Mono_c1-CD14-CCL3 was characterised by high expression of CCL3, TNF and IL-1R [65].

We previously shown that macrophage polarization does not match with monocyte activation [97] and alternative stratification strategies would be necessary. The COVID-19 enabled a better characterisation of functional monocyte subpopulations with the identification of hyper-inflammatory populations of monocytes in severe presentations of the disease and monocyte subsets associated with COVID-19 sequelae.

4.3 | Changes in Macrophages Populations

The limitations of macrophage polarization concept have been observed with macrophages during COVID-19. Most of the studies involve alveolar macrophages because of the access to BAL. The $FABP4^{+}$ alveolar macrophages are dominant in mild to moderate COVID-19 patients whereas $FCN1^{+}$ MDM are dominant in ARDS patients [98]. The FABP4 is upregulated in M1-type macrophages [99] and FCN1 is expressed by pro-inflammatory macrophages and contributes to IL-1β maturation [100]. The role of these two subsets in the evolution of COVID-19 cannot be explained by M1/M2 dichotomy. ST. Chen et al. conducted a study of immune cell dynamics in lung compartment using BAL from COVID-19 patients and scRNA-seq. They found the presence of $IL\text{-}1\beta^{+}$ monocytes and alveolar macrophages that highly expressed *IL1B*, *CCL3*, *CCL4*. According to the stage of the disease, monocytes and alveolar macrophages expressed early phase (monocyte phenotype) or late phase (macrophage phenotype) markers [70]. X. Ren et al.

conducted a comparative study of new myeloid subtypes in blood and BAL. Hence, they identified 5 hyper-inflammatory cell subtypes comprising Macro_c2-CCL3L1 macrophages, 3 monocytes and neutrophils subtypes. The signature of Macro_c2-CCL3L1 subtypes specifically expressed CCL8, CXCL10/11 and IL-6, which is clearly distinct from M1 inflammatory type [65]. The limits of patient studies justify the use of animal models and rhesus macaques reproduce COVID-19. The infection of rhesus macaques with SARS-CoV-2 elicited enrichment of cytokines (IL-4, IL-6, IL-10, IL-12, IL-23, TNF, IFNA), chemokines (CXCR3, CXCR4) and immunosuppressive pathways (PD-1, CTLA-4) in PBMCs and BAL. The inflammatory context is associated with a shift in airway macrophages. Among them, there was an increase in $CD163^{+}MRC1^{+}TREM2^{+}$ cells that account for most of the production of IL-6, IL-10 and TNF. The authors also show that $CD163^{+}MRC1^{+}TREM2^{+}$ cell is congruent with $SPP1^{hi}$ human subsets, underlying that M1/M2 dichotomy cannot account for the dynamics of functional macrophage subsets [101].

Macrophages are involved in tissue damage in severe COVID-19 and in long term sequelae. ARDS is a complication of SARS-CoV-2 infection which requires prolonged respiratory support and results in high mortality. The ARDS consists of three phases: exudative followed by proliferative and fibrotic that determines functional prognosis. Distinct macrophage phenotypes have been associated to ARDS evolution. Inflammatory macrophages are involved in exudative phase whereas M2-type macrophages are found in exudative and fibrotic phases [102]. M2 polarization of macrophages or IL-4 macrophage response have been considered as a central contributor of fibrosis [103]. However, inflammatory cytokines can induce fibrosis in a pathway involving TGFβ [104]. Hence, M1 (IFNγ) and M2 (IL-4) dichotomy does not seem convenient to investigate fibrosis mechanism. The idiopathic pulmonary fibrosis is a model disease of fibrosis. scRNAseq investigation of fibrotic explants from patients revealed the enrichment with a macrophage population called $SPP1^{hi}$ with a signature comprising genes such as *SPP1, MERTK, SIGNLEC* and *MMP9* that were overexpressed. The examination of M2 markers (IL-4, IL-13, MRC1, TGM2) did not provide specific markers of fibrosis [105]. The presence of pulmonary fibrosis has been observed in severe COVID-19. In a study of tissue and samples from patients with severe COVID-19, macrophages accumulated in lung tissue and contained SARS-CoV-2 RNA. A more precise investigation of myeloid population by scRNAseq identified at least six populations of monocytes/macrophages. One of them, CD163/LGMN subset was present in the first weeks of ARDS and exhibited a transcriptional signature like that of macrophages in idiopathic pulmonary fibrosis [106]. The CD163/LGMN subset was significantly increased in patients with acute hypoxaemic respiratory failure who died. This subset that belongs to $CD206^{+}$ macrophages considered as M2-type, needs the combination of CD71 and CD163 to be identified [107].

5 | Conclusion

The study of myeloid compartment in SARS-CoV-2 infection revealed an uncontrolled inflammatory response that cannot be summarised by macrophage polarization concept. This latter is often based on molecules such as CD163 (haemoglobin scavenger receptor) considered as a promising marker of M2 polarization or a phenotypic marker of macrophages [108]. CD206, mannose receptor is another marker of M2 polarization and was considered as canonical marker of alveolar macrophages [109]. The $CD206^{+}$ alveolar macrophages from patients are present in patients with idiopathic pulmonary fibrosis and healthy donors but the expression of fibrotic genes was dramatically higher in former patients than latter controls [110]. The situation with M1 polarization is even more complex because the markers belong to cytokines and chemokines that are very sensitive to the PAMP and DAMP and to individual variations. In COVID-19 patients, the upregulation of inflammatory cytokines and chemokines was never isolated since immunoregulatory cytokines such as IL-10 or TGBFβ are often associated. The use of macrophage polarization concept to stratify patients with COVID-19 provides poor information. This statement is emphasised by the nature of the cells (monocytes and alveolar macrophages usually), which vary strongly among the patients and during the disease [93]. The high throughput methods provided an alternative approach by identifying new functional subsets. Similarly, the identification of $IL\text{-}1\beta^{+}$ macrophages may represent an interesting approach since the role of IL-1β has been shown in COVID-19 evolution and as a therapeutic target. The identification of pro-fibrotic macrophages that express CD9, CD63, SPP1 [111] may provide an interesting tool to follow COVID-19 with a risk of fibrosis evolution. The identification of new macrophage subsets directly in the tissues would provide information about the features of host response without isolating the cells. At the same time, recent studies identifying the ontogeny of classical monocytes contributing to macrophage populations [112] may provide a better understanding of the study of macrophages in patients' peripheral tissues.

The mobilisation of monocyte subpopulations in various pathologies is widely documented [113]. However, it remains to be determined whether the modulation of the expression of these subpopulations is consequent to the disease or whether it contributes directly to the inflammatory process related to the pathological context [114]. A better identification of the phenotype of monocyte subpopulations could better document their role in pathologies and to improve specific therapeutic targeting. Regarding COVID-19, the study of monocytes subsets based on CD14 and CD16 expression was not sufficient to assess systemic response to SARS-CoV-2 and new subsets resulting from scRNAseq or mass cytometry should be considered as biomarkers.

The concept of macrophage polarization may allow a rapid screening of macrophage responses to viruses and antiviral drugs. The characterisation of macrophage responses to SARS-CoV-2 variants may benefit from the use of polarization signature and may be useful in case of emerging pathogens. Some therapeutic strategies have been proposed at the beginning of the pandemic before the development of vaccines; they share the ability to reprogrammate macrophages towards anti-inflammatory profile. This was the case of hydroxychloroquine or remdesivir [115, 116] and more efficiently anti-cytokines molecules or corticosteroids [117]. It can be speculated that the use of macrophage polarization to assess the impact of

macrophage targeting molecules would allow a better harmonisation of data in clinical trials.

Author Contributions

S.M. and J.L.M. contributed to the conception and design of the review and to the writing of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data are available in the main text.

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