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Mini Review

# Future Oncology Concerns from Post-COVID19 Macrophage Aberrations

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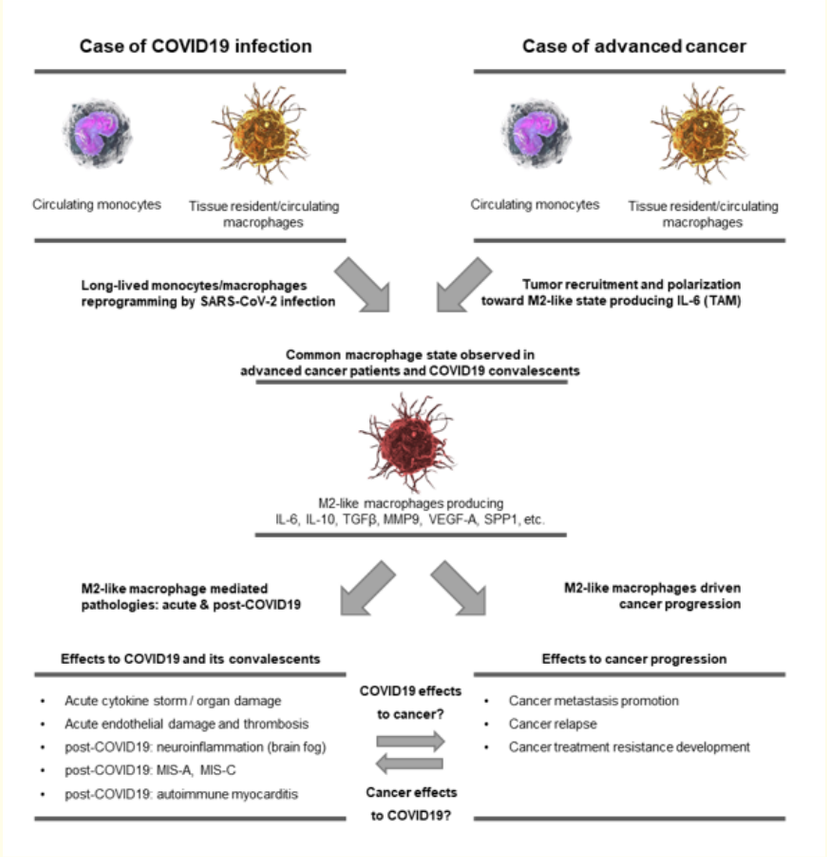
## Abstract

Since the global spread of COVID19, it is expected to become an endemic that will eventually infect the majority of human population. Unlike other endemics, however, emerging evidence suggests lasting changes in the innate immunity behavior post-COVID19 due to transcriptome-wide reprogramming of macrophages toward a unique M2-like state resembling tumor-associated macrophages (TAM). This review compares the functional phenotypes of post-COVID19 macrophages to those of TAM and discusses the consequent risks in COVID19 convalescent cancer patients.

## Graphic Abstract

***Keywords:*** *Oncology; COVID19; Tumor-Associated Macrophages (TAM)*



## Introduction

COVID19 has become a global pandemic counting over 185 million estimated cases (as of July 2021) with continuing outbreaks in different parts of the world. Some of the recovered patients from COVID19 may suffer lasting post-COVID19 syndromes (also known as long-COVID) that include neuroinflammations [1], multisystem inflammatory syndrome in children (MIS-C) [2], multisystem inflammatory syndrome in adults (MIS-A), or autoimmune myocarditis [3], all of which commonly feature pathologies involving aberrantly activated macrophages by the previous SARS-CoV-2 virus infection. Recently, a study on convalescent COVID19 patients showed the aberrant macrophage activation to be the result of persistent transcriptome-wide inflammatory macrophage reprogramming by the viral infection independent of the disease severity, suggesting causal roles of the reprogrammed macrophages toward the post-COVID19 inflammatory syndromes [4]. Unfortunately, the lasting changes in the macrophage behavior may be expected with further health effects, especially relating to cancer and its response behavior to treatments.

In cancer immunology, macrophage polarization status has long been identified as a major contributing factor toward cancer metastasis [5], relapse [6] and treatment resistance development [7,8]. Naturally, altered cancer treatment responses may be expected in patients with recent COVID19 history due to the reprogrammed macrophage behavior, prompting urgent needs to incorporate post-COVID19 immunology knowledge in designing more successful cancer treatment regimens.

### Macrophage subtypes in cancer - M1, M2, and everything in between

Macrophages are differentiated immune cells from tissue-migrated monocytes, and they are capable of polarizing into uncountable number of functional states from M1-like phenotype (anti-cancer and pro-inflammatory) to M2-like phenotype (pro-cancer and anti-inflammatory) and everything in between. Depending on the migrated tissue sites and differentiation status, different nomenclatures are also used in naming the tissue-resident macrophages such as microglia (brain), osteoclasts (bone), Kupffer cells (liver), or Langerhans cells (skin) (a dedicated review on the topic is available [9]). On one extreme, textbook M1-polarized macrophage is described with NO and citrulline production from arginine metabolism, which leads to its killer and proliferation inhibitory capacity involving efficient production of inflammatory cytokines such as IL-1β, TNF and IL-6. In comparison, M2-polarized macrophage is described with ornithine and polyamine production from arginine metabolism, which leads to its proliferation and repair promoting capacity featuring collagen synthesis, tissue fibrosis, and secretion of anti-inflammatory cytokines such as IL-10, TGF-β, and glucocorticoids. In real-world cases, macrophages are observed with mixed features between the M1 and M2 states, thus requiring the use of M1-like or M2-like nomenclatures with added descriptions on their functional profiles.

Termed as tumor-associated macrophages (TAMs), macrophages that populate in the tumor microenvironment (TME) have been reported as the main driver of cancer metastasis (a dedicated review on the topic is available [10]). TAMs generally acquire M2-like immunosuppressive phenotype in supporting the tumor progression and metastasis, but often produce inflammatory cytokines such as IL-6 and IL-8 in the process to enhance further TAM recruitment and cancer malignancy [11]. Taking non-small cell lung cancer (NSCLC) as an example, a retrospective CD163 immunohistochemistry study involving 160 consecutive patients who underwent NSCLC resection demonstrated significantly reduced disease-free survival rate and overall survival rate in patients with stromal M2 TAM-high tumors versus those with stromal M2 TAM-low tumors ($p = 0.0270$ and $p = 0.0162$, respectively) [12]. Furthermore, a comparative plasma cytokine panel study between 77 NSCLC patients and 91 healthy subjects demonstrated significantly lower overall survival rate in the patients with high systemic IL-6 ($p = 0.001$, IL-6 cut-off value at 8.05 pg/mL) versus those with low systemic IL-6 [13]. Together with the reports of negative correlation between patient survival and tumor IL-8 level in NSCLC cases [14], these real-world data collectively suggested M2-like TAMs producing IL-6 and IL-8 as the key driver of tumor aggressiveness. Another important secreted product by M2-like TAMs in advanced tumors include secreted phosphoprotein1 (SPP1), which serves to maintain M2-polarization in the TME and aid cancer immune evasion [15].

### COVID19 infection leads to lasting macrophage polarization toward TAM-reminiscent phenotype

Since the earliest of COVID19 case reports, heavy accumulation of IL-6 and IL-8 producing M2-like macrophages in the afflicted tissues has been cited as a hallmark feature of severe COVID19 infection [16,17]. With evidence from multiple groups corroborating direct binding of SARS-CoV-2 to macrophages [17,18], the resulting macrophage infection by live SARS-CoV-2 virus was reported with polarizing effects toward IL-6 producing M2-like phenotype [18,19]. In further similarity with the M2-like TAMs from advanced tumors that orchestrate tumor metastasis, infected lung macrophages were reported to be the main source of circulating SPP1 during severe COVID19 infection episodes [20] and capable of efficient NLRP3 inflammasome production upon stimulation [4,21,22]. Recently it was discovered that the COVID19-mediated macrophage polarization was a result of transcriptome-wide macrophage reprogramming, which resulted in altered innate immune functions for several months [4]. This report of long-lived macrophage reprogramming effects by COVID19 infection is consistent with the timing and the duration of the macrophage-mediated inflammation pathologies found in various Long-COVID syndromes [1-3], thereby setting sufficient time context for producing changes to symptomatic cancer status.

### Evidence of real-world pathological interactions between COVID19 and cancer

Given the plethora of evidence that highlight the functional similarity between the COVID19-reprogrammed macrophages driving the COVID19 pathology and those found in the TMEs of metastatic malignant cancers, bilateral pathological interactions between COVID19 severity and cancer progression may be hypothesized. Indeed, while formal controlled studies have not been reported, several anecdotal clinical reports that substantiate the macrophage-mediated pathological interaction have been published. Namely, a nation-wide prospective study in China revealed greatly increased risk of severe COVID19 events among patients with cancer versus those without (HR = 3.56, 95%CI: 1.65 - 7.69) [23], while a systemic review involving meta-analysis of global cohort studies also indicated escalated 30-day mortality rate of 30% among COVID19 patients with cancer vs. 21% among those without cancer, making cancer an independent risk factor toward COVID19 mortality [24]. Conversely, a retrospective survivability test study using UK Biobank's 21-day fatality data post COVID19 diagnosis revealed that cancer patients with COVID19 showed HR of 7.76 (95% CI: 5.78 - 10.40) versus the patients without COVID19 after multivariate controlling for age, ethnicity, sex, and cancer metastasis status [25], implicating COVID19 infection to be a strong independent risk factor of death among cancer patients. While the body of evidence on the increased COVID19 death risk from cancer is still growing, a current review on this dedicated topic is available [26].

### Potential consequences to cancer patients with aberrant macrophages from COVID19

### Increased risk of metastasis and relapse in the COVID19-recovered cancer patients

On contrary to the growing evidence on cancer contribution to COVID19 severity, there has not been a published study that experimentally assessed COVID19 contribution to clinical cancer progression, perhaps due to the requirement of lengthy observation time in designing such studies and limited BSL-3 lab access for performing SARS-CoV-2 experiments. Nevertheless, a perspective review by Francescangeli., *et al*. proposed that severe COVID19 episodes could lead to dormant cancer cell reawakening and metastatic relapse via activation of neutrophils and monocytes/macrophages with resulting production of neutrophil extracellular traps (NETs) and IL-6, collectively forming pro-cancer microenvironment [27]. Extension of this hypothesis to current cancer patients implicate increased risk of metastasis and future relapse as the most immediate consequence of COVID19 infection, especially when the functional similarities between the M2-like TAMs and COVID19-repgrammed macrophages are additionally considered.

Tumor metastasis is known to be a five-step sequence involving (a) invasion in the primary sites, (b) intravasation into the vasculature, (c) cancer cell survival in the circulations, (d) extravasation out of the vasculature, and (e) adaption and growth in the metastatic sites (a detailed review on the topic available) [10]. TAMs from aggressive tumors with M2-like polarization are capable of orchestrating all

five of the metastasis sequence through production of the needed growth factors, proteolytic enzymes, and various inhibitory immune checkpoint proteins against T cells, making the TAMs prominent metastasis promotors. While more studies will be needed in validating the functional equivalence between the M2-like TAMs and the M2-like macrophages from COVID19 reprogramming in cancer metastasis promotion, the observed capacity by the COVID19-reprogrammed macrophages toward efficient production of metastasis drivers such as IL-6 [11,16], SPP1 [15,20] and NLRP3 inflammasomes [4,21,22] adds plausibility to the danger.

### Increased risk of treatment resistance development in the COVID19-recovered cancer patients

Another important risk to cancer patients post-COVID19 may be the development of cancer treatment resistance, aided by the COVID19-reprogrammed macrophages. It has been long known that M2-like TAMs generally accumulate in tumors after chemotherapy and contribute to tumor recurrence by initiating wound healing programs involving macrophage-induced recruitment of natural regulatory T cells (nTreg) that suppress T cell effector functions and activation of tumor revascularization (a detailed review available [28]). More specifically, nTreg recruitment by TAMs is mediated through its secretion cytokines/chemokines, namely TGFβ and IL-10. Tumor revascularization promotion by macrophage is mediated through its secretion of VEGF-A and MMP9. Given the global similarity between the TAMs and COVID19-reprogrammed macrophages, it is of no surprise that post-COVID19 macrophages were shown to produce elevated levels of TGFβ [18], IL-10 [18], MMP9 [29] and VEGF-A [30]. Again, pending real-world confirmatory studies, the close functional resemblance of post-COVID19 macrophages to those of the TAMs that impart cancer treatment resistance development suggest potential risks of reduced treatment response among cancer patients with recent COVID19 history.

## Concluding Remarks

Immune pathology similarities between macrophage-led autoimmune syndromes of COVID19 and macrophage-promoted cancer malignancy led to repurposing of cancer treatment drugs for treating COVID19, to name a few, tocilizumab (IL-6 inhibitor) [31], acalabrutinib (BTK inhibitor) [32] and bevacizumab (VEGF inhibitor) [33] with some clinical success. In view of the strengthening link between the COVID19 and cancer immunology, it is also reasonable to peruse their inverse cases whereby the post-COVID19 macrophages promote cancer progression. With mounting evidence on the long-lived macrophage reprogramming toward TAM-like state that may entail possibilities of increased metastasis risk and/or treatment resistance development risk, relevant experimental studies are urgently needed. If these risks prove to be true, continued global spread of COVID19 and its transition into endemic may require validation studies on routinely utilized standard cancer treatment and follow-up protocols. In the meantime, it would be prudent to closely monitor cancer patients for new distant metastasis, as exemplified in the recent report of increased brain metastasis incidence (39%) among Stage IV NSCLC patients during pandemic period (June 2020 - November 2021) versus the historical rate (25%) [34].

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## Conflicts of Interest

JFC is a director of Xylonix PTE. LTD. JFC owns shares of Moderna Inc. and Xylonix PTE. LTD.

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