Human Cell (2022) 35:1304–1305
https://doi.org/10.1007/s13577-022-00718-0

LETTER TO THE EDITOR

Flt3-ITD mutated acute myeloid leukemia patients and COVID-19: potential roles of autophagy and HIF-1α in leukemia progression and mortality

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Received: 24 March 2022 / Accepted: 8 May 2022 / Published online: 31 May 2022

Dear Editor,

Nowadays, the Coronavirus disease-2019 (COVID-19) pandemic is a serious crisis in the worldwide population specially in patients with primary diseases [1]. It has been suggested that SARS-CoV-2 infection is associated with higher rates of morbidity and mortality in patients with hematological malignancies and other cancers [2, 3]. However, the evidence is sparse for acute myeloid leukemia (AML) [4,].

Recently, Raman et al. have suggested that Flt3 (FMS-like tyrosine kinase-3 receptor) mutations and a lower hematocrit (HCT) index may reflect AML's more symptomatic presentation during the COVID-19 pandemic [5]. In AML patients' genomes, based on cytogenetic data, a variety of genetic mutations and molecular markers have been identified that include Flt3-ITD, Runx1, CEBPA, MLL-PTD, NPM1, and ASXL1 [6]. Mutations in the Flt3 gene have been estimated to be occurred in 25% of AML cases. Patients with Flt3 gene mutations are associated with a poor prognosis. Two important types of Flt3 mutations include (a) internal tandem duplications (ITD) of 3 to over 100 amino acids in the juxta-membrane domain, and (b) point mutations in the tyrosine kinase domain (KD) [6].

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Living in the middle of the pandemic, we faced this question: what will happen to these patients when they are infected by SARS-CoV-2?

A recent study by Palanques-Pastor et al. [4] has characterized COVID-19 in adult patients with AML. They included four more frequent mutations in their study, among them, patients with a positive Flt3-ITD mutation seemed to be more prone to death by COVID-19. It has been suggested that, whereas long-term cytotoxic chemotherapy leads to pancytopenia, treatment of Flt3-mutated AML patients with severe COVID-19 with a kind of Flt3 inhibitor called Gilteritinib could be beneficial. Palanques-Pastor et al. [4] did not provide enough information about the possible impact of Flt3 inhibitors on severity or mortality rate among these patients with COVID-19. There may be some mechanisms downstream of Flt3-ITD that accelerate the severity of COVID-19, i.e., induction of autophagy and Hypoxia-inducible factor-1α (HIF-1α).

There is an evolutionarily conserved process known as autophagy in which intracellular components such as damaged organelles and protein aggregates are encapsulated into an autophagosome, a membrane-bound organelle, fusing with a lysosome to generate an autolysosome for degradation. Several viruses have been reported to hijack the autophagy mechanisms of cells. One of these viruses is SARS-CoV-2, and targeting autophagy during SARS-CoV-2 infection has been suggested as a possible therapeutic approach for COVID-19 patients [7].

Additionally, it has been reported that during COVID-19, SARS-CoV-2 stimulates the HIF-1α, thereby aggravating inflammatory responses and viral infection. Hence, HIF-1α exerts a critical role in enhancing SARS-CoV-2 infection and triggering pro-inflammatory responses to COVID-19 [8].

Meanwhile, autophagy and induction of HIF-1α can also be linked to the Flt3-ITD mutation in AML patients. Flt3-ITD signaling pathway activates phosphatidylinositol

3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway [9]. While mTOR signaling upregulates HIF-1α level [8], the Flt3-ITD mutation can be considered as an upstream pathway in HIF-1α induction in AML patients with this genetic abnormality, as noticed before. Similarly, increased autophagy is reported in AML patients with Flt3-ITD expression [10].

The roles of autophagy in failure of therapeutic response and development of AML with Flt3 mutations have been shown. Flt3-ITD mutations have been shown to promote autophagy in AML cells through ATF4, resulting in enhanced leukemia cell survival and resistance to Flt3 inhibitors. Furthermore, studies have shown that treatment of Flt3-mutated AML with Flt3-inhibiting agents in combination with autophagy inhibitors is more effective [11]. Also, in a study by G. Deeb et al. [12] it was found that in older AML patients with normal karyotypes, upregulated cytoplasmic HIF-1α expression was associated with a poor prognosis following standard chemotherapy. As a consequence, we thought that both autophagy and HIF-1α induced by COVID-19 can be a hallmark for AML patients, especially for patients with Flt3-ITD mutations.

Based on the recent studies, it has been demonstrated that AML patients with Flt3-ITD mutations exhibit a high susceptibility to a severe course of COVID-19. We hypothesized that not only both COVID-19 and Flt3-ITD-dependent autophagy and HIF-1α upregulation could be a reason for susceptibility of these patients to experience severe course of COVID-19 and high rate of mortality, but also can lead to leukemia progression and drug resistance in these patients. In conclusion, we suggest that using Flt3 inhibitors and pharmacological targeting autophagy may be a promising treatment for Flt3-ITD mutated patients with COVID-19 to lower the risk of death and prevent leukemia progression and drug resistance. However, more investigations are required to confirm this claim.

Author contributions HZ: conceived the study and designed the headings. HZ, MR, and SY: wrote the paper. HZ and MGH: edited the final manuscript text. MGH: supervised the study. All authors approved the final manuscript.

Funding There is no funding support for this study.

Declarations

Conflict of interest The authors declare no competing financial interests.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication The content of the manuscript has not been previously published and is not under consideration for publication elsewhere.

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