Different Behavioral Patterns of SARS-COV-2 in Patients with Various Types of Cancers: A Role for Chronic Inflammation Induced by Macrophages

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Abstract

SARS-CoV-2 is a single strand RNA virus that causes ongoing pneumonia-like and severe respiratory disease. This disease is very important in immunosuppressed patients. Since not many studies have been done in people with cancer as high risk group, in this study we examined the different behaviors of this virus in different types of cancer. In this study, patients with a variety of solid and hematologic cancers were screened for SARS-CoV-2. The rates of infection, the rate of mortality, in patients with various cancers, as well as in the families of these patients have been studied. In this study, it was found that the prevalence of SARS-CoV-2 in patients with solid cancers was significantly lower than hematological cancers. Also, the mortality rate in hematological cancers was higher than in solid cancers ($P<0.05$). Assessments the families of these patients, it was found that patients with solid cancers were also less infected than their family members ($P<0.05$). Researchers of this study attributed these results to the chronic inflammation and M1 macrophages in these patients. It is essential that additional studies are conducted, especially in terms of biological function.

Introduction

Coronavirus disease of 2019 (COVID-19) is an infectious disease caused by a member of the coronavirus family (single-strand RNA viruses) named SARS-COV-2 that infects humans. It was reported for the first time in Wuhan, China in December 2019 (Surveillances, 2020; Wang et al., 2020b; Zhou et al., 2020) and is currently spreading over more than 150 countries around the world (Tavakoli et al., 2020; Yousefi et al., 2020). SARS-COV-2 causes a broad spectrum of clinical manifestations and most infected people show mild to moderate respiratory symptoms and recover without any special treatment (Bai et al., 2020; Cascella et al., 2020; Recalcati, 2020; Xu et al., 2020; Zhou et al., 2020). But, in high-risk patients with underlying diseases such as diabetes (Gupta et al., 2020), cardiovascular diseases (Chen et al., 2020; Zheng et al., 2020b), cancer (Tian et al., 2020; Wang and Zhang, 2020; Xia et al., 2020), and chronic respiratory diseases (Halpin et al., 2020; Jordan et al., 2020) serious forms of the disease and even in some cases death are observed. The increased human-to-human transmission rate is the main characteristic of the new coronavirus that consequently led to the pandemic spread of COVID-19 (Bai et al., 2020; Kucharski et al., 2020). Transmission of the disease occurs through infected droplets or discharges generated while speaking, sneezing, or coughing by the infected individuals (Qian et al., 2020). Prevention practice is applicable by washing hands, using an alcohol-based rub regularly and not touching the face (Hellewell et al., 2020; Wang et al., 2020a). Although countless clinical trials are ongoing to evaluate the potential efficacy of different treatments in COIVID-19 cases, there is no specific therapeutics or vaccines available yet (Cascella et al., 2020; Yousefi et al., 2020). The knowledge regarding lymphocyte subsets and the consequence of immune responses in patients with this disease are very limited. Cancer is considered as a very important risk factor for COVID-19 and based on many previous works; the rate of COVID-19 in patients with cancer has been significantly higher than healthy individuals (Burki, 2020; Cortiula et al., 2020; Liang et al., 2020). Also, most studies suggest that patients with cancer are more prone to develop the new coronavirus disease than others (Wang and Zhang, 2020).

However, our information regarding the incidence and severity of COVID-19 disease in various types of cancer is presently very little and more studies are needed to show the relationship between different types of cancer and incidence of COVID-19. Therefore, this study was designed and conducted to evaluate the incidence of COVID-19 in patients with different types of cancer.

Materials And Methods

Sampling and patients

This retrospective study with the approval number of 99-0213a was carried out on patients with cancer who were referred to the different cancer centers in Tehran, Iran, from November 2019 to May 2020. Hospitalized cancer patients were previously diagnosed by laboratory and imaging techniques. COVID-19 was clinically diagnosed at the first step according to the World Health Organization (WHO) protocols with different manifestations including more common symptoms such as dry cough, fever, tiredness; less common symptoms such as sore throat, diarrhea, conjunctivitis, loss of taste or smell, headache, discoloration of fingers, toes, or skin rashes, aches and pains as less common; and serious symptoms such as chest pain or pressure, difficulties in breathing or shortness of breath and loss of speech or movement. Then, patients with symptoms detected through the questionnaire results were checked by lung CT scan and Real-Time PCR tests.

COVID-19 real-time RT-PCR assays

All samples were handled according to laboratory biosafety guidelines of WHO for COVID-19 and RNAs were extracted using a QIAamp viral RNA extraction mini kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. 250 µl of each respiratory tract specimen was used for RNA extraction and the extracted RNAs were kept at -80°C until use.

Reverse-transcriptase real-time PCR (RT-PCR) assays for COVID-19 were performed using QuantiNova Probe RT-PCR kit (Qiagen) and a LightCycler system (Roche, Basel, Switzerland). Each RT-PCR reaction that was prepared contained 5 µl of RNA, 12.5 µl of 2× reaction buffer, 1.6 µl of forward and reverse primers at 10 pM concentration (5'-GTGARATGGTCATGTGTGGCGG-3' (Forward), 5'-CARATGTTAAASACACTATTAGCATA-3' (Reverse)), 0.5 µL of probe (5'-CAGGTGGAACCTCATCAGGAGATGC-3' (Probe in 5-FAM/3'-BHQ format)), 1 µL of 25× enzyme mixture in a final volume of 25 µl. RT-PCR reaction program composed 40 cycles of 10 min at 45°C for reverse transcription, 5 min at 95°C for PCR initial activation, and 45 cycles of 5 s at 95°C and 30 s at 55°C using an ABI 7500 Fast instrument (Thermo Fisher Scientific) (Fang et al., 2020).

Data analysis

The Shapiro-Wilk test was used to assess the normality of the data distribution. All data were analyzed with GraphPad Prism software (GraphPad Software, Inc.) and Fisher's exact test was used to compare the results. *P*-value of < 0.05 was considered statistically significant.

Results

In the current study, 571 cancer patients who have been admitted to three designated cancer research centers in Tehran, Iran, from November 2019 to May 2020 were enrolled.. Out of 571 patients, 362 (63.39%) and 209 (36.60%) had solid and hematologic malignancies, respectively. With regard to sex, 241 (42.20%) patients were male and 330 (57.79%) were female. Age analysis showed that 106 (18.56%), 263 (46.05%) and 202 (35.37%) of patients were 15–35, 35–55, and > 55 years old, respectively. 309 (54.11%) patients were local residents of Tehran and 262 (45.88%) were from other regions Iran.

The Demographic and baseline clinical characteristics of COVID-19 patients in solid cancers are described in Table 1. Among cancer patients, Breast, Gastric, and Lung cancers were the most prevalent forms of cancer ($P < 0.05$). Also, most of the patients were in stage I or II of their disease. Based on clinical manifestations, 86.74% (314/362) of patients with solid tumors showed no clinical signs and only 5 (1.38%) patients indicated severe clinical manifestations of COVID-19 that these differences were statically significant ($P < 0.001$). Results of the confirmatory tests indicated that 9 (2.48%) patients with different types of solid tumors were positive for COVID-19, whereas, 46 (12.70%) patients had close contact with COVID-19 patients in their family and were closely exposed (Fig. 1).

Table 1
Demographic and baseline clinical characteristics of COVID-19 patients in solid tumors

Characteristics		Patients (n = 362)
Tumor diagnosis	Breast Cancer	76 (20.99%)
	Lung Cancer	35 (9.66%)
	Esophageal Cancer	13 (3.59%)
	Head and neck Tumor	29 (8.01%)
	Nasopharyngeal Cancer	12 (3.31%)
	Laryngeal Cancer	11 (3.03%)
	Liver Cancer	25 (6.90%)
	Gastric Cancer	53 (14.64%)
	Prostate Cancer	17 (4.69%)
	Cervical Cancer	18 (4.97%)
	Uterine Tumor	12 (3.31%)
	Ovarian Cancer	12 (3.31%)
	Colon Cancer	38 (10.49%)
	Rectal Cancer	11 (3.03%))
Tumor stage	Stage I	144 (39.77%)
	Stage II	126 (34.80%)
	Stage III	67 (18.50%)
	Stage IV	25 (6.90%)
Symptoms and signs at on admission	No clinical sign	314 (86.74%)
	Mild symptoms	43 (11.87%)
	Severe symptoms	5 (1.38%)
Chemotherapy	Before 1–4 weeks	53 (14.64%)
	Before 1–6 months	142 (39.22%)
	No treatment	167 (46.113%)
Confirmation tests	Serology	23 (6.35%)
	Real time PCR	116 (32.04%)
	chest CT	223 (61.60%)

Characteristics		Patients (n = 362)
COVID-19 result	Positive	9 (2.48%)
	Negative	353 (97.51%)
COVID-19 in patients family	Positive	46 (12.70%)
	Negative	316 (87.29%)

Table 2
Demographic and baseline clinical characteristics of COVID-19 patients in hematologic malignancies

Characteristics		Patients (n = 209)
Tumor diagnosis	DLBL	65 (31.10%)
	AML	53 (25.35%)
	ALL	41 (19.61%)
	CML	8 (3.82%)
	CLL	6 (2.87%)
	Hodgkin Lymphoma	12 (5.74%)
	Granulomatous Lymphoma	8 (3.82%)
	Kaposi Sarcoma	17 (8.13%)
Tumor stage	Stage I	235 (64.91%)
	Stage II	54 (14.91%)
	Stage III	43 (11.87%)
	Stage IV	30 (8.28%)
Symptoms and signs at on admission	No clinical sign/death (Excluded)	113 (54.06%)
	Mild symptoms	55 (26.13%)
	Severe symptoms	41 (19.61%)
Chemotherapy	Before 1–4 weeks	46 (22.00%)
	Before 1–6 months	139 (66.50%)
	No treatment	24 (11.48%)
COVID-19 result	Positive	47 (22.48%)
	Negative	49 (23.44%)
COVID-19 in patients family	Positive	16 (7.65%)
	Negative	80 (38.27)

Among different types of malignancies, DLBL (Diffuse large B-cell lymphoma) was the most frequent type (31.10%), followed by AML (25.35%) and ALL cancers (19.61%). The morbidity rate of COVID-19 in hematologic malignancies (54.96%) was significantly higher than the solid tumors (P = 0.004). Also, in patients with hematologic malignancies, the rates of clinical manifestations (mild (26.13%) and severe (19.61%)) were higher in comparison to the solid type.

Most of the patients in both groups of malignancies (hematologic and solid) had a history of antitumor chemotherapy and were divided into two main clusters according to the received treatments: 1) patients with chemotherapy during the last 1–4 weeks, 2) patients with chemotherapy during 1–6 months. Clinical manifestations of these two clusters are shown in Table 3.

Table 3
The clinical manifestations of patients with solid and hematologic malignancies and different regimes of chemotherapy.

Chemotherapy	Solid Cancer		Malignancies		P-value
	Mild signs	Severe signs	Mild signs	Severe signs	
Last 1–4 weeks	13 (3.59%)	2 (0.55%)	21 (10.04)	24 (11.48%)	0.001
Last 1–6 months	19 (5.24%)	2 (0.55%)	25 (11.96%)	36 (17.22)	0.001
P-value	0.001				

Patients with clinical manifestations of COVID-19 who had received chemotherapy during the last 4 weeks were examined using CT-scan and Real-Time PCR tests and our results showed that the sensitivity of the real-time PCR test was significantly higher than the CT-scan.

Discussion

In the current study, the clinical characteristics of 571 cancer patients (with solid or hematologic cancer) were described. Cancer patients who were referred to the cancer research centers during the past 8 months were primarily examined using a questionnaire. Patients were divided into different clinical categories based on the clinical signs (mild and severe) recorded in the Iranian Coronavirus Control Organization. Patients with clinical symptoms of the new coronavirus disease and chemotherapy in the last 4 weeks were re-examined using confirmatory tests for COVID-19 (CT-scan and Real-Time PCR). Also, all family members of patients with cancer were examined for COVID-19 to determine if the patients were at risk for the disease. The results of our study revealed that the rates of mortality, manifestations, and especially severe manifestations of COVID-19 in hematological malignancies were significantly higher than solid cancers and patients with solid cancers showed more resistance to the disease. Interestingly, patients with solid tumors who had close contact with SARS-COV-2 infected individuals in their families were resistant and not infected. This resistance existed even after chemotherapy. Patients with different types of hematological malignancies showed severe symptoms of the new coronavirus disease after chemotherapy, and some even died. The mortality rate of COVID-19 in the group of solid cancers was much lower and no death was reported. Different behavioral patterns observed in patients with various types of cancers in the face of COVID-19 disease are very important and the researchers of the current study noticed this difference during the last 3 months.

Inflammatory cells play important roles in cancer (Fulop et al., 2020; Grizzi et al., 2020; Tseng et al., 2020). Cancer expansion and development are multifaceted processes that are also regulated by the

surrounding microenvironment generated by the innate and adaptive immune cells such as dendritic cells, T cells, and macrophages (Katz and Rabinovich, 2020; Rezaei et al., 2020). Macrophages are present in all tissues and play imperative roles in the preservation of homeostasis in tissues (Nouwen and Everts, 2020; Wu and Lu, 2020). Macrophages are regularly differentiated from peripheral blood monocytes and categorized into three types, namely, tissue-resident macrophages (TRM), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAMs) (Beatson et al., 2020; Etzerodt et al., 2020; Gross-Vered et al., 2020; Heideveld et al., 2020; Liu et al., 2020b).

In terms of their function Macrophages are divided into two types; classically activated M1 or good macrophages and alternatively activated M2 subtypes or bad macrophages (Klichinsky et al., 2020). M1 macrophages are presented in T-helper type 1 (Th1) responses that are promoted by Th1 cytokines such as interleukin-12 (IL-12) and IL-18. This type of macrophages generate reactive oxygen/nitrogen species and pro-inflammatory cytokines such as IL-1β, IL-6, tumor necrosis factor α (TNF-α), and are important in innate host defense and killing tumor cells (Zhang et al., 2014; Genin et al., 2015; Chunying Xie, 2020). M2 is another type of macrophages that produces IL-4, IL-10, IL-13, and TGF-β as Th2 cytokines to promote tumor development (Sica et al., 2006; Na et al., 2013; Comito et al., 2014) (Fig. 2).

Cytokine release syndrome (CRS) is a complete response to the inflammation caused by usual infections. Many drugs and other factors have been designed to induce the production of a large amount of pro-inflammatory cytokines and increase the strength of the immune system (Hirano and Murakami, 2020). CRS is commonly happening during immune system-related diseases or immune-related therapies and also in infectious diseases such as viral infections (Hirano and Murakami, 2020; Liu et al., 2020a). IFN-γ is one of the most important functional cytokines which plays an important role in defense against intracellular pathogens and also cancers (Liu et al., 2020a; Mehta et al., 2020; Zheng et al., 2020a). The results of various studies have shown that the levels of pre-inflammatory cytokines and IFN-γ in patients with solid cancers are naturally elevated (Gaire et al., 2020; Zhang et al., 2020). The study conducted by Qing et al (2020) reported that the levels of IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 (MCP-1) in patients with COVID-19 was significantly high. These cytokines are Th1 activators and are key factors for the activation of specific immunity and unfortunately are positively correlated with the severity of COVID-19 (Ye et al., 2020).

CRS and cytokine storms have shown a direct association with COVID-19 in acute inflammations, but the behavior of the disease in chronic inflammations is completely different. In chronic inflammations, the interaction between macrophages and solid tumors leads to the production of IFN-γ by M1 TAMs. The high levels of IFN-γ in chronic inflammations result in the resistance of the patients with solid tumors to COVID-19 in comparison to the patients with hematologic malignancies. In a comparable study, many studies revealed that vaccinations with BCG vaccine cause chronic and non-specific immunity that surprisingly decreases the incidence and mortality of COVID-19 (Bodova et al., 2020; O'Neill and Netea, 2020).

One of the important aspects of this study, which is different from other investigations, is the survey of family and people who are in contact with the patient. Our study and other similar studies have shown that many people with no clinical symptoms were molecularly positive. These people are carriers and can transmit the disease.

The importance of this group (asymptomatic carriers) will be much greater if they are in contact with cancer patients. Chemotherapy weakens the immune system and increases the risk of developing the disease. Researchers are concerned about the presence of asymptomatic carriers in contact with candidates for chemotherapy. Therefore, it is recommended that either all patients await chemotherapy and families and individuals in contact with them undergo a molecular analysis prior to chemotherapy, or chemotherapy is performed under hygienic and supervised measures.

In this study, the incidence rate of COVID-19 in patients with cancer was investigated. Two groups of patients were studied, including patients with solid cancer and patients with hematological malignancies. The results showed that COVID-19 was much less common in patients with solid cancers in comparison to patients with hematological malignancies. Even in cases that family members of patients were infected with COVID-19, patients with solid tumors were not infected. Researchers of this study attributed these results to the chronic inflammation and M1 macrophages in these patients. Due to the importance of COVID-19 and cancer in the world and based on the results of this study, it is essential that additional studies are conducted, especially in terms of biological function. Finally, researchers of this study invite other researchers from all research centers around the world to cooperate and participate in further supplementary studies.

Declarations

Ethics approval and consent to participate

This study is ethically approved by Ethics committee of Tehran University of Medical Sciences with the code of: IR.TUMS.VCR.REC.1397.866 and Required coordination with Hospital Cancer clinics was made to provide the patients with the questionnaires.

Consent for publication

All of our co-authors are agreement for publication.

Data availability

The data is held by the Imam Khomeini hospital, and access to the data can be requested and authorized by the Cancer research center group. Which, at the time of the high prevalence of Covid-19, it was the first diagnostic and treatment center and is still the reference center in Iran.

Availability of data and material

All data of the patients unless name and other private information are sent to journal as supplementary files.

Competing interests

There are not any conflicts of interest.

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Author contributions

EM. Hypotheses, E.M., B.R.E. and H.M. designed and do most of the experiments, B.R.E., F.H and B.A contributed to sample selection, E.M., B.R.E and S.H. performed the analysis of data, B.R.E. and E.M write the draft and the draft is reviewed by K.W. and H.M.

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Figures

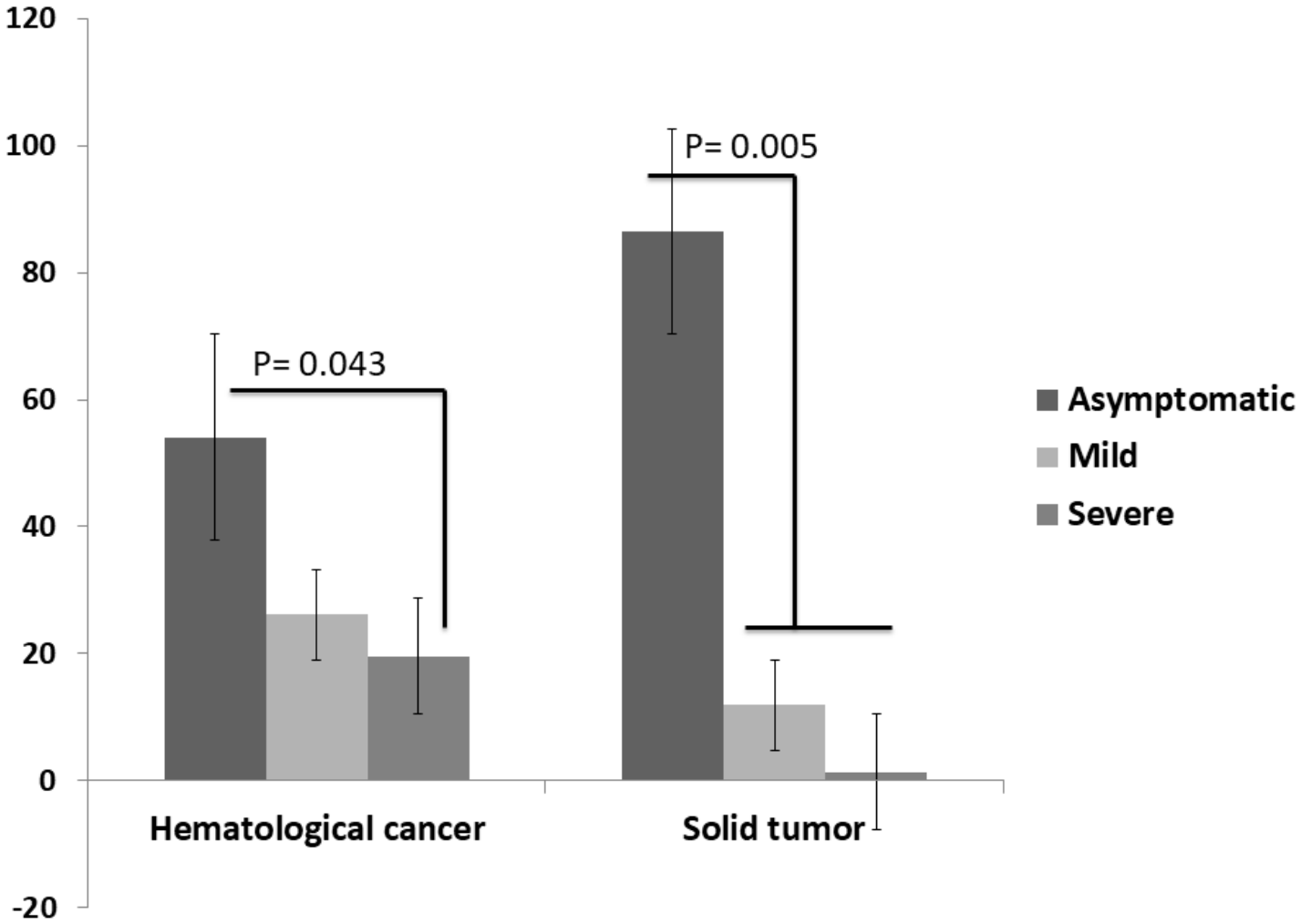

Figure 1

Results of the confirmatory tests indicated that 9 (2.48%) patients with different types of solid tumors were positive for COVID-19, whereas, 46 (12.70%) patients had close contact with COVID-19 patients in their family and were closely exposed

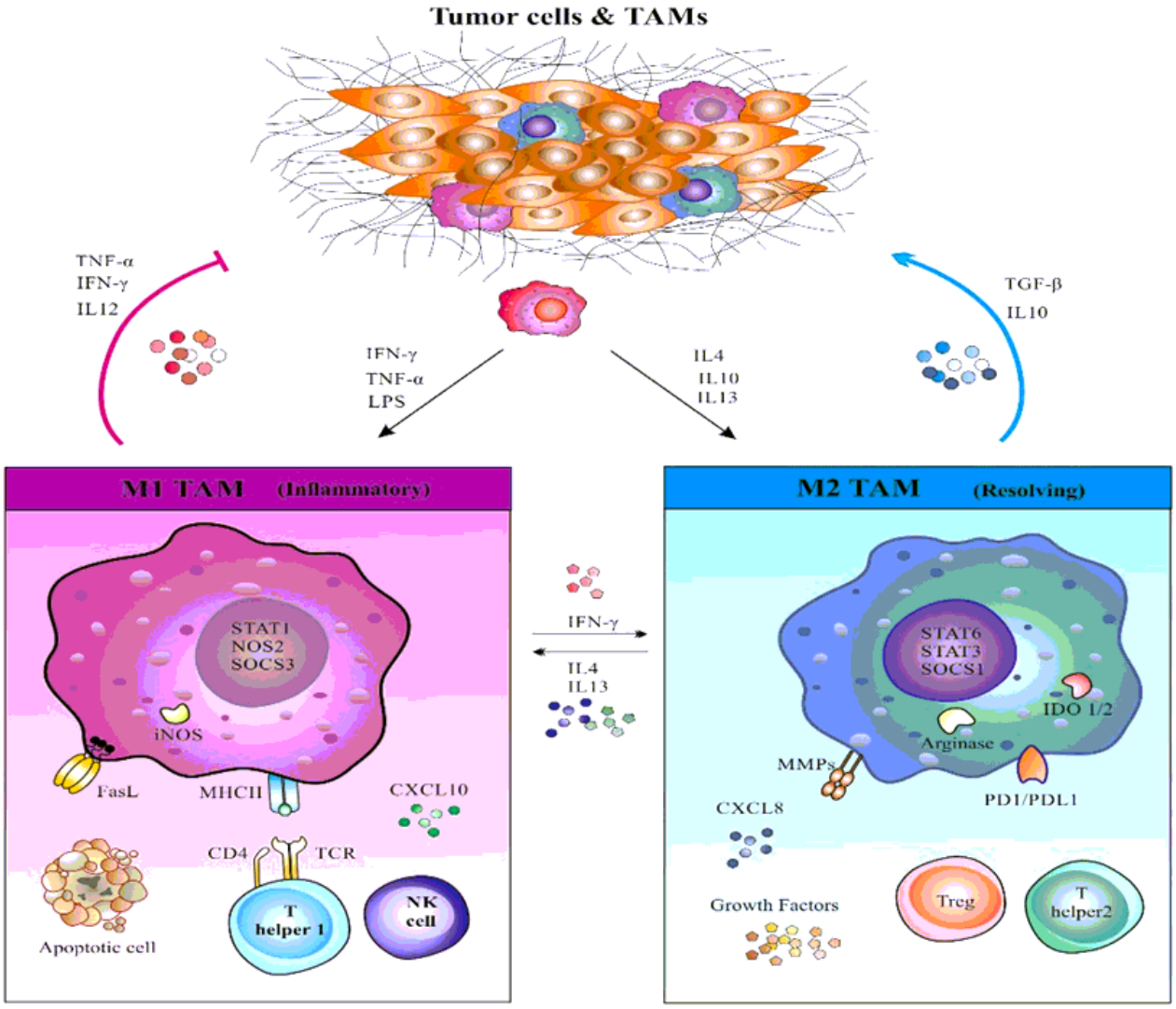

Figure 2

M2 is another type of macrophages that produces IL-4, IL-10, IL-13, and TGF-β as Th2 cytokines to promote tumor development (Sica et al., 2006; Na et al., 2013; Comito et al., 2014)

Supplementary Files

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