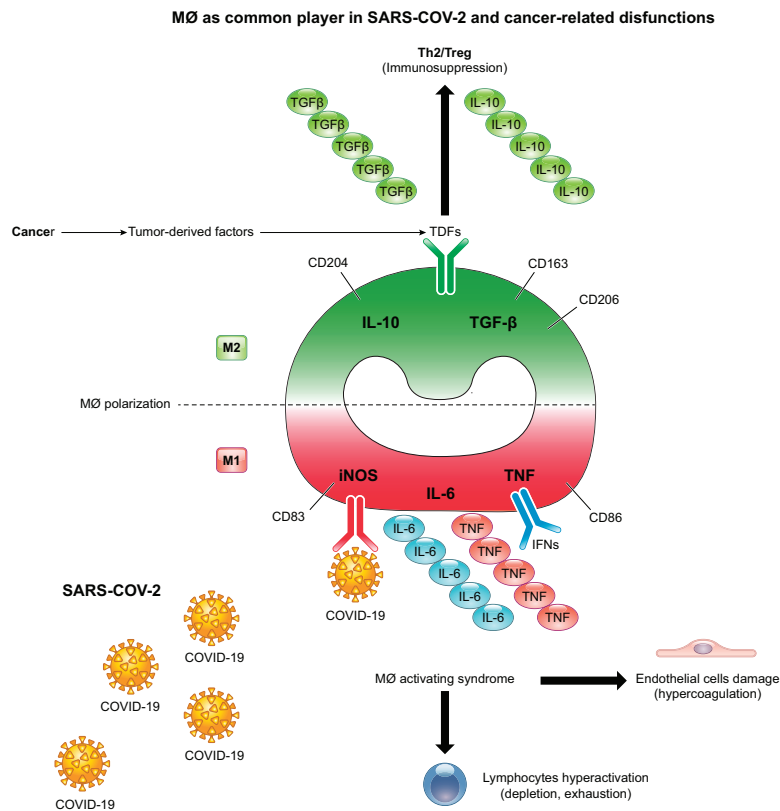


IMMUNOMETABOLIC STATUS OF COVID-19 CANCER PATIENTS

GRAPHICAL ABSTRACT



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KEYWORDS

cancer; comorbidity; COVID-19; SARS-CoV-2

CLINICAL HIGHLIGHTS

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in coronavirus disease 2019 (COVID-19), can lead to acute respiratory distress syndrome, requiring hospitalization and sometimes death in a subset of patients. The elderly and immunosuppressed subjects are particularly vulnerable to COVID-19, and these characteristics are often present in cancer patients. It is therefore conceivable that patients with cancer are at a greater risk of infection and may present a more serious form of COVID-19 disease. The epidemiological data, derived by case series and retrospective studies, do not offer a coherent interpretation regarding the increased propensity of cancer patients to be diagnosed with COVID-19, but suggest that these patients may have more severe COVID-19 symptoms compared with the general population. The data can be explained by the understanding of immunometabolic pathways that intersect patients with infection and cancer. In particular, macrophages play a central role in dysfunctions associated with cancer and COVID-19 infection. Tumors induce an alternative macrophage activation state (M2) that promotes immunosuppression and tumor progression. This situation coincides with decreased antiviral activity, exposing it to an increased susceptibility to infections. Viral

infections (e.g., COVID-19) directly or indirectly promote classical M1 type inflammatory activation, associated with macrophage-activating syndrome, lymphopenia, endothelial damage, and hypercoagulation. Although macrophages develop opposite functional programs in the two pathologies, in both cases they appear as the coordinators of pathological changes, representing common therapeutic targets.

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Sica A, Colombo MP, Trama A, Horn L, Garassino MC, Torri V. Immunometabolic Status of COVID-19 Cancer Patients. *Physiol Rev* 100: 1839–1850, 2020. First published July 28, 2020; doi:10.1152/physrev.00018.2020.—Cancer patients appear to be more likely to be diagnosed with coronavirus disease 2019 (COVID-19). This is supported by the understanding of immunometabolic pathways that intersect patients with infection and cancer. However, data derived by case series and retrospective studies do not offer a coherent interpretation, since data from China suggest an increased risk of COVID-19, while data from the United States and Italy show a prevalence of COVID-19 in cancer patients comparable with the general population. Noteworthy, cancer and COVID-19 exploit distinct patterns of macrophage activation that promote disease progression in the most severe forms. In particular, the alternative activation of M2-polarized macrophages plays a crucial role in cancer progression. In contrast, the macrophage-activation syndrome appears as the source of M1-related cytokine storm in severe COVID-19 disease, thus indicating macrophages as a source of distinct inflammatory states in the two diseases, nonetheless as a common therapeutic target. New evidence indicates that NAMPT/NAD metabolism can direct both innate immune cell effector functions and the homeostatic robustness, in both cancer and infection. Moreover, a bidirectional relationship exists between the metabolism of NAD and the protective role that angiotensin converting enzyme 2, the COVID-19 receptor, can play against hyperinflammation. Within this immunometabolic framework, the review considers possible interference mechanisms that viral infections and tumors elicit on therapies and provides an overview for the management of patients with cancer affected by COVID-19, particularly for the balance of risk and benefit when planning normally routine cancer treatments and follow-up appointments.

cancer; comorbidity; COVID-19; SARS-CoV-2

I.	INTRODUCTION	1839
II.	AGING, HOMEOSTATIC FRAGILITY,...	1843
III.	GENDER AND VIRAL INFECTION	1843
IV.	MECHANISMS OF VIRUS-INDUCED...	1843
V.	ACE2 AND INFLAMMATION	1845
VI.	MUTUAL INTERFERENCE OF...	1845
VII.	CONCLUSION	1847

speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).

Initial reports suggested that patients with comorbidities had a higher risk of mortality or developing more severe forms of COVID-19. In particular, patients with cardiovascular diseases, hypertension, cancer, and diabetes were thought to be particularly at risk (5, 6). Patients with cancer are generally more susceptible to infection and therefore to SARS-CoV-2 as well. A report of 1,524 cancer patients who were screened at Zhongnan Hospital of Wuhan University identified COVID-19 in 12 (0.79%) patients, 7 of whom had non-small-cell lung cancer (NSCLC), leading the authors to conclude that patients with cancer had a higher risk of infection with SARS-CoV-2 compared with the community (12). Other data reported the prevalence of cancer among COVID-19 patients with a range varying from 1 to

I. INTRODUCTION

In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of coronavirus disease 2019 (COVID-19) (10). The rapid global spread led the World Health Organization (WHO) to declare a pandemic in early March 2020 (WHO Director-General’s opening remarks at the media briefing on COVID-19, March 11, 2020: <https://www.who.int/dg/>

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in coronavirus disease 2019 (COVID-19), can lead to acute respiratory distress syndrome, requiring hospitalization and sometimes death in a subset of patients. The elderly and immunosuppressed subjects are particularly vulnerable to COVID-19, and these characteristics are often present in cancer patients. It is therefore conceivable that patients with cancer are at a greater risk of infection and may present a more serious form of COVID-19 disease. The epidemiological data, derived by case series and retrospective studies, do not offer a coherent interpretation regarding the increased propensity of cancer patients to be diagnosed with COVID-19, but suggest that these patients may have more severe COVID-19 symptoms compared with the general population. The data can be explained by the understanding of immunometabolic pathways that intersect patients with infection and cancer. In particular, macrophages play a central role in dysfunctions associated with cancer and COVID-19 infection. Tumors induce an alternative macrophage activation state (M2) that promotes immunosuppression and tumor progression. This situation coincides with decreased antiviral activity, exposing it to an increased susceptibility to infections. Viral infections (e.g., COVID-19) directly or indirectly promote classical M1 type inflammatory activation, associated with macrophage-activating syndrome, lymphopenia, endothelial damage, and hypercoagulation. Although macrophages develop opposite functional programs in the two pathologies, in both cases they appear as the coordinators of pathological changes, representing common therapeutic targets.

6% in Asian populations (20a) and as high as 18% in western countries (5a, 31, 68). In all these studies, hypertension, diabetes, and cardiovascular and chronic obstructive pulmonary diseases were much more common than cancer. However, these analyses were limited by the sample size and inherent bias in symptomatic patients being screened (32) (TABLE 1).

Results from China, although limited in sample size, showed that patients with cancer deteriorated more rapidly than those without cancer and were at higher risk of severe complications from COVID-19 including death (17). Recent data from the English collaboration OPENSafely (~6,000 deaths from COVID-19; Ref. 78a) support previous evidence showing a three times higher risk of death in patients diagnosed with a hematological malignancy up to 5 yr before SARS-CoV-2 infection. The excess risk of death seemed to be lower for other cancer types than that of hematological tumors but was also significant (hazard ratio 1.56), especially for subjects diagnosed with cancer within 1 yr of SARS-CoV-2 infection (78a). These results were confirmed by other multicenter and single center studies (17, 36).

However, these publications are limited as the majority described hospitalized patients and the inherent bias that cancer patients could more likely be tested for SARS-CoV-2 because of their symptoms and of the frequent access to the health care facilities (14, 15). Data from outpatients with

mild symptoms or from suspected patients under home observation and awaiting a diagnosis are currently lacking. Thus to what extent cancer patients are vulnerable to COVID-19 and whether frailty may be driven by age, gender, and other comorbidities often present in cancer patients are still a matter of debate. A further question arises on variability of prognosis of COVID-19 cancer patients across cancer types. Cancer-specific data coming from cancer patient registries established recently (TERAVOLT; Ref. 86), a global consortium specifically created to address the impact of COVID-19 in patients with thoracic malignancies (NSCLC, small cell lung cancer, malignant pleural mesothelioma, thymic malignancies, and neuroendocrine tumors), provide some preliminary indication. TERAVOLT results from 200 patients showed that ~33% patients died. Importantly, 74% of these patients were on active treatment, and 54% of them were on a first line (38a, 86). In addition, TERAVOLT results suggested an increased risk of death in patients treated with steroids or anticoagulation before diagnosis and showed that chemotherapy, alone or in combination with immunotherapy, was associated with increased risk of death, while immunotherapy and tyrosine kinase inhibitors were not. The high COVID-19-related mortality in thoracic cancer patients is indirectly confirmed by further data; in ASCO 2020, results from CCCN-19 were also presented on 926 cancer patients (45). Mortality in this pan-cancer population was 13%, with ECOG-PS at diagnosis, sex, older age, and smoking associated with the increased risk of death.

Another observational registry enrolled 800 patients with active cancer into the United Kingdom Coronavirus Cancer Monitoring Project (UKCCMP): 412 (52%) patients had a mild COVID-19 disease course, 226 (28%) patients died, and risk of death was significantly associated with advancing patient age [odds ratio 9.42; 95% confidence interval (CI) 6.56–10.02; $P < 0.0001$], being male (odds ratio 1.67; 95% CI 1.19–2.34; $P = 0.003$), and the presence of other comorbidities such as hypertension (odds ratio 1.95; 95% CI 1.36–2.80; $P < 0.001$) and cardiovascular disease (odds ratio 2.32; 95% CI 1.47–3.64).

The authors found no significant effect on mortality for patients with chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or radiotherapy use within 4 wk.

Data from 205 patients from 9 hospitals in Hubei, China, were enrolled in a retrospective study (88); 183 (89%) had solid tumors, and 22 (11%) had hematological malignancies. Clinical characteristics, laboratory data, and cancer histories were compared between survivors and non-survivors. Results showed that patients with cancer and COVID-19 who were admitted to the hospital had a high case-fatality rate, and chemotherapy within 4 wk before symptom onset and male sex were associated with high risk of fatal outcomes (47).

Table 1. COVID-19 patient data

Reference	Number	Age	Sex	Comorbidities	COVID-19 Symptoms	COVID-19 Pulmonary Signs	COVID-19 Outcomes
CDC China	72,314	No. with data 44,672; <49 yr, 46%; 50-69 yr, 42%; >70 yr, 2%	F 49%; M 51%	No. with data 20,812; missing 53%; hypertension 13%; diabetes 5%; cardiovascular disease 4%; chronic respiratory disease 2%; cancer 0.5% ; none 74%	NA	NA	Case fatality rate by comorbidity: no. of deaths 504; cardiovascular disease 11%; hypertension 6%; diabetes 7%; chronic respiratory disease 6%; cancer 6% ; none 1%; missing 3%
Wang D	138	Age in yr., median (IQR): 56, (42-68)	F 46%; M 54%	Hypertension 31%; cardiovascular disease 15%; diabetes 10%; cancer 7% ; cerebrovascular disease 5%; COPD 3%; chronic kidney disease 3%; chronic liver disease 3%; HIV infection 1%	Fever 99%; fatigue 70%; dry cough 59%; anorexia 40%; myalgia 35%; dyspnea 31%; expectoration 27%; pharyngalgia 17%; diarrhea or nausea 10%; dizziness 9%; headache 7%; vomiting 4%	All patients: bilateral involvement of chest CT scan (patchy shadows and ground glass opacity)	Admitted to ICU by comorbidities: no. with data 38; hypertension 58%; cardiovascular disease 25%; diabetes 22%; cancer 11%; cerebrovascular disease 17%; COPD 8%; chronic kidney disease 6%; still in hospital 62%
Shi H	81	Age in yr., no. (%): >50, 49%; ≤50, 51%	F 48%; M 52%	Hypertension 15%; diabetes 12%; chronic pulmonary disease 11%; cardiovascular disease 10%; hepatitis or liver cirrhosis 9%; cerebrovascular disease 7%; cancer 5% ; chronic renal failure 4%; any 26%	Fever 73%; cough 59%; dyspnea 42%; rhinorrhea 26%; chest tightness 22%; sputum 19%; weakness 9%; headache 6%; vomiting 5%; diarrhea 4%; dizziness 2%; anorexia 1%	Bilateral lung involvement 79%; peripheral distribution 54%; diffuse distribution of CT abnormalities 44%	Discharged 77%; still in hospital 20%; died 4% (one 60 yr-old with COPD; another 73 yr old with type 2 diabetes; the third was 77-yr-old man with hypertension, cardiovascular disease, and cerebrovascular disease)
Wu C	201	Age in yr., median (IQR): 51, (43-60); age in yr., %: ≥65, 20%; <65, 80%	F 36%; M 64%	Hypertension 19%; diabetes 11%; cardiovascular disease 4%; liver disease 4%; chronic lung disease 3%; cancer 0.5%	Fever 94%; cough 81%; productive cough 41%; dyspnea 40%; fatigue 32%	Chest infiltrate unilateral 5%; bilateral 95%	As of February 13, 2020: discharged 72%; still in hospital 6%; died 22%
Yang X	52	Age in yr., mean (SD): 59.7 (13.3)	F 33%; M 67%	Diabetes 17%; cerebrovascular disease 14%; chronic cardiac disease 10%; COPD 8%; cancer 4% ; dementia 2%; malnutrition 2%; chronic medical illness 40%	Fever 98%; cough 77%; dyspnea 64%; malaise 35%; myalgia 12%; rhinorrhea 6%; headache 6%; vomiting 4%; arthralgia 2%; chest pain 2%	NA	As of February 9, 2020: died 62%; survived 38%
Zhou F	191	Age in yr., median (IQR): 56, (18-87)	F 38%; M 62%	Hypertension 30%; diabetes 19%; coronary heart disease 8%; COPD 3%; cancer 1% ; chronic kidney disease 1%; other 12%	Fever 94%; cough 79%; sputum 23%; fatigue 23%; myalgia 15%; diarrhea 5%; nausea, vomiting 4%	Consolidation 59%; ground-glass opacity 71%; bilateral pulmonary infiltration 75%	Discharged 72%; died during hospitalization 28%
Zhu W	32	Age in yr., median (IQR): 46, (35-52)	F 53%; M 47%	Hypertension 22%; diabetes 13%; cancer 6% ; liver disease 6%; coronary heart disease 6%; cerebrovascular disease 3%; mental disorder 3%; renal diseases 3%	Fever 84%; cough 66%; myalgia or fatigue 16%; expectoration 16%; chest stiffness 9%; headache 3%; diarrhea 3%	Bilateral involvement 91%; ground glass opacity 47%; consolidation 13%; spider web sign 13%	Outcomes assessment is out of the scope
Chen N	99	Age in yr., mean (SD): 55.5, (13.1)	F 32%; M 68%	Cardio and cerebrovascular diseases 40%; digestive system disease 11%; endocrine system disease 13%; cancer 1% ; nervous system disease 1%; respiratory system disease 1%	Fever 83%; cough 82%; shortness of breath 31%; myalgia 11%; headache 8%; sore throat 5%; rhinorrhea 4%; diarrhea 2%	Unilateral pneumonia 25%; bilateral pneumonia 75%; multiple mottling and ground-glass opacity 14%	Discharged 31%; still in hospital 58%; died 11%
Huang C	41	Age in yr., median (IQR): 49, (41.0-58.0)	F 27%; M 73%	Any comorbidities 32%; diabetes 20%; hypertension 15%; cardiovascular disease 15%; COPD 2%; cancer 2% ; chronic liver disease 2%	Fever 98%; cough 76%; myalgia 44%; dyspnea 55%; sputum 28%; headache 8%; diarrhea 3%	Bilateral involvement 98%	As of January 22, 2020: discharged 68%; still in hospital 17%; died 15%

Continued

Table 1.—Continued

Reference	Number	Age	Sex	Comorbidities	COVID-19 Symptoms	COVID-19 Pulmonary Signs	COVID-19 Outcomes
Liu K	137	Age in yr. (range): 57, (20–83)	F 56%; M 44%	Comorbidities 18%; diabetes 10%; hypertension 10%; cardiovascular disease 7%; COPD 2%; cancer 2% ; other chronic diseases 18%	Fever 82%; cough 48%; myalgia 32%; dyspnea 19%; headache 9.5%; diarrhea 8%; heart palpitations 7%; hemoptysis 5%; sputum 4%	Bilateral involvement 85%; early stage (multiple patchlike shadows) 31%; middle stage (bilateral ground- glass opacity) 47%; late stage (consolidation shadow) 22%	Discharged 32%; still in hospital 6%; died 12%
Guan W	1,099	Age in yr., median (IQR): 47.0, (35.0–58.0)	F 42%; M 58%	Hypertension 15%; COPD 11%; diabetes 7%; coronary heart disease 3%; HBV 2%; cancer 1% ; chronic renal disease 1%; cerebrovascular disease 1%; any 24%	Cough 68%; fever 44%; fatigue 38%; sputum 34%; shortness of breath 19%; myalgia 15%; sore throat 14%; headache 14%; chills 12%; nausea 5%; diarrhea 4%	Ground-glass opacity 56%; local patchy shadow 42%; bilateral patchy shadow 52%; interstitial abnormalities 15%	Discharged 5%; still in hospital 94%; died 1%
Grasselli G	1,591	Age in yr., median (IQR): 63, (56–70)	F 18%; M 82%	No. with data 1,043; hypertension 49%; cardiovascular disease 21%; hypercholesterolemia 18%; diabetes 17%; cancer 8% ; COPD 4%; chronic kidney disease 3%; chronic liver disease 3%; none 32%	NA	NA	Outcome, no. with data 1,581: discharged from ICU 16%; still in ICU 58%; died in ICU 26%
Richardson S	5,700	Age in yr., median (IQR): 63, (52–75)	M 60%	Hypertension 57%; obesity 42%; diabetes 34%; coronary artery disease 11%; cancer 6% ; asthma 9%; congestive heart failure 7%; COPD 5%; chronic kidney disease 5%; cirrhosis 0.4%; HBV 0.1%; HCV 0.1%; Charlson comorbidity index score, median (IQR) 4 (2–6)	Temperature >38°C 31%	NA	Discharged 37%; still in hospital 53%; died 553 10%
Myers LC	377	Age in yr., median (IQR): 61.0, (50.0–73.0)	F 44%; M 56%	Hypertension 44%; diabetes 31%; chronic kidney disease 13%; COPD 7%; congestive heart failure 6%; liver cirrhosis 6%; cancer 5%	In emergency department; shortness of breath 49%; fever 34%; cough 32%	None 16%; unilateral 16%; bilateral 64%	Required ICU 30%; of 321 patients with discharge dispositions, 16% died in hospital
Burn E	6,806 (US: 1,634, South Korea: 5,172)	Mainly in their 70s in US; younger patients in Korea	US: M >50%; Korea: F 56%	US: asthma 7–14%; diabetes 20–43%; heart failure 10–22%; cancer 8–18% ; Korea: asthma 14%; diabetes 18%; heart failure 7%; cancer 8%	NA	NA	NA

COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; ICU, intensive care unit; NA, not available; US, United States; yr, years.

All these epidemiological results, although still preliminary, are the starting point to deepen the immune pathogenesis and pathophysiological characteristics of prognostic factors potentially contributing to the vulnerability to SARS-CoV-2 of cancer patients.

II. AGING, HOMEOSTATIC FRAGILITY, AND VIRAL INFECTION

Pathophysiological changes and metabolic complications, which establish a subclinical syndrome of “homeostatic frailty,” are common among the elderly population and are associated with greater susceptibility to infection (75). These changes determine immune-senescence and an imbalance between inflammatory and anti-inflammatory mechanisms (23) [e.g., high levels of inflammatory mediators such as interleukin (IL)-6, tumor necrosis factor- α , and C-reactive protein]. Consistent with these data in elderly subjects, failure to resolve the inflammatory process often occurs, undermining both the metabolic and immune pathways (75).

The system composed by the intracellular adipokine visfatin (iNAMPT) and the NAD-dependent protein deacetylase SIRT1 plays a key role in both maintaining a precise energetic metabolism and enhancing the robustness of physiological processes (13). Noteworthy, prior evidence shows an age-related loss of iNAMPT/NAD⁺/SIRT1 activity, which undermines antioxidant, metabolic, and anti-inflammatory systems (28, 75). Furthermore, iNAMPT guides differentiation of anti-inflammatory myeloid cells under stress conditions (80). Of interest, fluctuation in NAD⁺ bioavailability has been described during host-pathogen interactions, which interfere with pathogen persistence or clearance. Among these, human immunodeficiency virus, hepatitis virus B and C, influenza virus, Kaposi’s sarcoma virus, and herpes virus were found to alter intracellular NAD⁺ levels, either in innate or adaptive immune cells (55).

Overwhelming inflammation, consequent to loss of homeostatic robustness at the onset of COVID-19-induced pneumonia, was observed, and the anti-IL-6 monoclonal antibody tocilizumab has been shown to negate aberrant lung inflammation in some patients (51). Thus the sudden worsening of clinical conditions observed in COVID-19 patients appears in line with a virus-mediated breakout of physiological mechanisms of robustness, which becomes a dramatic event in the elderly with comorbidities including cancer.

III. GENDER AND VIRAL INFECTION

It has been proposed that hypovitaminosis (i.e., vitamin D deficiency) may contribute to viral disease development (78). Interestingly, the robustness of the NAMPT/NAD⁺/

SIRT1 system is controlled by a balanced nutritional supply of tryptophan and vitamin B₃, which provide the primary and the rescue pathways for the synthesis of NAD, respectively (5). Moreover, vitamin D increases NAD concentrations and SIRT1 activity (8). The greater female resilience to infections (42) and their higher risk for autoimmunity appear estrogen-linked (54). In this contest, frequent deficiency of the estrogen-inducible vitamin D receptor was found in COVID-19-positive patients (49). The alleged interplay between estrogen and physiological robustness systems (NAMPT/NAD⁺/SIRT1), together with the localization of the coding gene angiotensin converting enzyme 2 (ACE2) on the X chromosome (X-linked) (93), provides a possible rationale for higher female resilience to COVID-19 infection. On the other hand, males might be more susceptible and prone to poor outcomes in relation to the androgen receptor AR (57, 76). SARS-CoV-2 cell entry through the ACE2 receptor requires the shortage of the virus spike (S) protein by the cellular serine protease TMPRSS2 (38), which is androgen regulated (85). In addition, single nucleotide polymorphism within an androgen-responsive element could impact on TMPRSS2 expression (15), whereas no clear genetic variants in the ACE2 gene have been associated with virus entry to date (7).

IV. MECHANISMS OF VIRUS-INDUCED IMMUNE AND METABOLIC DYSREGULATIONS

In stress/pathological conditions (e.g., infection and cancer), signals derived from the hematopoietic stem cell niche modify the magnitude and composition of hematopoietic output, a feature of immune regulation defined as “emergency” hematopoiesis, to guarantee an adequate supply of both lymphoid and myeloid cells with increased demand (61, 73). These alterations profoundly affect innate and adaptive immune response, as well as disease outcome. Furthermore, microenvironmental signals locally refine the activation state of immune cells, acting through specific receptors and leveraging their functional plasticity (74).

Airway macrophages (AM Φ s) detect airborne pathogens, including viruses, through surface and endosomal pathogen-recognition receptors (PRRs), whose engagement triggers an antiviral interferon (IFN)-mediated response (10). Highly pathogenic human coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were reported to predominantly infect lower airways and cause fatal pneumonia (37, 46). Of relevance, in SARS-CoV infection, CCL2 is a major chemoattractant for pathogenic inflammatory monocytes, which produce monocyte chemokines, hence enhancing disease severity (9). In MERS-CoV patients, the severity of lung lesions has been shown to correlate with extensive infiltration of neutrophils and macrophages within the lungs and in peripheral blood

(60). In support of a central role of NAD⁺ metabolism in myeloid cells, the IFN-induced antiviral cascade operated by macrophages utilizes the metabolic regulators NAMPT and Sirt6 serially (18). In addition, extracellular (e)NAMPT can behave as alarmin or damage-associated molecular pattern (DAMP) and has been found to be elevated in patients with comorbidities including diabetes, obesity, and cancer (3) that worsen patient frailties to SARS-CoV-2, while it marks sepsis and septic shock. Nevertheless, eNAMPT promotes macrophage survival via the IL-6/STAT-3 pathways (48).

In COVID-19 patients, characterization of peripheral lymphocyte subsets showed a decreased frequency of CD4⁺ T cells, CD8⁺ T cells, B cells, and natural killer cells, whereas neutrophil count remains unchanged or elevated. Given the diffuse evidence of vasculitis and coagulopathies, together with recent description of associated antiphospholipid antibodies (92), a role for neutrophils is foreseen. Indeed, sera and plasma of patients with antiphospholipid syndrome have elevated levels of both cell-free DNA and neutrophil extracellular traps (NETs) (87). Of relevance, the NAD⁺/SIRT1 system also guarantees the production of hydrogen sulfide (H₂S), which acts as an endothelial signaling network that ensures vascular wellness (19). According to this scenario, the possible direct viral infection of endothelial cells should be taken into account, since these cells express the COVID-19 receptor ACE2 (22). This hypothesis appears substantiated by the lymphocytic endothelitis developing in the lung, heart, kidney, small intestine, and liver of COVID-19 patients (81). As such, integrity of NAD-dependent system in endothelial cells may be relevant, since its intracellular activity ensures vascular repair after ischemic insults (84). Therefore, the observed antiphospholipid syndrome and endothelial damages that characterize COVID-19 patients would require further study on the involvement of the complement cascade, as a possible driver of COVID-19-associated coagulopathies (11).

Immunohistochemistry of minimal invasive autopsies from coronavirus pneumonia patients displayed massive damage in the alveolar structure, associated with robust infiltration of inflammatory cells, mainly macrophages, monocytes, and neutrophils (89). An extended series of 38 autopsies, performed in the north of Italy, showed the inflammatory infiltrate composed by alveolar macrophages and interstitial lymphocytes, along with capillary congestion, necrosis of pneumocytes, hyaline membrane, interstitial edema, pneumocyte hyperplasia and reactive atypia, and signs of platelet-fibrin thrombi in small arterial vessels (7a).

Transcriptome sequencing of the RNAs isolated from the bronchoalveolar lavage fluid and peripheral blood mononuclear cells specimens of COVID-19 patients revealed distinct host inflammatory cytokine profiles, highlighting the association between COVID-19 pathogenesis and release of inflam-

matory chemokines, such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP-1B. In addition, T cells showed a significant association with the inflammatory status in COVID-19 patients, and CD8⁺ T cells, in particular, tended to be an independent predictor of disease severity and treatment efficacy (83), whereas chronic viral infection can induce expression of negative cosignaling molecule programmed-death 1 (PD-1) and consequent T cell exhaustion (63). Nevertheless, the observed patient's lymphopenia correlated with induced activation of apoptosis and the p53 signaling pathway in lymphocytes (66). Within this scenario, inflammation-driven hyperactivation of CD95-expressing (FasR) T lymphocytes can lead to their depletion through a mutual suicide mechanism and therefore establish immunosuppression (21).

Comorbidities can heavily influence the immunological scenario associated with COVID-19. It is known that cancer-related inflammation alters the myelopoietic output, giving rise to expansion of immature myeloid populations, with anti-inflammatory and immunosuppressive functions (73). Hence, the emerging skewing of monocytes/macrophages towards an anti-inflammatory M2 activation state (74) would potentially counteract the overwhelming classical inflammation imposed by viral infection, slowing down tissue damage. In contrast, viral spreading might increase due to ablation of specific immunity operated by the M2 polarized and immunosuppressive innate immunity (24, 74).

While the net action of innate immune cells in COVID-19 remains to be clarified, a direct role of alveolar macrophages (AMΦs) was demonstrated in influenza virus infection, since their depletion increased susceptibility to virus infection, independent of cytotoxic T cells (69). It appears that selective targeting of innate immune components could disclose therapeutic approaches. In this context, iNAMPT was recently identified as a critical modulator of immunometabolism and mobilization of M2-polarized anti-inflammatory myeloid cells to the periphery in cancer bearers (80). Furthermore, NAMPT metabolism participates in macrophage antiviral activity (18), hence highlighting its potential relevance in the surveillance of homeostatic and immune functions exercised by alveolar and interstitial macrophages. Preexisting antiviral response might suppress anti-bacterial Th17 via IFN-induced IL-23 downregulation (12), an effect that can be surpassed by the indiscriminate lymphopenia occurring along disease progression. Finally, within the search for candidate vaccines against viral replication, the activation state of macrophages should be taken into account, as anti-spike IgG can cause lung injury during the early stages of infection, promoting recruitment and accumulation of proinflammatory monocytes/macrophages, an effect reduced by FcγR blockade (50). According to these premises, new evidence supports a massive metabolic change in the serum of severe patients

COVID-19, including macrophage, lipid, and amino acid metabolism (71).

V. ACE2 AND INFLAMMATION

ACE2, strongly expressed in the heart and lungs, has been identified as a functional SARS-CoV-2 receptor, through binding and priming of the viral spike (S) proteins by the serine protease TMPRSS2 (38). SARS-CoV-2 has also evolved a unique S1/S2 protease cleavage site that is identical to a FURIN cleavable peptide present on human epithelial sodium channel α -subunit (ENaC- α) and coexpressed with ACE2 on the same cells of cardiovascular-renal-pulmonary epithelia (41) and that is controlled by the renin-angiotensin-aldosterone system. The issue of anti-proteases has even broader application by targeting plasmin(ogen), which is elevated in several disease conditions, all known to worsen COVID-19 patients outcome including hypertension, diabetes, as well as cardiovascular and renal disease (41). Importantly, sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry (38), and incoming evidences suggest that greater expression of ACE2 is associated with most serious disease manifestations. Along this line, soluble human ACE2 is an effective decoy receptor engaging and subtracting the virus from the cellular receptor, inhibiting early stages of SARS-CoV-2 infection (56). In spite of its enzymatic nature, the net effect of COVID-19 on ACE2 enzymatic activity is still unknown. This question is of potential relevance considering that ACE2, a key carboxypeptidase of the renin-angiotensin system (RAS), efficiently catalyzes the conversion of the inflammatory angiotensin II into the anti-inflammatory and antagonist peptide angiotensin-(1-7) (4). As a whole, SARS-CoV-2 downregulates ACE2, causing a decrease in the anti-inflammatory component of angiotensin-(1-7), capable of improving oxygenation and reducing lung injury and fibrosis (14). As a consequence, accumulation of the proinflammatory angiotensin II occurs (40).

An emerging link exists between homeostatic pathways (i.e., the NAMPT/NAD⁺/SIRT1) and the RAS, the latter involved in acute lung failure (40), cardiovascular function (16), and SARS infections (44). The robustness of the NAMPT/NAD⁺/SIRT1 system is controlled by a balanced nutritional supply of tryptophan, which together with vitamin B₃ provide the primary and rescue pathways for the synthesis of NAD (5).

This metabolism-linked hypothesis appears to be supported by genetic and pharmacological evidence, showing a protective role of ACE2 in acute lung injury (35, 40, 90), kidney injury, and intestinal inflammation (34). Of relevance, NAD availability depends on the de novo synthesis by the kynurenine pathway from tryptophan, whose circulating levels are strongly reduced during viral infection, resulting in exacerbated inflammation and low CD4⁺ T cell recovery

(20). Furthermore, ACE2 modulates tryptophan levels in peripheral blood and, in a model of malnutrition, supplementation of tryptophan and “nicotinamide/vitamin B₃” restored ACE2 activity and prevented exacerbated inflammation (34).

As suggested by **FIGURE 1**, the hyperinflammatory syndrome associated with COVID-19 therefore requires an in-depth analysis of the interactions between homeostatic systems (i.e., NAMPT/NAD/SIRT1) and the activation states of inflammatory/immune populations. Its relevance emerges clearly in the elderly where chronic inflammation (inflammaging) contributes to NAMPT downregulation in multiple tissues, hence establishing a self-sustaining circuit which favors homeostatic fragility, inflammatory/metabolic complications, and increased susceptibility to infections (23).

VI. MUTUAL INTERFERENCE OF THERAPEUTIC INTERVENTIONS IN COVID-19 AND CANCER

As discussed, NAMPT/NAD metabolism is modulated both in response to viral infections and tumor growth, suggesting that the metabolic rewiring of the tumor may influence the patient’s response to COVID disease. NAMPT inhibitors have entered clinical trials for solid and nonsolid tumors, due to their ability to lower NAD and ATP levels and, in turn, interfere with malignant cell growth (25). Interestingly, peripheral blood mononuclear cells from patients with acute-type adult T cell leukemia (ATL) expressed significantly higher levels of NAMPT protein, as compared with healthy subjects, and a NAMPT inhibitor (FK866) induced apoptosis of both ATL cells *ex vivo* and HTLV-1-infected T cell lines *in vitro*, and markedly decreased the *in vivo* growth of human ATL tumor xenografts (43). Moreover, in a model of GVHD, FK866 inhibited expansion of alloreactive but not memory T cells, while promoting expansion of FoxP3⁺ regulatory T cells and reducing the tumor burden in mouse leukemia and graft-versus-leukemia models (27). This may be particularly relevant since recent reports identified the β 2GPI-reactive T cells as a driver of autoantibody production in anti-phospholipid syndrome (66), providing a possible link with the anti-phospholipid syndrome and endothelial damages that characterize COVID-19 patients (92). Activation of the early growth response-1 (EGR-1), a member of early growth response proteins family, is critical for the growth of cells and the replication of numerous viruses, including coronavirus (6). Of relevance, inhibition of NAD⁺-dependent deacetylase Sirt-1 leads to acetylation and prolonged expression of EGR-1 in hyperglycemic conditions and establishes proinflammatory and prothrombotic responses in diabetic atherosclerosis (82). These observations could underscore the possible association between NAMPT/NAD metabolism, comorbidities, and aggressive disease in COVID-19 patients.

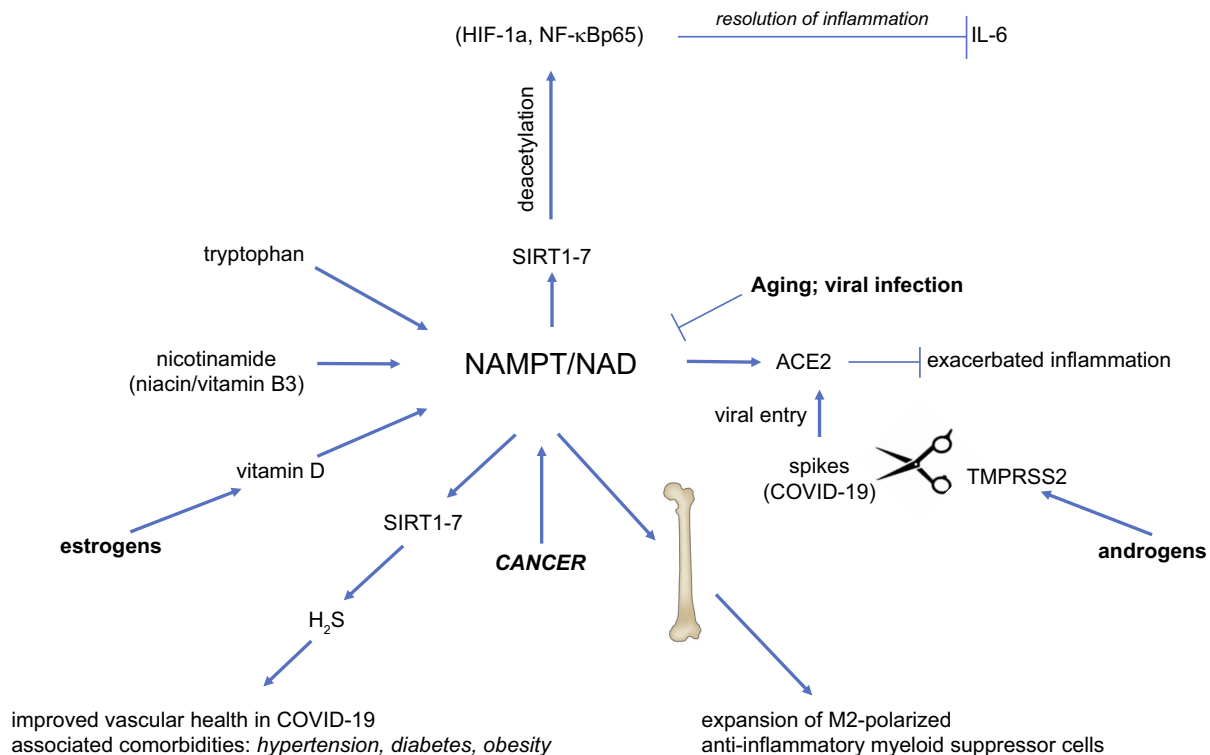


FIGURE 1. NAD metabolism in viral-induced inflammatory and metabolic dysregulation. NAD supply by food sources (tryptophan, niacin, vitamin D) may compensate for COVID-19-induced hypovitaminosis, providing the quantity needed for the deacetylating activity of SIRT1–7 targeting the transcription factors hypoxia inducible factor (HIF)-1 α and nuclear factor (NF)- κ B p65, thus promoting the resolution of inflammation. Estrogen-induced expression of the vitamin D receptor supports consumption of vitamin D, strengthening NAD-dependent events. Furthermore, NAD-mediated SIRT1–7 activity guides the production of the gasotransmitter hydrogen sulfide (H₂S), which favors vascular homeostasis and endothelial cell health. Aging and viral infections weaken the NAMPT/NAD system favoring a state of fragility, typical of the comorbidities associated with COVID-19 infection. The levels of androgens and estrogens act as protective and risk factors, respectively. Cancer enhances NAMPT/NAD metabolism, promoting mobilization and differentiation of anti-inflammatory myeloid-suppressor cells, as well as their alternative M2-polarization, which potentially buffers COVID-19-related inflammation. While it remains to be established whether the anti-inflammatory action of angiotensin converting enzyme 2 (ACE2) is directly promoted by NAMPT/NAD, it is known that ACE2 supports tryptophan levels, which in turn feeds NAMPT/NAD metabolism. IL-6, interleukin-6.

From a therapeutic perspective, the COVID-19-induced increase of PD-1, along with the viral capacity to alter the intracellular NAD levels of immune cells (43), would improve anticancer efficacy of immune checkpoint inhibitors (ICIs). Indeed, the reduced levels of NAD reduce mobilization and differentiation of suppressive myeloid populations in COVID-19 cancer patients, thereby removing an inhibitory brake for immune stimulation through ICIs (58). However, this conclusion remains questionable because of the accentuated lymphopenia observed in COVID-19 patients. Another aspect shared by COVID-19 and ICI-treated cancer patients is the cytokine release syndrome (CRS), which generates immune-related adverse effects (irAEs). Emerging evidence indicates that ICI-induced irAEs arises through a combination of pathways involving autoreactive T cells, autoantibodies, and cytokines (64).

In contrast, the hyperinflammatory response in COVID-19 patients appears to be governed by innate immune responses, specifically the hematophagocytic lymphohistiocytosis (HLH) mediated by macrophage activation syndrome (MAS) (70), which is characterized by CRS, lymphopenia, and multiorgan failure (70). According to this, a high number of activated macrophages are found in the lungs of patients with COVID-19 (79). Importantly, in both types of hyperinflammation (COVID-19 patients vs. cancer patients undergoing ICIs), the elective treatments are steroids and tocilizumab (1). Strategies blunting M1 polarization of macrophages are expected to mitigate hyperinflammation. Hydroxychloroquine, which is being now considered in COVID-19 therapy, acts as both an oral hypoglycemic agent (67) and an anti-inflammatory agent, by promoting an M1 to M2 switch of macrophage polarization (72), which eventually would support tumor progression (74).

The definition of myeloid cell plasticity in pathology has been recently reformulated by the concept of innate immune memory, comprising a set of epigenetic and metabolic events promoting the functional reprogramming of the myeloid cells and myeloid progenitors, in response to second-

ary stimulation with pathogens, Toll-like receptor agonists, and cytokines (59). *Bacillus Calmette-Guérin* (BCG) is a live attenuated vaccine originally developed against tuberculosis (52) and is now used as the gold-standard treatment for non-muscle-invasive bladder cancer at high risk of recurrence or progression (62). Noteworthy, recent studies have suggested that countries and regions that mandate BCG vaccination for the population have a lower number of infections and a reduced mortality from COVID-19 (33). This response appears to be associated with epigenetic changes in monocytes (i.e., innate immune immunity) (58) that correlate with improved antiviral responses (2).

The prominent role of macrophages in tumor progression and COVID-19 hyperinflammation suggests the possible usefulness of macrophage-depleting drugs, such as clodronate and zoledronic acid (74). The macrophage colony stimulating factor (M-CSF) promotes differentiation of tissue macrophages involved in tissue homeostasis (39) and tumor progression (65). CSF-1 receptor (CSF-1R) inhibitor promotes macrophage depletion and has been administered orally, and also induced clinical regression in patients with tenosynovial giant-cell tumors (77). Of relevance, a number of chemotherapeutics display immunostimulatory properties and strongly influence myelopoiesis, revealing new mechanisms with implications for immunotherapy (73). As an example, trabectedin displays antitumor and macrophage-depleting properties (26).

VII. CONCLUSION

Patients with cancer seem to be particularly vulnerable to COVID-19 because cancer, as a COVID-19 comorbidity, can heavily influence the immunological scenario associated with viral infection. In fact, cancer-induced myelopoietic alterations, accompanied by expansion of immunosuppressive immature myeloid populations, can limit antiviral immunity (24, 29, 74). These alterations impact on the virus-mediated breakout of physiological mechanisms of robustness making it a dramatic event especially in elderly male patients (20, 30, 42, 55, 91).

Both cancer and COVID-19 exploit distinct inflammatory patterns expressed by macrophages, which promote disease progression in their most severe forms. Converging evidence indicates the primary involvement of macrophages in inflammatory states associated with COVID-19 and cancer. Of relevance, macrophages can express different functional proteins in response to microenvironmental signals, a property defined as functional plasticity. The extremes of their functional flexibility are generally defined as classical M1- and alternative M2-activation, which respectively identify a cytotoxic inflammatory as opposed to an anti-inflammatory, immunosuppressive activation state (74). The shift between these antithetical activation states plays a distinct role in infection and cancer (74), and new evidence also

supports its key role in hyperinflammation associated with COVID-19 (53). Current literature data support a key role for anti-inflammatory M2-polarized macrophage in cancer-related inflammation and tumor progression. In contrast, accumulating evidence indicates the MAS as the source of M1-related cytokine storm, associated with severe COVID-19 disease. These data suggest that distinct macrophage activation states distinguish the two diseases, while offering a common cellular target. In addition, NAMPT/NAD metabolism is modulated both in response to viral infections and tumor growth, suggesting that the metabolic rewiring of the tumor may influence the patient's response to COVID-19 disease. Overall, understanding the immunometabolic settings in tumors and viral infections becomes a crucial new challenge to define pathogenetic mechanisms in COVID-19 cancer patients.

To conclude, this review should be considered in a new framework of cancer-specific data coming from cancer patient registries recently established. These longitudinal studies, together with the better understanding of the molecular mechanisms of COVID-19 and cancer, support the increased vulnerability of cancer patients, leaving the question of whether the risk of death from COVID-19 changes across different cancer types open. Additional data coming from pan cancer registries and population-based cancer registries could address this question hopefully in the coming months.

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