



# Learning from cancer to address COVID-19

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## Abstract

Patients with cancer have been disproportionately affected by the novel coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Knowledge collected during the last three decades of cancer research has helped the medical research community worldwide to respond to many of the challenges raised by COVID-19, during the pandemic. The review, briefly summarizes the underlying biology and risk factors of COVID-19 and cancer, and aims to present recent evidence on cellular and molecular relationship between the two diseases, with a focus on those that are related to the hallmarks of cancer and uncovered in the first less than three years of the pandemic (2020–2022). This may not only help answer the question “Why cancer patients are considered to be at a particularly high risk of developing severe COVID-19 illness?”, but also helped treatments of patients during the COVID-19 pandemic. The last session highlights the pioneering mRNA studies and the breakthrough discovery on nucleoside-modifications of mRNA by Katalin Karikó, which led to the innovation and development of the mRNA-based SARSCoV-2 vaccines saving lives of millions and also opened the door for a new era of vaccines and a new class of therapeutics.

**Keywords** Cancer · Cancer hallmarks · COVID-19 · mRNA vaccines · Risk factors

## Introduction

Cancer is a leading cause of death worldwide, and this disease accounted for nearly 10 million deaths in 2020 (Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer 2021). Since the outbreak of the Coronavirus Disease 2019 (COVID-19) pandemic, it caused more than 6.45 million deaths and more than 596 million cases worldwide (World Health Organization, WHO 2020). It is well known that patients with cancer are especially vulnerable to this newly emerging disease (e.g., Dai et al. 2020; Yang et al. 2020). Consequently, the COVID-19 pandemic has affected virtually all aspects of cancer medical care and research (Vrdoljak et al. 2020; American Association for Cancer Research 2022).

On the contrary, major breakthroughs of cancer research against cancer that are generated over decades, among others, in biology/genetics, immunology, vaccinology, and drug development have uniquely positioned cancer researchers

and physicians to respond to the many challenges posed by COVID-19. They could extensively assist the development of COVID-19 diagnostics, treatments, and vaccines, from early phase of the pandemic (Bakouny et al. 2020; Elkrief et al. 2022; American Association for Cancer Research 2022).

The main area that merits special attention, where researchers have gained knowledge from the biology of cancer, is the *immune response* to COVID-19 (e.g., Bakouny et al. 2020; American Association for Cancer Research 2022). For example, the vast amount of knowledge on human papilloma viruses, HPVs and vaccines (zur Hausen 2008) and adaptation of the tests routinely used to monitor T-cell responses to proteins of HPVs could be well utilized for determining the effectivity of COVID-19 vaccines in eliciting immune responses with special regard to cancer patients undergoing treatment.

In a broader sense, *cancer immunology* is a key area of cancer research and medicine that have contributed very important elements to the understanding of COVID-19. In 2013, *Science* nominated cancer immunotherapy as the Breakthrough of the Year (Couzin-Frankel 2013). In the past decade, advanced cancer immunotherapies—chimeric antigen receptor (CAR)-modified T cell therapy

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and inhibitors of immune regulatory checkpoints—have revolutionized the treatment of an increasingly broad array of cancer types (Schuster et al. 2017; Ribas and Wolchok 2018). Knowledge drawn from CAR T-cell therapy has largely contributed to our understanding of “cytokine storm” in severe COVID-19 (discussed in later sessions).

Beyond scientific discoveries, *state-of-the-art technologies*, for instance, next-generation sequencing (NGS) (Mardis 2008), which is routinely used worldwide to detect a broad range of cancer-related pathogenic genetic alterations, were effectively applied to identify the genomic sequence and novel variants of SARS-CoV-2, in early phase of the pandemic.

This review provides a brief summary of the underlying molecular biology of COVID-19 and cancer, presents recent evidence on cellular and molecular relationship between the two diseases, covering common risk factors, shared molecular markers and overlapping signaling pathways/cancer hallmarks and illustrates how have the insights from cancer by research community may be applied to mitigate this new disease. To this end, the review examines the mRNA research conducted over decades that have led to the tremendous success of development of the mRNA-based SARSCoV-2 vaccines and novel mRNA-based cancer therapies.

## SARS-CoV-2 and COVID-19

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan, China. World Health Organization, WHO declared the COVID-19 outbreak to be a pandemic in March 2020. SARS-CoV-2 belongs to a large family of coronaviruses (CoVs) that exist widely in nature (Hartenian et al. 2020). Three out of the seven coronaviruses that are capable of infecting humans have caused the deadly global outbreaks of severe acute respiratory syndrome (SARS) in 2002–2004, Middle East respiratory syndrome (MERS) in 2012, and COVID-19 (Hartenian et al. 2020).

The genetic material of SARS-CoV-2 is RNA that encodes four major structural proteins: envelope proteins, nucleocapsid, membrane, and the spike. However, CoVs, SARS-CoV-2 possesses higher infectivity and pathogenicity than other CoVs, what is largely due to its special key sites within the receptor binding domain of spike protein which are different from other types of CoVs (Yi et al. 2020).

In the early phase of the pandemic, great attention was paid to understand the mechanisms by which SARS-CoV-2 enters the host cell—another area where researchers have relied on knowledge from cancer biology (Hoffmann et al. 2020). The first known entry factor is a receptor called

angiotensin-converting enzyme 2 (ACE2) located on the surface of certain human cells in the nasal passages, lungs, and gastrointestinal tract, among others (Hoffmann et al. 2020). To infect a human host, the spike protein of SARS-CoV-2 attaches to the ACE2 receptor, which is abundantly expressed in the lung, heart, kidney, and intestine and induces an unwarranted immune response (Kuba et al. 2005). This could be an explanation for the vast array of symptoms that is manifested in patients with COVID-19. The other entry factor of SARS-CoV-2 internalization, on the surface of the host cell is a protein, called transmembrane serine protease 2 (TMPRSS2). The enzyme is needed to cleave SARS-CoV-2 spike protein and facilitate viral entry in human cells (Hoffmann et al. 2020).

COVID-19 has been referred to as a disease of the lungs, the main target of severe COVID-19. However, it has turned out that not only the lung but an increasing number of other organs may suffer from COVID-19. These extrapulmonary manifestations frequently affect major organs as the heart, brain, kidneys, liver, but intestines, blood vessels, blood, and immune system may also be affected (Gupta et al. 2020). Many effects of COVID-19 could be potentially long-lasting, leading to development of Post COVID-19 or Long COVID-19 syndrome, which represents an emerging global crisis and consequently it is a hot area of contemporary research efforts (Gupta et al. 2020; Soriano et al. 2022).

## Risk factors of COVID-19 susceptibility and severity

SARS-CoV-2 infections show a significant inter-individual variability, ranging from life-threatening disease to asymptomatic infections (Buitrago-Garcia et al. 2020). Environmental, clinical and social risk factors, host factors (e.g., increasing age, being a man and higher body-mass index) together with the genetic make-up of an individual may explain the variability in disease severity observed across individuals (Zhou et al. 2020).

Researchers are extensively investigating the role of *genetic risk factors* that are associated with a person's susceptibility to COVID-19 (Callaway 2021). From early period of the COVID-19 pandemic, several large concerted efforts have been launched to identify the genetic determinants of COVID-19 susceptibility and severity. These studies have uncovered several genetic alterations associated with severe COVID-19 (Severe Covid-19 GWAS Group 2020; Tangye et al. 2021). There are many genes that are able to boost our defense against various viral infections, for example members of the *interferon pathway*. It is shown that inborn errors of, and autoantibodies directed against, type I interferons (IFNs) are responsible for about 20% of severe COVID-19 cases among SARS-CoV-2-infected individuals (Zhang et al. 2020a).

Most recently, the *OAS1/2/3* cluster (a subgroup of interferon-stimulated genes) has been identified as an important risk factor locus for severe COVID-19 among individuals of European ancestry (Pairo-Castineira et al. 2021). Moreover, Zeberg and Pääbo recently reported that both a major genetic risk factor for severe COVID-19 and a genomic region associated with protection against severe COVID-19 are inherited from Neandertals (Zeberg and Pääbo 2020, 2021).

Describing the role of a missing transposable element in SARS-CoV-2 infected cells, a most recent study provides further evidence on the significance of IFN-related genes in COVID-19, giving also a possible functional explanation for SARS-CoV-2 success in the combat against the host immune system (Sorek et al. 2022).

Increasing evidence support that *SARS-CoV-2 entry factors* (e.g., ACE2) influence COVID-19 risk and yields risk scores associated with severe disease (Hou et al. 2020). In addition, several novel genes of currently unknown significance were identified. Using whole-genome sequencing (WGS), the GenOMICC (Genetics of Mortality in Critical Care) project has discovered and replicated 23 independent variants that significantly predispose to severe COVID-19 (Kousathanas et al. 2022).

More recently, a large global effort has also launched to exploit genetic determinants of *protective* effects against SARS-CoV-2 infection. This was achieved by genetically analyzing individuals who show natural resistance to SARS-CoV-2 infection (Andreaskos et al. 2022). Notably, early in the pandemic, several studies have provided convincing data that individuals with certain blood types were less susceptible to COVID-19 compared to those with other blood types (Barnkob et al. 2020; Severe Covid-19 GWAS Group 2020). However, according to a more recent research, blood type is not associated with disease susceptibility or severity (Anderson et al. 2021).

Genome-Wide Association Study (GWAS) have identified dozens of genomic regions associated with susceptibility and severity of COVID-19 (e.g., Severe COVID-19 GWAS Group 2020; Pairo-Castineira et al. 2021). However, the causal variants in these genomic regions have not been identified yet, which is hindering our ability to understand the pathophysiology of COVID-19.

## Biology of cancer development

There is compelling evidence that cancer is, in essence, a genetic disease caused by the accumulation of a series of genetic and/or epigenetic changes that lead to changes in gene expression, and eventually to cancer. In a long-term microevolution process, a cell population develops that can ignore the normal controls of proliferation, differentiation and death and has the ability to transform to cancer (e.g.,

Nowell 1974; Fearon and Vogelstein 1990; Baylin et al. 2000).

Cancer is a multifactorial disease: beyond host factors (for example, age, comorbidities) several other factors can enhance development of the disease. The genetic events on the cancer pathway are arising during normal cell multiplication, and by endogenous mutagens or because of environmental exposures, or lifestyle factors (International Agency for Research on Cancer: <http://monographs.iarc.fr>).

In the past fifteen years the availability of the human genome sequence (International Human Genome Sequencing Consortium 2004), then the construction of HapMap containing single nucleotide polymorphisms (SNPs) (International HapMap Consortium 2005), together with the huge progress in next-generation sequencing (NGS) (Mardis 2008) and other novel genomic technologies now offer an unprecedented opportunity for the identification of all the genetic changes associated with a human cancer. Large-scale sequencing analyses have identified "cancer genes" (Futreal et al. 2004). These are mutated genes that are causally implicated in tumorigenesis. Cancer genes that are broadly grouped into oncogenes and (inactivated) tumor suppressor genes arise from normal cells by intragenic mutations that can drive oncogenesis via genetically determined molecular pathways (e.g., Kuenzi and Ideker 2020).

It is well established that each tumor contains a collection of various cancer cell populations with a wide range of genetic variations. So, when we think about genetics and genomics of cancer, it is really complex, inborn/inherited (germline) and somatic mutations act together. In the cancer pathway, there are mostly (about 90%) somatic genetic mutations of oncogenes and tumor suppressor genes which acquired somatically during an individual's lifetime, but in the hereditary cancer syndromes, one of the mutations is inherited. The cardinal feature of the syndromic *hereditary cancers* is a germline mutation associated with an increased risk for certain cancers and transmission to offspring through the maternal or paternal side. Most importantly, they often have an early age at onset and exhibit positive family history due to an autosomal dominant inheritance pattern (Ponder 1990). In 2022, we know over 125 hereditary cancer syndromes where pathogenic germline mutations of susceptibility genes put very high risk of cancer (Online Mendelian Inheritance in Man®, OMIM® 2022). With few exceptions, hereditary cancers of the inherited cancer syndromes are due to predisposing genetic variations (mutations) of the tumor suppressor genes. *BRCA1* gene, the first 'breast cancer susceptibility gene' (*BRCA1* gene with pathogenic germline mutation) was discovered by Mary-Claire King, American geneticist in 1990 (Hall et al. 1990). Identification of several dozens of genetic susceptibility genes to cancer followed in the next decades, including that of the *EPCAM* (also known as *TACSTD1*) gene with a new class of mutation

predisposing to Lynch-syndrome (a hereditary non-polyposis colorectal cancer syndrome) that is discovered by our Lab (Kovács et al. 2009).

Elucidation of the *genetic risk factors* (inherited predisposition) to cancer has been one of the most successful areas of biomedical research (Oláh 2021). Studying germline susceptibility to cancer we not only gained new insights into cancer biology, but could also make risk assessment, and translate the new knowledge to clinical oncology practice. Genetic testing for inherited mutations in strongly predisposing genes of breast, ovarian, colorectal and other types of cancer is now part of the standard of clinical care for families suspected to have a strongly predisposing germline mutation. (Singer et al. 2019).

Over the past two decades, an expanding new knowledge has been generated on the complex nature of *cancer genome* (including also germline genome). Large international collaborative studies on genomics and epidemiology of cancer, for example by The Breast Cancer Association Consortium (2021) and The Consortium of Investigators of Modifiers of *BRCA1/2*, CIMBA (Chenevix-Trench et al. 2007) have made a great progress in uncovering the complex *architecture of cancer susceptibility* and cancer risk that involves germline pathogenic variants in high and moderate risk genes and polygenetic factors (Zhang et al. 2020b). It is now widely accepted view that genetic susceptibility to cancer—particularly in genetically unexplained families—is linked to variant patterns rather than single alternative variants (Mavaddat et al. 2015; Lakeman et al. 2019). For example, the rare, but strongly predisposing germline mutations of *BRCA1/2* genes confer very high (around 70%) lifetime risk for breast or ovarian cancer (Kuchenbaecker et al. 2017), and the combined contribution to overall breast cancer incidence of these mutations is less than 10%. By contrast, a set of weakly predisposing, but common alleles could account for up to 40% of breast cancer incidence (Michailidou et al. 2017).

It is widely demonstrated that the tumor(s) of every cancer patient have a unique combination of genetic variations (mutations). The identification of the critical somatic genetic differences is particularly important in determining the appropriate treatment strategies for each patient. The expanding new knowledge on both germline and somatic genome is rapidly improving our understanding of cancer biology and has the ability to transform the practice of oncology at a rapid pace not seen before (Meric-Bernstam et al. 2013).

### Hallmark features of cancer

Hanahan and Weinberg in their prominent "Hallmarks of Cancer" position paper have laid down the framework of knowledge on cancer as a disease (Hanahan and Weinberg 2000). In this review, they identified six hallmark features

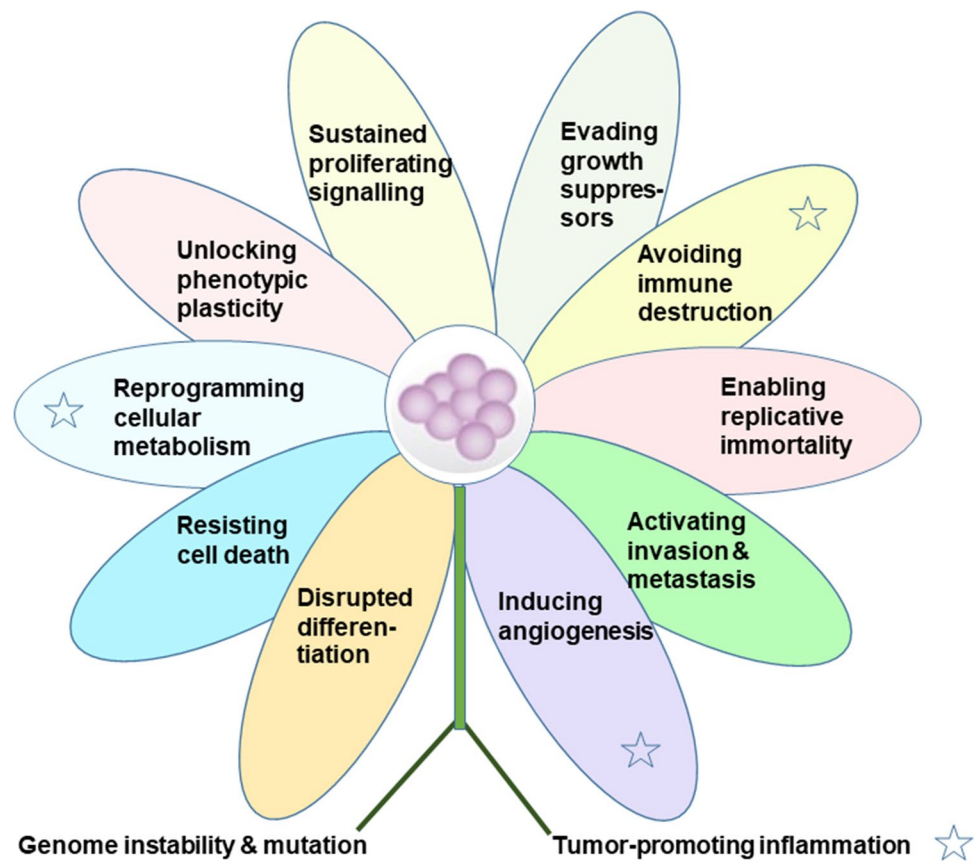
(capabilities) of the cancer cells that are essential to be acquired during development and progression of human tumors. These include: "sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis." They also suggested that *genome instability* and *inflammation* are underlying these hallmarks (Hanahan and Weinberg 2000). Genome instability generates genetic diversity, due to acquired or inherited defects in DNA repair or in cell-cycle checkpoints, thus expediting the acquisition of hallmark capabilities. Inflammation is a known intrinsic defense mechanism activated by the immune system against infection or injury that fosters multiple hallmark functions (Hanahan and Weinberg 2000).

A few years after the publication of this position paper, it has also become increasingly evident that mutated cells on their way leading to a tumor manifestation have to acquire further capabilities such as, how to thrive in a chronically inflamed microenvironment, evade immune recognition, and suppress immune reactivity (Cavallo et al. 2011). The recognition of these capabilities have verified that *evading immune destruction* is an essential hallmark of cancer (Hanahan and Weinberg 2011). *Reprogramming of cellular metabolism*, has also been added, a decade later (Hanahan and Weinberg 2011). Importantly, it is shown that most of the hallmarks of cancer are interconnected with an altered cancer cell-intrinsic metabolism (Kroemer and Pouyssegur 2008). As knowledge of cancer mechanisms has progressed due to applying more advanced computational tools, genomic technologies and "big data" approaches, other potential hallmark features of cancer have been identified (Hanahan 2022). Out of these both *disrupted differentiation* and *unlocking phenotypic plasticity* have recently been added as a "discrete hallmark capability", while both *non-mutational epigenetic reprogramming* (Baylin et al. 2000; Hanahan 2022) and *polymorphic microbiomes* (Senga and Grose 2021; Hanahan 2022) have been added as "distinctive enabling characteristics" that enhance the procurement of hallmark capabilities (Hanahan 2022). *Altered neuronal signaling* has also been proposed for considering as distinctive enabling characteristics (Senga and Grose 2021). Recent studies have also demonstrated that *splicing regulatory factors* play an important role in nearly all hallmarks of cancer (Koedoot et al. 2019). Notably, the role of alternative splicing in breast tumorigenesis was proposed for *BRCA1* gene even in the absence of deleterious inherited mutations (Orbán and Oláh 2003).

In addition, it is now increasingly clear that *tumor microenvironment*—which is made up of heterogeneous and interactive populations of cancer cells, cancer stem cells and various stromal cells—plays an integral role in tumorigenesis and malignant progression (Beck and Blanpain 2013; Hanahan 2022).



**Fig. 1** Hallmark flower of cancer, 2022. Other emerging hallmarks and "enabling characteristics" that facilitate the acquisition of hallmark capabilities are described in the session of "Biology of cancer development." After: Hanahan and Weinberg (2000), Hanahan and Weinberg (2011), Senga and Grose (2021), Hanahan (2022). Asterisk denotes those hallmarks where interplay is demonstrated between cancer and COVID-19



The lucid conceptualization of complex cancer biology by Hanahan and Weinberg (2000, 2011) is widely accepted and has also inspired development of advanced cancer therapeutics and therapies by targeting the various hallmarks.

In summary, Fig. 1 shows major hallmarks of cancer.

**COVID-19 and cancer**

Numerous studies have shown that older adults and individuals with certain preexisting health conditions, such as patients with cancer, are at a higher risk of SARS-CoV-2 infection (e.g., Liang et al. 2020) and are more likely to experience severe disease, including mortality, from COVID-19 (Bakouny et al. 2020). Several studies have reported a poor prognosis for the patients with cancer and COVID-19, especially those who if they are affected those with hematological malignancies, and male patients who have lung cancer have a higher risk of death (e.g., Yang et al. 2020). Furthermore, therapeutic interventions, including surgery, chemotherapy, radiotherapy, and immunotherapy, have been associated with worse COVID-19 outcomes among cancer patients (Lee et al. 2020a; Derosa et al. 2020).

**The interplay between COVID-19 and cancer biology**

Early in the pandemic, it became clear that there were several risk factors shared by COVID-19 and cancer, which increase the risk for both diseases. These include comorbidities (such as cardiovascular and respiratory diseases), advanced age and smoking, obesity, or cancer type and staging (e.g., Lee et al. 2020; Pinato et al. 2020). These risk factors may significantly weaken the host immune system, making cancer patients more vulnerable to infectious agents, including SARS-CoV-2 (e.g., Swann and Smyth 2007; van Dam et al. 2020).

Recent studies on genetic risk factors for severe COVID-19, such as the OAS gene family, have also shown potential overlap with cancer research (Pairo-Castineira et al. 2021).

A recent study by Zhang and Yu (2020) shed new light on the prognostic roles of OAS in breast cancer. The study found that high mRNA expression of OAS1 and OAS3 was associated with a worse prognosis for all breast cancer patients, while OAS2 was linked to a favorable prognosis. Furthermore, a subgroup of interferon-stimulated genes, including the OAS family, STAT1, IRF7, and BST2, collectively known as the interferon-related DNA damage resistant signature (IRDS), were found to be upregulated in various cancer types. The upregulation of these genes

promotes resistance to DNA damaging chemotherapy and radiotherapy (Padariya et al. 2021). Targeting the IRDS genes has been suggested as a potentially effective strategy to resensitize tumor cells and improve the outcome of anti-cancer treatment (Padariya et al. 2021).

While cancer and COVID-19 have different origins, development, and effects on the body, there are some shared manifestations between the two diseases. Although much remains to be learned about the interplay between cancer and COVID-19, researchers have already leveraged knowledge from cancer biology in the first two years of the pandemic to gain insight into the effects of COVID-19. Multiple lines of evidence have emerged, revealing clinical and molecular similarities between cancer and COVID-19 (e.g., Bakouny et al. 2020; Zong et al. 2021; American Association for Cancer Research 2022).

### Entry factors of SARS-CoV-2 internalization

The first biological link between COVID-19 and cancer was reported on *entry factors of SARS-CoV-2 internalization* (Hoffmann et al. 2020). Based on the correlations seen between age-related elevation of ACE2 protein in human lung tissue and the most common incidence of cancer in the same age group (65 and older), it is suggested that the abundance of lung ACE2 may contribute to severe COVID-19 among elder patients with lung cancer (Sinha et al. 2021). Moreover, it has also reported that the highly elevated ACE2 levels seen in the lungs of individuals who are regular smokers may explain why smokers, or patients with smoking-related chronic obstructive pulmonary disease (COPD) or lung cancer, are especially sensitive to adverse outcomes from COVID-19 (e.g., Bakouny et al. 2020; Sinha et al. 2021).

Another potential point of connection between cancer and COVID-19 involves *TMPRSS2 protein*, the other entry factor of SARS-CoV-2 internalization (Hoffmann et al. 2020). Insights into this link have been derived from research in *prostate cancer*, where *TMPRSS2* protein is present in high levels. Research has revealed that *TMPRSS2* is not only highly altered in prostate cancer cells, as demonstrated by Stopsack et al. (2020), but it is also regulated by androgen—a hormone that signals the cell to grow and develop male characteristics. As androgen-targeting therapies are already in use for treating prostate cancer, *TMPRSS2* has become an attractive target for potential COVID-19 therapies (Montopoli et al. 2020). Therefore, there are ongoing clinical studies to assess whether therapeutics that lower *TMPRSS2* levels or inhibit its function could alleviate COVID-19 symptoms (Zong et al. 2021).

Moreover, researchers have gained critical insights into the interplay between the biology of cancer and COVID-19 from other active research areas, including immune

interactions, arterial and venous thrombotic events, and reprogrammed metabolism, which are all associated with the currently accepted hallmarks of cancer (discussed in the next sessions and see Fig. 1).

### Immune interactions between cancer and COVID-19

Important research discoveries in cancer immunology, such as the immune system's response to cancer cells and the mechanisms used by tumors to evade the immune system, have provided crucial insights into the *immune response* to COVID-19 (Costello et al. 1999; Seliger 2005; Derosa et al. 2020). These findings have uncovered significant dysregulation in multiple components of the immune system and provided further data supporting the biological link between COVID-19 and cancer, as recently reviewed (e.g., Bakouny et al. 2020; Zong et al. 2021; American Association for Cancer Research 2022).

As mentioned earlier, evading *immune destruction* is a crucial hallmark of cancer (Hanahan and Weinberg 2011). Unfortunately, both cancer cells and SARS-CoV-2 can avoid the immune system by suppressing the host's defense mechanisms. The immune system can be suppressed by lowering levels of major histocompatibility complex (MHC) proteins, which are required to flag virus-infected cells or cancer cells for recognition and elimination by immune cells, among other factors (Derosa et al. 2020). Another mechanism that is also able to suppress the immune system is known as “T-cell exhaustion,” which results in reduced numbers of T-cells. This can occur when T cells are persistently stimulated due to chronic inflammation, which is often associated with cancer or long-term infection (Coussens and Werb 2002). These exhausted T-cells are also seen in patients with severe COVID-19. Furthermore, overlapping hyper-inflammatory reactions and arterial and venous thrombotic events have been linked to immune system dysfunction, as outlined below.

*Overlapping hyperinflammatory reactions* in severe COVID-19 and in cancer patients treated with CAR T-cell therapy:

*Cytokine release syndrome (CRS)* is an immune system dysfunction with uncontrolled production of pro-inflammatory cytokines and chemokines and manifest as “*cytokine storm*.” This serious life-threatening condition is frequently seen in patients with severe COVID-19. CRS is similar to the known adverse event seen for certain cancer patients treated with CAR T-cell therapy (Turnquist et al. 2020; Moore and June 2020). Recently, shared inflammatory pathways (Iovino et al. 2021) and *common biomarkers* have been identified that are characteristic for both COVID-19 and CAR T-cell therapy-induced CRS, such as IL-6 (e.g., Turnquist et al. 2020; Zong et al. 2021). These similarities between the mechanisms of CRS in cancer patients treated with CAR

T-cell therapy and severe COVID-19 led to repurposing of “immunotherapy-inspired” agents to reduce the cytokine release in COVID-19 (e.g., Agarwal and June 2020).

*Arterial and venous thrombotic events* in the interplay between SARS-CoV-2 and cancer biology:

It is demonstrated that development of thrombotic events, at least in part, may be related to inflammation and the activation of the innate immune system, which can activate systemic coagulation pathways (Engelmann and Massberg 2013; Connors and Levy 2020; Bakouny et al. 2020). Understanding the effects of COVID-19 on blood vessels, blood, and immune system is another important area of research because an overactive inflammatory response and abnormal blood clotting (a prominent coagulation disorder) are important factors in severe COVID-19. Moreover, these coagulation disorders are associated with the formation of new blood vessels in the patient’s lungs. Discussed before that abnormal vasculature known as *pathological neoangiogenesis* is another hallmark of solid tumors (Hanahan and Weinberg 2011). It is well documented that patients with cancer are at somewhat elevated risk of thrombotic complications, particularly those patients who are complicated with both cancer and COVID-19 (Lee and Levine 2003). Recently, it has been shown that several proteins that are related to tumor angiogenesis, such as VEGF, HIF and others are also elevated in the plasma or lungs of patients with COVID-19. These data are suggested to be considered in utilization of antiangiogenic cancer therapeutics for the treatment of COVID-19 (Smadja et al. 2021).

### Parallels and intersections in cancer cell metabolism with COVID-19

Complexity of malignant phenotype includes *metabolic reprogramming* of cancer cells,—either as a consequence or as a cause what is an essential hallmark feature of cancer (Kroemer and Pouyssegur 2008; Hanahan and Weinberg 2011). It is demonstrated that multiple alterations in signal transduction pathways and/or enzymatic machineries are responsible for metabolic reprogramming of cancer cells that serve to the advantage of these transformed cells (Kroemer and Pouyssegur 2008). Recently, evidence was provided for the direct link of SARS-CoV-2 infection with Warburg effect/elevated glucose levels in association with inflammatory response, exploring that SARS-CoV-2 infection can elicit metabolic reprogramming in tumor cells and perhaps also tumor progression (Icard et al. 2021; Codo et al. 2020).

The elevated activity of *guanylate synthetic pathways* of cancer cells is largely due to increased activity of inositide-5’-monophosphate dehydrogenase (EC 1.1.1.205) (IMPDH), the rate-limiting enzyme of GTP biosynthesis. It was suggested and was proven by Weber that IMPDH is a sensitive and selective target for enzyme-pattern-targeted

chemotherapy (Weber 1983). Here, we briefly present the impact of three clinically significant inhibitors of IMPDH (Tiazofurin, Ribavirin and Mycophenolic acid), on metabolic reprogramming and its links with other capabilities (later nominated as hallmarks) of cancer. It is demonstrated that targeting of the deregulated de novo purine biosynthesis leads to a strong anti-proliferative effect with restoring of normal cell differentiation and apoptosis program through inhibiting of IMPDH activity/depleting GTP production, and down-regulation of gene expression programs important for proliferation and adaptive survival of cancer cells (Oláh et al. 1988, 2006). Early studies with *Tiazofurin* provided the first evidence that the proliferative arrest, the differentiation toward the erythroid pathway and the apoptosis of BCR-ABL positive, K562 human leukemia cells, induced by strong inhibition of IMPDH, are mediated, at least in parts, by the down-regulation of the *K-RAS* and by the profound down-regulation of *c-MYC* oncogenes (Oláh et al. 1990). Tiazofurin also exhibited remarkable anti-metastatic activity (a hallmark of cancer progression) in different human and experimental tumors (Timar et al. 1996). Moreover, it has demonstrable anti-leukemia effects, when used to treat patients with BCR-ABL positive acute myelogenous leukemias, which are resistant to standard anti-leukemia chemotherapy (Tricot et al. 1990). *Ribavirin*, a potent anti-viral drug with a wide anti-viral spectrum (Sidwell et al. 1972) that is clinically used for hepatitis C-related liver diseases, such as hepatocellular carcinoma. Some data on its anti-cancer activity, were also reported, in human cancer cell lines (Kökény et al. 2009). It was demonstrated, that treatment with Ribavirin—similarly to Tiazofurin, caused a significant growth inhibition via activating the differentiation and more profoundly, the apoptosis pathway, in response to sub-toxic and toxic doses of the drug, respectively. *Mycophenolic acid*, by inhibiting de novo purine biosynthesis, functions as an antifungal, antibacterial, antiviral, and immunosuppressive agent and used to prevent rejection following organ transplantation and to treat autoimmune conditions (Bentley 2000). Interestingly, but not surprisingly, HL-60 promyelocytic leukemia cells treated with sub-toxic and toxic doses of mycophenolic acid, respectively, also undergo terminal differentiation and apoptosis (Görtz et al. 1997).

Quite early in the pandemic, IMPDH inhibitors—among many other anticancer/antiviral agents—were repurposed to assess their *impact against SARS-CoV-2*. Preliminary data showed that Ribavirin can suppress the replication of SARS-CoV-2 at a low molar concentration (Elfiky 2020). However, the efficacy of various agents, including ribavirin, hydroxychloroquine, lopinavir/ritonavir that were initially proclaimed to be effective against SARS-CoV-2, was later disproved (Drożdżal et al. 2021). Also, there are data for the activity of mycophenolic acid against SARS-CoV-2 (Kato et al. 2020; Han et al. 2021), however, further in-depth

**Table 1** Milestones of mRNA-development for therapy. (After: Karikó 2022; Hou et al 2021; Dolgin 2021)

1961	Discovering mRNA	Brenner et al. (1961)
1984	First in vitro synthesis of mRNA and its in vitro translation into a functional protein	Melton et al. (1984) Krieg and Melton (1984)
1990	First use of mRNA to accomplish a protein production in vivo	Wolff et al. (1990)
1995	mRNA tested as a polynucleotid cancer vaccine in mice Antitumor T cell response induced by mRNA melanoma vaccine	Conry et al. (1995) <sup>a</sup> Zhou et al (1995) <sup>a</sup>
1996	Human dendritic cells (DC) pulsed with RNA: demonstration the efficacy of mRNA DC vaccines	Boczkowski et al (1996) <sup>a</sup>
2005	Discovery of nucleoside modified mRNA	Karikó et al (2005)
2008	Direct injection of mRNA tested for melanoma treatment	Weide et al. (2008) <sup>a</sup>
2010	Preclinical study with intranodally injected DC-targeted mRNA	Kreiter et al. (2010) <sup>a</sup>
2012	Nonviral delivery of self-amplifying RNA vaccines by lipid nanoparticles, LNPs	Geall et al. (2012)
2013	CRISPR–Cas9 mRNA for gene editing	Hwang et al. (2013)
2017	Lipid nanoparticle (LNP) systems for enabling gene therapies First mRNA vaccine for clinical trials	Cullis and Hope (2017) Alberer et al. (2017)
2021	FDA approval of COVID-19 LNP-mRNA vaccine	

<sup>a</sup>mRNA vaccine research in cancer

studies would be needed to assess the real impact of the inhibitors of IMPDH against SARS-CoV-2.

It is demonstrated above, that targeting deregulated cellular metabolism of cancer with clinically significant selective inhibitors offers an efficient strategy to uncover all cancer hallmarks that are intertwined with altered cancer cell-intrinsic metabolism.

Recent studies also demonstrate that *cancer cell metabolism links epigenetic modifications to transcriptional regulation* through modulation of gene expression programs important for proliferation and adaptive survival of cancer cells (Morrison et al. 2022). The close link of metabolic and epigenetic pathways in cancer cells may provide further opportunities to therapeutically target malignant growth via the hallmark features of cancer (Morrison et al. 2022).

### Transposable elements in cancer and COVID-19

Transposable elements (TEs) are mobile DNA sequences that constitute about 45% of the human genome. TEs are important for genome plasticity and evolution as they can create new genes and functions. However, TE activation can contribute to cancer and other human diseases (Solyom and Kazazian 2012; Grundy et al. 2022). TE insertion in human genomes may cause genetic dysfunction and alteration of gene expression, contributing to plasticity, a hallmark of cancer (Grundy et al. 2022). A recent report suggests that TEs (transposases) may play a role in SARS-CoV-2's ability to evade the host immune system, indicating that TEs could be potential drug targets for COVID-19 in gene therapies (Sorek et al. 2022). These findings suggest that TEs, the understudied residents of our genome, could uncover further interactions between COVID-19 and cancer, serving as potential drug targets for both diseases.

### Messenger RNA (mRNA): from a highly immunogenic molecule to mRNA-based vaccines and therapies

mRNA was first discovered in 1961 (Brenner et al 1961). A further 60 years passed until finally the first mRNA became a FDA-approved product in the form of COVID-19 mRNA vaccine (Food and Drug Administration FDA 2021). During those years, however, particularly during the past more than three decades, a lot of progress has been made toward mRNA-based therapies and vaccination by hundreds of scientists, including cancer researchers. Due to the extensive literature, the last part of this review briefly summarizes the key discoveries and breakthrough events that contributed to the rise of mRNA technology in vaccinology and cancer therapy, giving the milestones in Table 1.

In 1984, the first successful in vitro synthesis of mRNA and its subsequent translation into functional proteins were accomplished, enabling the production of large amounts of protein from any cDNA clone (Melton et al. 1984; Krieg and Melton 1984). Initially, in the early 1990s, in vitro-transcribed (IVT) mRNA was mainly used for vaccines by ex vivo pulsing of dendritic cells. In 1990, reporter gene mRNAs were injected into mice, and protein production was successfully detected, marking the first successful use of IVT mRNA to produce protein in animals (Wolff et al. 1990). RNA technology was initially motivated by the fight against cancer, and the first RNA cancer vaccines were published more than 25 years ago (Conry et al. 1995; Zhou et al. 1995; Boczkowski et al. 1996).

IVT mRNA encoding therapeutic proteins or viral antigens had great potential for treating or preventing various diseases, but for years the innate immunogenicity and instability of mRNA hampered its medical use.



## Development of non-inflammatory, nucleoside-modified mRNA for therapy and vaccine

Katalin Karikó Hungarian biochemist began her pioneering work with mRNA in the mid-1980s, and generated functional, highly processed proteins from IVT mRNA transfected into cultured cells, with the goal of developing *mRNA encoding therapeutic proteins* that has the potential for treating various diseases (Karikó et al. 1998, 1999).

In the late 1990s, Karikó continued studying IVT mRNA and began uncovering the mechanisms of its inflammatory activity with Drew Weissman, American immunologist at the Perelman School of Medicine, University of Pennsylvania. Over the following years, they identified innate immune receptors, including TLR3, TLR7 and TLR8 that responded to the transfected mRNA (Karikó et al. 2004).

Based on their interesting findings that tRNAs (known to contain many modified nucleosides) were non-immunogenic, Karikó and Weissman developed and tested a hypothesis that nucleoside modification of mRNA avoids activation of RNA sensors and inflammation. They achieved a monumental breakthrough when they successfully warded off the inherent immunogenic response of mRNA and improved translational efficiency, by incorporating naturally-occurring modified nucleosides, including pseudouridine into the mRNA, so thus preventing activation of RNA sensors (TLR7 and TLR8) (Karikó et al. 2005). In parallel studies, Karikó and colleagues demonstrated that uridine in mRNA was responsible for triggering the immune reaction and most importantly, also demonstrated that exchanging the uridine to pseudouridine in the mRNA resulted in an optimal transcript that is non-inflammatory, more stable and translates very efficiently, thus making *pseudouridine-containing mRNA an ideal platform for delivering therapeutic proteins* (Karikó et al. 2008). They also invented a purification procedure to remove contaminating double-stranded byproducts from the IVT mRNA that further increased the translational capacity of the mRNA and eliminated its remaining immunogenicity by avoiding activation of TLR3, showing that *the nucleoside-modified mRNA encoded proteins were functional, thus enabling the use of mRNA for therapy* (Karikó et al. 2011). Moreover, utilizing the discovery, that lipid nanoparticles (LNPs) are appropriate carriers for mRNA as RNA vaccines (Geall et al. 2012), they formulated a *potential mRNA vaccine with LNP* (Pardi et al. 2015).

### Anti-SARS-CoV-2 mRNA vaccines

Patent coinvented by Katalin Karikó and Drew Weissman on nucleoside-modified mRNA (Karikó K and Weissman D Issued patents 2012–2019) were used to create the *anti-SARS-CoV-2 mRNA vaccines*, BNT162b2 by BioNTech/Pfizer and mRNA-1273 by Moderna/NIH. When the

SARS-CoV-2 pandemic emerged, biotechnology companies BioNTech and Moderna immediately jumped to action, testing nucleoside-modified mRNA vaccine against the virus in mice (Laczkó et al. 2020) and soon after in clinical trials (Sahin et al. 2020).

While the COVID mRNA vaccines have rolled out in an unprecedentedly short time: researchers have gone from identification of SARS-CoV-2, the causative agent of disease to mass production of multiple vaccines, in less than 1 calendar year, but the achievements began decades earlier, in the devoted work of hundreds of scientists—including that of cancer researchers on mRNA (e.g., Weissman 2015; Kwok et al. 2021), (Table 1). mRNA experts now consider pseudouridine an essential component of the mRNA technology, as the chemical modification of selected nucleotides was the groundwork that solved the two most concerning issues in mRNA, immunogenicity and stability (Sahin et al. 2014; Weissman 2015).

Many different vaccine platforms against SARS-CoV-2 have been developed, but the mRNA vaccines developed with the *nucleoside-modified mRNA technology of Karikó and Weissman* (Karikó et al. 2005) formulated with LNPs rivals the best available conventional vaccine manufacture methods, as it is more safety, more efficient and much more reproducible vaccine as compared to the use of other (subunit, killed and live attenuated virus, as well as DNA-based) vaccines (Pardi et al. 2018). Priority COVID-19 vaccination began in patients with cancer, the largest risk population, during the pandemic (Ribas et al. 2021), confirming the results of the early studies that COVID-19 vaccines are effective in most patients with cancer, with few to no side effects (Sahin et al. 2020).

### Applications of mRNA technology

The rapid success of mRNA-based COVID-19 vaccines has highlighted the vast potential of mRNA technology (Polack et al. 2020; Baden et al. 2021). Accumulated knowledge and technical advancements have led to the emergence of various mRNA-based applications in many branches of medicine, including cancer, infectious diseases, autoimmune diseases, and regenerative medicine. These applications encompass viral vaccines, protein replacement and supplementation therapies, cancer immunotherapies, cell-based therapies, and reprogramming strategies (e.g., Weissman 2015; Chabanovska et al. 2021). Protein replacement and supplementation therapies and vaccination approaches have been developed primarily for cancer and infectious diseases.

## mRNA cancer vaccines and other cancer immunotherapies

Vaccination is a highly effective therapeutic modality that has saved countless lives every year, with preventive vaccines being particularly successful (World Health Organization 2022). *Most cancer vaccines are therapeutic* and aim to stimulate cell-mediated responses capable of clearing or reducing tumor burden (Coulie et al. 2014). The goals of cancer and antiviral vaccines are similar, as they aim to elicit potent antigen-specific immunity. However, while antiviral vaccines generate neutralizing antibodies against exposed virion proteins, antitumor immunity depends on T-cell reactivity against HLA-restricted tumor antigens, making their identification critical (Coulie et al. 2014; Kwok et al. 2021). Earlier research on RNA vaccines was primarily focused on cancer treatment, and the response to the COVID-19 pandemic has leveraged data from years of preclinical and clinical trials exploring mRNA vaccines for cancer treatment (Dolgin 2021; see Table 1).

Despite the formidable barriers presented by the genomic and phenotypic heterogeneity of cancer, as well as the immune-dampening effects of cancer cells, significant progress has been made in the development of cancer vaccines, including mRNA-based cancer vaccines, over the past few years (e.g., Pardi et al. 2018; Kwok et al. 2021).

*Advanced immunotherapies*, such as immune checkpoint inhibitors and CAR T-cell therapy, have led to remarkable treatments for previously untreatable or refractory cancers (Ribas and Wolchok 2018; Schuster et al. 2017). The success of mRNA-based COVID-19 vaccines has reignited interest in mRNA-based cancer immunotherapies. Recent advancements in next-generation sequencing (NGS), such as whole-exome and transcriptome sequencing, have facilitated the precise identification of immunogenic epitopes for each tumor by integrating mutational and gene expression data obtained from NGS (Wells et al. 2020). This has significantly improved the rational design of neoepitope cancer vaccines in a patient-specific manner. Enhancing cell-mediated immunity through the use of cancer vaccines is considered one of the most promising options for modern cancer immunotherapy, nevertheless, several challenges in mRNA vaccine immunogenicity and efficacy still need to be addressed (Bidram et al. 2021).

In recent years, mRNA-based drug discovery in cancer immunotherapy has advanced significantly (Di Trani et al. 2022), leading to the enrollment of patients in various clinical trials exploring the efficacy of mRNA-based cancer vaccine therapies. Early results from these trials, both as monotherapy and in combination with checkpoint inhibitors, have been encouraging (Lorentzen et al. 2022; ClinicalTrials.gov). Importantly, these mRNA-based immunotherapies have shown promise in treating previously untreatable

diseases, including stage IV non-small cell lung cancer (Papachristofilou et al. 2019), unresectable/advanced solid tumors (Haanen et al. 2022), and glioblastomas (Meister et al. 2022). Promising results have also been seen with advanced melanoma (De Keersmaecker et al. 2020), highlighting the potential of mRNA-based cancer vaccines in treating various types of cancer.

## Concluding remarks

Karikó's and Weissman's discovery in the field of mRNA vaccines and therapeutics was a groundbreaking achievement that has revolutionized the delivery of effective and safe vaccines, therapeutics, and gene therapies across the spectrum of medicine. Katalin Karikó has already received numerous prestigious prizes, including the Breakthrough Prizes and the Lasker award, for her seminal contributions in mRNA field. The limitless opportunities of the mRNA platform and the immense interest in it from both academic communities and mRNA companies, together predict that the novel mRNA-based therapeutics, including vaccines, are poised to become a key strategy in cancer treatment in the near future.

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