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Current Opinion in Biotechnology

Review

Multifaceted metabolic role of infections in the tumor microenvironment☆

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The impact of bacteria and viruses on tumor growth has long been recognized. In recent decades, interest in the role of microorganisms in the tumor microenvironment (TME) has expanded. Infections induce metabolic reprogramming and influence immune responses within the TME that may either support proliferation and metastasis or limit tumor growth. The natural ability to infect cells and alter the TME is also utilized for cancer detection and treatment. In this review, we discuss recent discoveries about the mechanisms of bacteria and viruses affecting TME, as well as strategies in cancer therapy focusing on metabolic alterations. Infections with engineered bacteria and viruses represent promising therapeutic approaches to develop novel and more effective therapies to constrain tumor growth.

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Abbreviations: 6PGDH, 6-phosphogluconate dehydrogenase; AdV, Adenovirus; Ad5, Type-5 adenovirus; AhR, Aryl hydrocarbon receptor; AM, Alveolar macrophages; ATP, Adenosine triphosphate; BDEPT, Bacterial-directed enzyme prodrug therapy; CAP-Flu, Chimeric antigen peptide influenza virus; CCSC, Colorectal cancer stem cell-like; CRC, Colorectal cancer; CXCL1, C-X-C motif chemokine ligand 1; DAMP, Damage-associated molecular pattern; DC, Dendritic cell; ECAR, Extracellular acidification rate; EcN, Escherichia coli Nissle 1917; Fn, *Fusobacterium nucleatum*; G6PDH, Glucose-6-phosphate dehydrogenase; HCMV, Human cytomegalovirus; HCV, Hepatitis C virus; HPV, Human papillomavirus; HMGB1, High mobility group box 1 protein; IAV, Influenza A virus; IL, Interleukin; IFN, Interferon; MDSC, Myeloid-derived suppressor cells; mi-IL-2, Microbial IL-2; NK, Natural killer cell; OCR, Oxygen consumption rate; PAMP, Pathogen-associated molecular pattern; PD-L1, Programmed death-ligand 1; Pks, Polyketide synthase; ROS, Reactive oxygen species; STING, Stimulator of interferon genes; T-VEC, Talimogen-laherparepvec; TAM, Tumor-associated macrophage; TAN, Tumor-associated nucleophile; TCA, Tricarboxylic acid; TME, Tumor microenvironment; Treg, T-regulatory cell; OV, Oncolytic virus

Current Opinion in Biotechnology 2024, **89**:103183

This review comes from a themed issue on **Systems Biology**

Edited by **Thekla Cordes** and **Seth Parker**

For complete overview of the section, please refer to the article collection, "Systems Biology (2024)"

Available online 27 August 2024

https://doi.org/10.1016/j.copbio.2024.103183

Introduction

Tumor microenvironment (TME) is a complex network of cancer cells and various other cellular and noncellular components. Microorganisms such as bacteria, viruses, fungi, phages, and protozoa naturally occur in the TME, modulating the metabolic composition and promoting or inhibiting tumorigenesis. In the last decades, a growing interest has emerged in microorganisms in the TME and their potential applications for cancer therapy [1,2].

Bacterial and viral infections have been long associated with cancer development and have been used in cancer therapy decades ago. Bacteria have various effects on cancer cells through different modes of action, for instance, depending on the strain, tissue, and environment [1,2]. Viruses also naturally occur in the TME, and some strains promote cancer growth, such as the human papillomavirus (HPV) [3], while others have oncolytic activity, such as the influenza A virus (IAV) [4]. The different mechanisms through which bacteria and viruses affect tumor proliferation and metastasis include altering immune responses [5–7], secreting cytotoxic molecules such as formate or colibactine [8,9], and al-

☆ Given the role as Guest Editor, Thekla Cordes had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Seth Parker.

terations of metabolic and signaling pathways [8,10]. The natural abilities of microorganisms to colonize and alter the TME can also be used for cancer detection and therapy with the help of engineered bacteria and viruses [2,11,12]. However, the metabolic interactions among viruses, bacteria, cancer cells, and TME are not well understood. Metabolites function as signaling molecules, and we are just beginning to understand the functional role of small molecules within the TME [13–15]. For instance, the immunometabolite itaconate has antimicrobial properties but may also affect tumor progression by altering cancer cell metabolism or the composition of the TME [16–19]. Thus, further research is needed to identify the key players within the TME that affect immune responses and tumor progression.

In this review, we discuss the role of bacterial and viral infections in modulating the TME influencing tumor proliferation and metastasis. Given the complexity of this research field and its extensive possibilities, we aim to provide insight into the mechanisms through a few examples, focusing on the metabolic interactions and alterations in the TME. Furthermore, we will discuss the possibilities of using engineered bacteria and viruses in cancer therapy. With increasing knowledge and technological advancements, infections with engineered bacteria and viruses represent promising approaches to fighting cancer.

Bacteria altering the tumor microenvironment, promoting tumor growth and metastasis

Our knowledge about the role of bacteria in cancer has dramatically improved, specifically due to technological advancements in metabolism research [20]. Several bacteria developed strategies to influence the composition of the TME, thereby promoting tumor growth and metastasis. Dysbiosis, an imbalance in the gut microbiome, is linked to different kinds of cancer. For example, *Helicobacter pylori* is a well-characterized oncomicrobe promoting colorectal cancer (CRC) [1,2,5], and *Escherichia coli* strains possessing the polyketide synthase (pks) virulence factor are also associated with CRC [21]. Furthermore, *Salmonella enterica* is associated with gall bladder cancer, and *Fusobacterium nucleatum* and *Clostridioides difficile* are associated with colon cancer, besides many other associations between bacteria strains and cancer types. However, the complex interactions between microorganisms and cancer were already discussed elsewhere [1,22]. Here, we focus on how *Fusobacterium nucleatum* (*Fn*), associated with CRC, influences host–pathogen interactions as well as the composition of the TME.

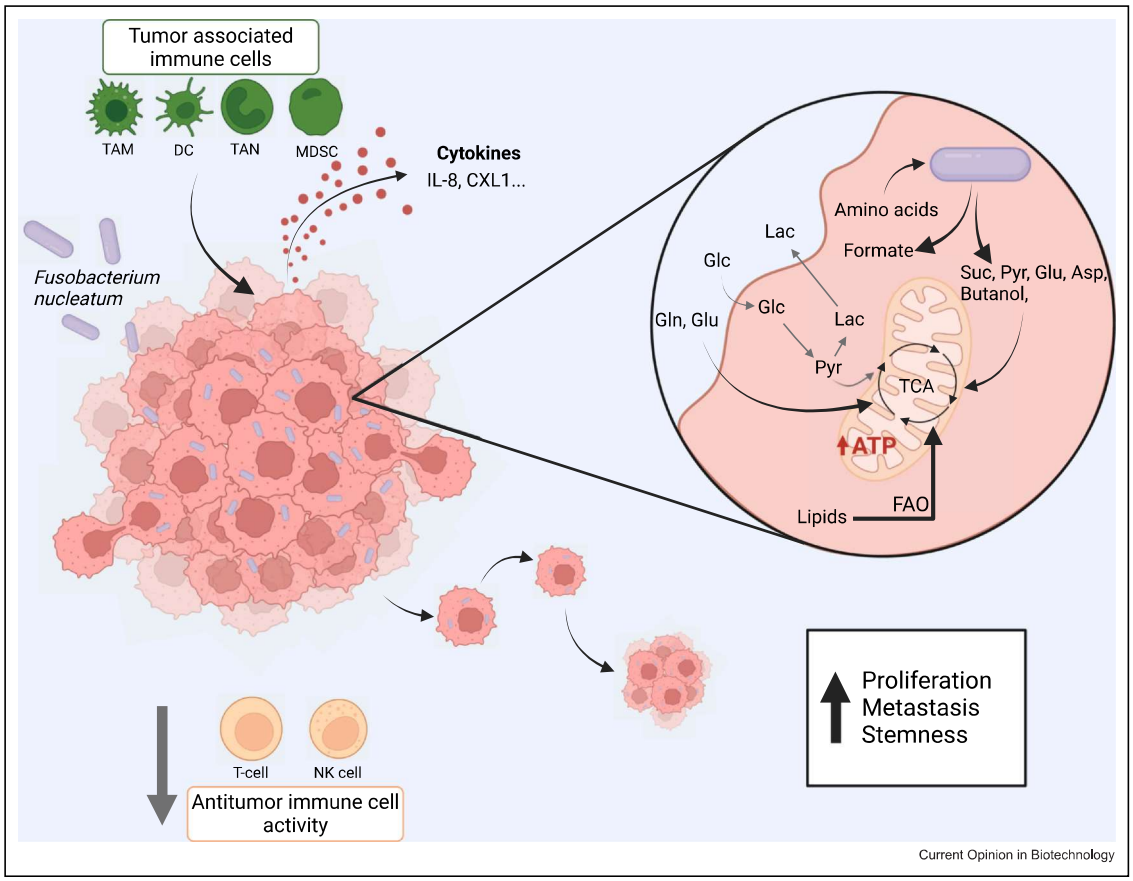
The anaerobe bacterium *Fn* is predominantly located in the oral region but is also increased in various types of cancers [23]. *Fn* builds a symbiotic relationship with the cancer cells, promoting tumor growth and enabling a stable colonization in the cells and the TME [8,23,24]. *Fn* alters the immune response within the TME. High levels of *Fn* are associated with an enrichment of tumor-promoting immune cells, including tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs), dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs) [8,24] while also inhibiting the function of T-cells and natural killer (NK) cells [25] (Figure 1). Multiple virulence factors, including Fap2, FadA, RadD, and FomA, enable *Fn* to bind and infiltrate cancer cells and modulate signal pathways and cytokine secretion. Among others, interleukin (IL)-8, Wnt, C-X-C motif chemokine ligand 1 (CXL1), aryl hydrocarbon receptor (AhR), and nuclear factor kappa B are affected in CRC upon infections, promoting proliferation and metastasis [6,8,26] (Figure 1). *Fn* secretes outer membrane vesicles that promote autophagy in oral cancer, further facilitating metastasis [27].

Fn uses amino acids from the cells as an energy source and secretes small molecules that affect cell metabolism [8]. Specifically, *Fn* influences glycolysis, oxidative phosphorylation, and carbon fuel for tricarboxylic acid (TCA) cycle metabolism in cancer cells. However, the observed metabolic reprogramming might be specific to cell types or culture conditions [8,28] (Figure 1). *Fn* infections also increased expression of hypoxia-related genes, and the metabolic changes promoted cancer cell proliferation and metastasis as well as colonization and reproduction of *Fn* in the TME [8,28]. *Fn* secretes metabolites such as aspartate, butanol, succinate, and glutamate, which could fuel cancer cell metabolism [8] (Figure 1). Secreted succinate derived from *Fn* also increased chemoresistance of cancer cells by limiting $CD8^+$ T-cells trafficking to the TME [29]. Furthermore, secreted formate induced stemness of CRC cells and might be an important factor in the protumorigenic properties of *Fn*. Finally, *Fn* induces fatty acid oxidation in colorectal cancer stem cell-like cells (CCSC) for proliferation as well as fatty acid and triglyceride synthesis in non-CCSC promoting stemness features [8,30]. Collectively, various mechanisms contribute to the protumorigenic effect of *Fn*. A better understanding of the metabolic host–pathogen interactions, and the TME may help to develop novel strategies to limit cancer growth.

Engineered bacteria in cancer therapy

Some bacterial strains have anticarcinogenic effects, including *Listeria monocytogenes*, which activates $CD8^+$ T-cells with cancer-killing capabilities [2]. Furthermore, cancer-associated bacteria, such as *Clostridium symbiosum*, can be used for cancer screenings and may serve as a biomarker for CRC [31]. Generally, The hypoxic and

Figure 1



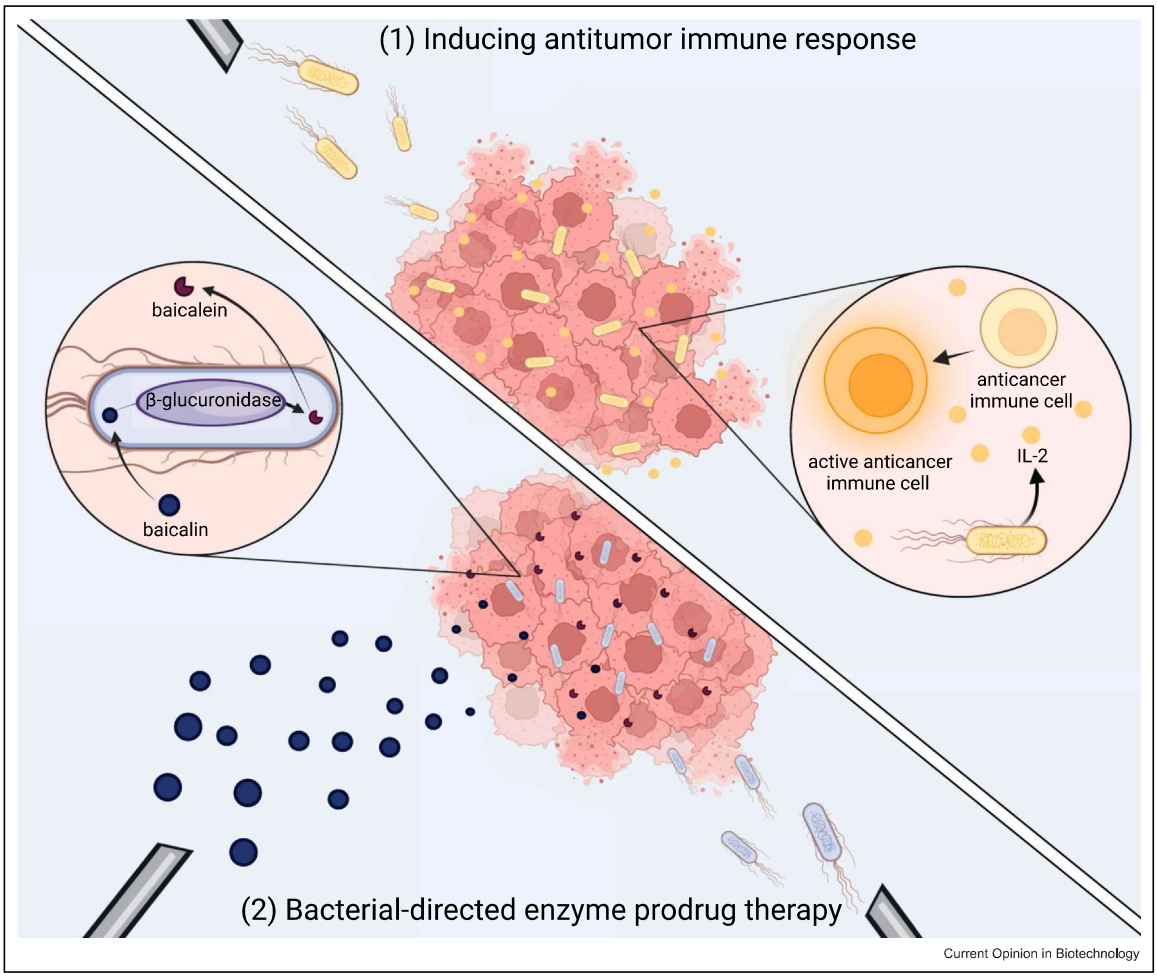
Fusobacterium nucleatum inducing proliferation, metastasis, and stemness in cancer. *Fn* colonizes the TME and infiltrates cancer cells, promoting proliferation, metastasis, and stemness. *Fn* alters cytokine secretion, increases the abundance of tumor-associated immune cells, inhibits antitumor immune cell function, and modulates the metabolic composition of TME through changes in bacterial and host cometabolism and secretion of oncometabolites. Gln, glutamine; Glc, glucose; Lac, lactate; Pyr, pyruvate; Suc, succinate; Asp, aspartate; FAO, fatty acid oxidation.

immune-suppressed TME is favorable for bacterial infections. Their ability to colonize and modulate the TME can be altered and optimized for potentially more effective cancer treatment than conventional methods [2,11].

Many approaches using engineered bacteria in cancer therapy are based on influencing the interaction between bacteria and the immune system. For example, Tumas et al. engineered *E. coli* Nissle 1917 (*EcN*) to secrete bioactive microbial IL-2 (mi-IL-2) in mouse tumors to reduce tumor growth through the activation of cancer-killing cells, including NK and $CD8^+$ T-cells [32] (Figure 2). Furthermore, SYNB1891 bacterial strain, engineered from *EcN*, activates the stimulator of interferon genes pathway in phagocytic-antigen-presenting cells inside tumors, thereby increasing antitumor immunity [33].

Bacteria can also be utilized to modulate the metabolic composition of the TME. For example, arginine is typically low abundant in the TME, reducing antitumor T-cell activity. By using an engineered *EcN* strain expressing genes for the synthesis of L-arginine from ammonia, the amount of tumor-infiltrating T-cells was increased. Combined with an immunotherapy treatment with antiprogrammed death-ligand 1 (PD-L1) antibodies, these bacteria were sufficient to reduce tumor growth [34]. Further, engineered bacteria are applied in combination with prodrugs in bacterial-directed enzyme prodrug therapy (BDEPT). For instance, *E. coli* DH5α-lux/βG was engineered to overexpress the β-glucuronidase to convert the prodrug baicalin to baicalein, thereby increasing its cytotoxicity. Since the bacteria strain specifically colonizes tumors, the cancer cells can be targeted and lysed, reducing tumor growth with less damage to healthy tissues [35] (Figure 2). Collectively, engineered bacteria are a promising approach to developing targeted cancer therapies that are less damaging to healthy tissues. However, reducing tumor-promoting bacteria should also be part of treating cancer such as

Figure 2



Possible applications of engineered *E. coli* strains in cancer therapy. Engineered *E. coli* strains colonize tumor regions and are modified, for instance, (1) to secrete bioactive IL-2 cytokine to induce an antitumor immune response or (2) to be employed in combination with prodrugs to induce cytotoxicity.

CRC, for instance, by using bacteriophage strategies [1]. Similar to bacteria, viruses have numerous applications in cancer therapy, particularly due to their oncolytic and oncogenic properties.

Oncolytic and oncogenic viruses

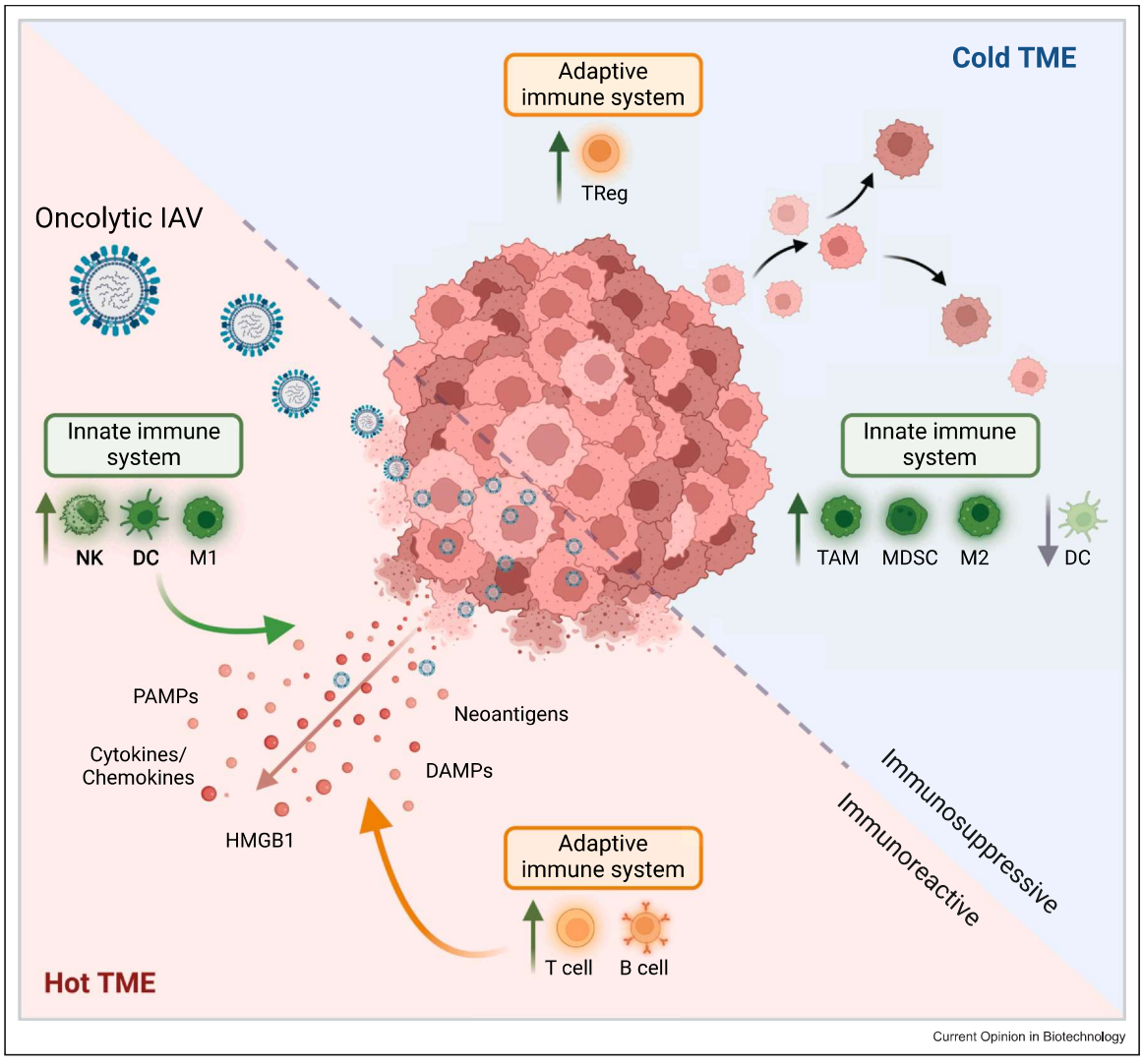
Viral infections, such as respiratory infections caused by IAV, adenoviruses (AdV), and coronaviruses, result in acute infections, some of which are associated with cancer. While IAV infections may correlate with a higher risk of lung cancer [36], long-term effects of coronavirus infections, specifically diseases associated with coronaviruses disease 2019, on cancer outcomes, or interactions with the TME remain to be explored. Viruses comprising cancer-promoting properties are termed oncogenic viruses. One example of oncogenic viruses is human papillomavirus (HPV), which is related to cervical cancer [37,38], and vaccination is one approach to prevention. HPV infections rewire the host cell metabolism and increase, for instance, glycolysis and reactive oxygen species (ROS) to promote virus production [10]. In addition to tumor-promoting viral pathogens, some oncolytic viruses (OVs) have anticancer properties [39]. Furthermore, vaccination approaches such as the IAV vaccination increased antitumor response in breast cancer models [40]. Contrary to the potential oncogenic effect of IAV [36], an early study reported regression of leukemia in patients following IAV infections [4]. Thus, the impact of viral infection on cancer might be influenced by diverse aspects that need to be identified in future studies. As recently reviewed by Peng et al. [41], various OVs, such as genetically modified AdV [42], wild-type IAV [7], engineered IAV [43], and recombinant vaccinia virus [44], present promising candidates for cancer therapy. These findings warrant further investigation into the potential use of viral oncolytic

properties in the clinical context, often referred to as virotherapy. In our current review, we focus on the oncolytic properties of IAV and discuss how infections induce rewiring of the TME, immunity, and metabolism affecting cancer growth.

Approaches in virotherapy

Virotherapy aims to transform the 'cold' immunosuppressive TME, characterized by high levels of TAMs, T-regulatory cells (Tregs), MDSCs, and activated M2-like macrophages, into a 'hot' immunoreactive TME (Figure 3). This transformation involves the recruitment of, for instance, NKs, DCs, and M1-like macrophages (Figure 3). OV administration targets different approaches in cancer therapies, such as making the virus dependent on specific genes within the cancer host cell to enable selective replication in malignant cells, followed by direct lysis. Furthermore, it is applied to deliver specific antibodies to inhibit tumor growth [45]. For instance, the recombinant human type-5 adenovirus (Ad5) selectively replicates in tumor cells with p53-defective influencing cancer cell growth [46]. OVs may also indirectly affect the TME and tumor growth by inducing the release of cytokines, such as interferon (IFN), damage-associated molecular patterns (DAMPs), high mobility group box 1 protein (HMGB1), or pathogen-associated molecular patterns (PAMPs) [41,47], leading to further recruiting and activation of the innate

Figure 3



Properties of OVs for priming antitumor immunity. Schematic overview depicting the impact of the oncolytic IAV via modulating the cellular TME. IAV transforms the immunosuppressive TME (cold) into the immunoreactive TME (hot) by activating the innate and adaptive immune system, thereby inducing the release of immunomodulators for subsequent recruitment of further tumor-killing cells or directly impacting the tumor-host cells by depleting the host resources. M1/M2, M1-like and M2-like polarized macrophages. MDSC, myeloid-derived suppressor cell; NK, naturally killer cell; PAMP, pathogen-associated molecular pattern; TAM, tumor-associated macrophage; Treg, regulatory T cell; TME, tumor microenvironment.

and adaptive immune system, including DCs (Figure 3). DCs play an elementary role in connecting both immune systems and are infrequently present in the cold TME. These findings highlight various targets that can be used to modulate the immune response in the TME through OVs, aiming to constrain tumor growth and increase patient outcomes.

Influenza A virus as a viral agent in cancer therapy

Several studies applied OVs as a promising therapy strategy targeting different cancer types [2,48]. These studies include treatments of melanoma with a recombinant herpes-simplex-virus named talimogen-laherparepvec (T-VEC) [49] or treatment of non–small cell lung cancer using the oncolytic Maraba virus simultaneously with the modified AdV vaccine [2]. Both therapies were used in combination with the humanized antibody pembrolizumab. Another promising strategy in the fight against cancer is the genetic modification of OVs to yield neoantigens within the tumor. For instance, in a recent study, the modification of a wild-type IAV resulted in a live but nonproductive IAV that induced innate and adaptive immune responses, thereby altering cancer growth [43]. The virus represents an attenuated chimeric antigenic peptide influenza virus (CAP-Flu) and functions to deliver antigenic peptides (neoantigens) to the tumor through the attachment of synthetic peptides to the viral surface. The authors observed a significantly lower number of lung tumor foci in mice treated with CAP-Flu one week after injection of B16-F10-OVA melanoma cells. Furthermore, they observed increased antigen uptake, prolonged duration, and enhanced presentation to DCs, as well as higher DC activation following internalization of the engineered virus. The study also inserted the gene for the immune checkpoint inhibitor, anti-PD-L1 nanobody, into the virus genome and observed a regression of lung metastases and increased survival *in vivo* after repeated B16–10 administration [43]. Thus, infections with engineered IAV may represent a potential tool for anticancer therapy.

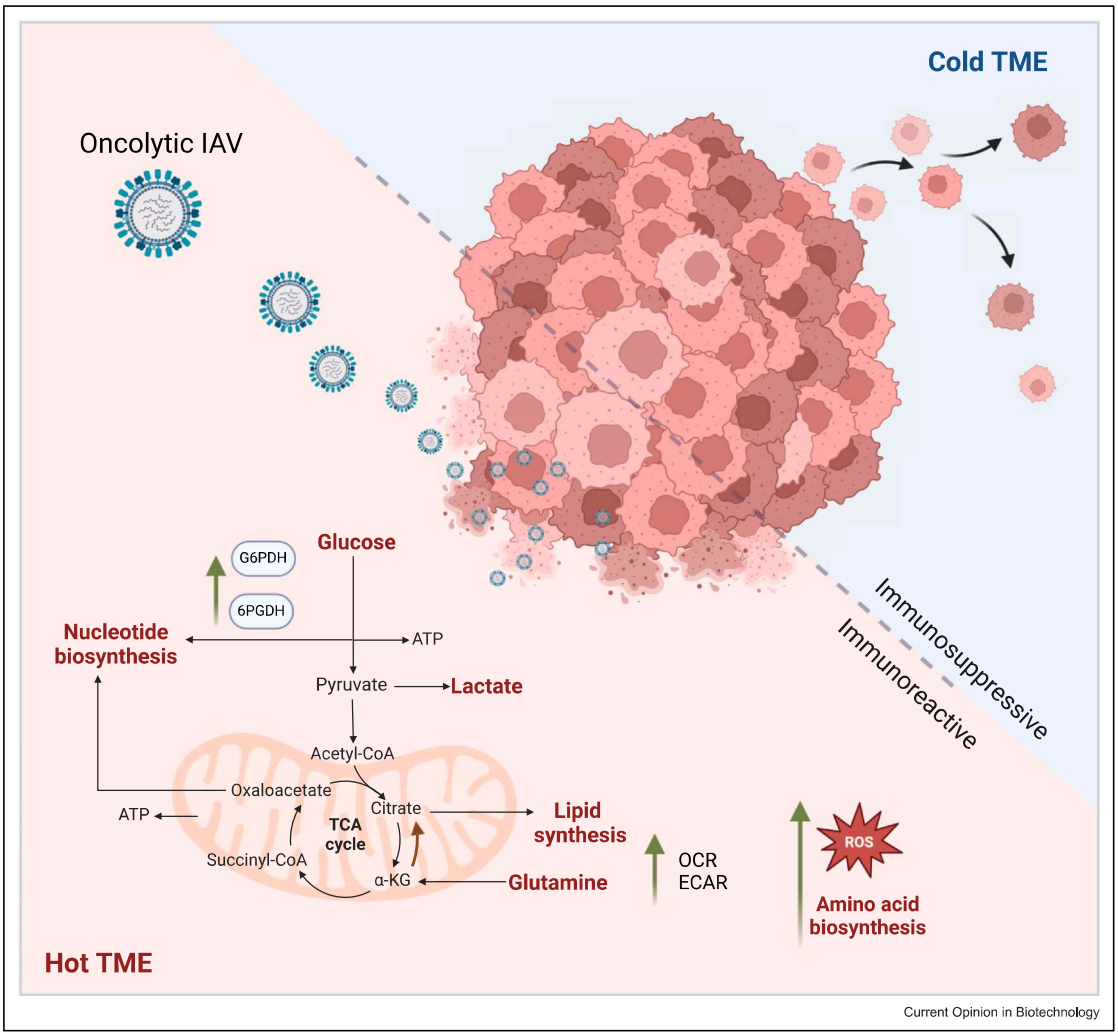
Furthermore, TAMs play a key role in cancer progression by escaping the immune system, an effect that may be influenced by IAV infections. A recent study elucidated the effective and long-lasting antitumor function of respiratory viral infections with IAV through training the mucosal-resident alveolar macrophages (AMs) *in vivo* [7]. However, IAV-trained AMs appear to be resistant to the immune suppressive mechanism of the TME, as evidenced by enhanced phagocytotic activity and antitumor function, which is regulated at the epigenetic and transcriptional levels [7]. Mice pretreated with IAV and subsequently injected with B16 melanoma cells depict a reduced tumor development in the lungs and prolonged survival compared with the control group, which was dependent on IFN-γ-secreting NKs. The study further demonstrated similar results depicting reduced tumor burden in the lungs developed by metastatic breast cancer *in vivo* [7]. Thus, altering immune cell metabolism and function via IAV might be a promising approach to modulating the TME. Further investigation is required to identify the metabolic reprogramming occurring in infected cancer cells to uncover the underlying immune mechanisms. Additionally, cancer cells can hijack immune cell metabolism, for instance, altering lipid metabolism in AMs to convert them into cancer fuel suppliers as demonstrated by *ex vivo* metabolic tracing approaches [50]. Thus, cancer cells may also influence IAV infections, and more research is needed to decipher the complex metabolic interactions between immune and cancer cells.

Metabolic profiling of the tumor microenvironment during influenza A virus infection

Cancer cells are experts in reprogramming cellular metabolism caused by environmental changes, such as limited oxygen and nutrient availability or altered growth stimuli to support growth. Wang et al. quantified metabolic rewiring in *ex vivo* AMs and observed increased oxygen consumption rates and extracellular acidification rates (ECARs) with altered expression levels of enzymes involved in glycolytic pathways upon IAV infection. Furthermore, alteration of mitochondrial oxidation reduced the antitumor activity in IAV-trained AMs, suggesting that glycolytic and TCA cycle metabolism might be vulnerable targets (Figure 4) [7]. Furthermore, upregulated activity of the glycolytic enzymes, glucose-6-dehydrogenase (G6PDH), and 6-phosphogluconate dehydrogenase (6PGDH) was also reported in IAV-infected cancer cells [51]. In line with this observation, influenza A/PR/8/34 infections *in vitro* resulted in increased lactate production, an end product of glycolysis [52]. Furthermore, some viruses increase fatty acid synthesis in the tumor, promoting cell growth [41]. A recent study described the link between obesity and a higher risk of a severe influenza A (H1N1pdm) infection that might be induced through metabolic alterations [53]. Thus, the metabolic reprogramming induced by IAV infections may influence other diseases besides cancer.

Viral infections with AdV, human cytomegalovirus, and hepatitis C virus and subsequent virus replication in the host cell require a higher glutamine utilization followed by increasing glutamine uptake [54–56]. Of note, a previous study determined AdV-induced reprogramming of the cellular metabolism inducing reductive carboxylation pathway fueling *de novo* lipogenesis from glutamine [57]. Thus, glutaminase activity may represent a

Figure 4



Properties of OVs for priming the antitumor immunity. The illustration depicts the synergy between IAV-infected and malignant cells in metabolic reprogramming of the host cell for either viral replication or tumor growth.

metabolic vulnerability in viral infections, including AdV, herpes simplex virus, and IAV [57]. The synergy between virally infected and cancer cells, upregulating anabolic metabolism of amino acids and nucleotides, presents a promising target in cancer therapy [58]. Utilizing the reductive TCA cycle metabolism for either viral replication [57] or tumor growth [59] further underscores the potential efficacy of viral infections in combating cancer (Figure 4).

Future directions

Numerous techniques have emerged on how to utilize bacteria and viruses for cancer therapy. Among them, intravesical bacillus Calmette-Guèrin immunotherapy is commonly used as a therapy against non–muscle-invasive bladder cancer [60]. Furthermore, viruses with oncolytic properties have undergone evaluation in multiple clinical trials [2,48,49], highlighting the potential of the IAV for future cancer treatments that warrants further investigations. A variety of clinical studies are currently exploring potential applications of viruses and bacteria in cancer treatments, including probiotics, viruses such as vaccinia virus, and the combination of bacteria and viruses with antibodies targeting cancer [2]. Current clinical trials, such as the combination of BMC128 with nivolumab, have potential in immunotherapy [61]. Advancements in bacterial and viral therapies could benefit from a deeper understanding of the interactions between the microbiome and cancer and may play an important role in future cancer therapies.

Conclusion

Bacterial and viral infections play a vital role in altering the composition of the TME, thus influencing its potential as pro- or anti-tumorigenic. Many bacteria and viruses influence TME, for instance, by secreting signal molecules, altering specific immune responses, causing DNA damage, or inducing metabolic rewiring. While promising approaches utilizing bacteria and viruses for cancer detection and therapy exist, how infections influence metabolism to promote either pro- or antitumor properties is still not well understood. Engineered bacteria and viruses could be optimized to work effectively against cancer with potentially less off-target effects compared with conventional therapies. For example, altering levels of cytokines or metabolites such as itaconate or arginine in the TME may promote an anticancer immune response, either alone or in combination with existing treatments. Expanding our current knowledge of the complex interaction of microorganisms and cancer cells will provide us with effective ways to develop new treatment strategies.

CRediT authorship contribution statement

Conceptualization: H.F.W., B.D., T.C. Funding acquisition: T.C. Project administration: T.C. Supervision: T.C. Visualization: H.F.W., B.D., T.C. Writing – review & editing: H.F.W., B.D., T.C. All authors read and accepted the final version of the manuscript.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgements

All figures were created with BioRender.com. We apologize to those authors who we were unable to cite in the field of infections and cancer metabolism.

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Papers of particular interest, published within the period of review, have been highlighted as:

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- •• of outstanding interest

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