Pathogen regulatory RNA usage enables chronic infections, T-cell exhaustion and accelerated T-cell exhaustion

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Abstract

Pathogens evade or disable cellular immune defenses using regulatory ribonucleic acids (RNAs), including microRNAs and long non-coding RNAs. Pathogenic usage of regulatory RNA enables chronic infections. Chronic infections, using host regulatory RNAs and/or creating pathogenic regulatory RNAs against cellular defenses, can cause T-cell exhaustion and latent pathogen reactivations. Concurrent pathogen infections of cells enable several possibilities. A first pathogen can cause an accelerated T-cell exhaustion for a second pathogen cellular infection. Accelerated T-cell exhaustion for the second pathogen weakens T-cell targeting of the second pathogen and enables a first-time infection by the second pathogen to replicate quickly and extensively. This can induce a large antibody population, which may be inadequately targeted against the second pathogen. Accelerated T-cell exhaustion can explain the relatively short median and average times from diagnosis to mortality in some viral epidemics, e.g., COVID-19, where the second pathogen can lethally overwhelm individuals' immune defenses. Alternatively, if an individual survives, the second pathogen could induce a very high titer of antigen–antibody immune complexes. If the antigen–antibody immune complex titer quickly becomes very high, it can exceed the immune system's phagocytic capability in immuno-deficient individuals, resulting in a Type III hypersensitivity immune reaction. Accelerated T-cell exhaustion in immuno-deficient individuals can be a fundamental cause of several hyperinflammatory diseases and autoimmune diseases. This would be possible when impaired follicular helper CD4$^+$ T-cell assistance to germinal center B-cell somatic hypermutation, affinity maturation and isotype switching of antibodies results in high titers of inadequate antibodies, and this initiates a Type III hypersensitivity immune reaction with proteinase releases which express or expose autoantigens.

Keywords T-Cell Exhaustion · Accelerated T-Cell Exhaustion · Hyperinflammatory Diseases · Regulatory RNA · MicroRNA · Non-Coding RNA

Introduction

Intracellular pathogens can manipulate cellular defenses during infections. Double pathogen infections of the same cells open a door to several significant and serious possibilities, but there have been relatively few discussions of multiple pathogen infections of cells. Specific cases of multiple pathogen interactions have been reported, such as γ-herpesviruses Epstein–Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV) co-infections of immune B-cells [1]. There have been reports on epithelial cell infections by human papillomavirus (HPV) concurrent with human immunodeficiency virus (HIV), the herpes simplex viruses (HSV) 1 and 2, human cytomegalovirus (HCMV), EBV or other viruses [2]. Herpesvirus EBV and the bacteria *Helicobacter pylori* can infect the same gastric epithelial cells [3].

Before discussing multiple pathogen infections and how this benefits pathogens, there will be a summary of how pathogens are assisted by human and pathogen regulatory RNA of short and long nucleotide lengths.

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Discussion

Pathogens manipulate existing regulatory RNA, or release their own regulatory RNA

Regulatory ribonucleic acids (RNA) are not translated for protein synthesis and extensively affect many cellular operations: the shorter regulatory RNA can be classified as short non-coding RNA, including endogenous single-stranded microRNA (miRNA) and exogenous double-stranded small interfering RNA (siRNA), and are composed of 15 to 25 nucleotides (miRNA and siRNA are typically composed of 18 to 22 nucleotides) [4–7]. Cells also utilize, or can be manipulated by, intermediate nucleotide length RNA (composed of 60 to 300 nucleotides) variously classified as small nucleolar RNA (snoRNA) or small nuclear RNA (snRNA), or RNA classified as long non-coding RNA (lncRNA), composed of more than 200 nucleotides, variously classified by their origins as intergenic (a genome located between two protein-coding genes), intronic (a genome located with an intronic region of a protein-coding gene), antisense (transcribed from complementary strands), bidirectional (originating from bidirectional transcription of protein-coding genes) and enhancer (originating from enhancer regions) lncRNA [4–8]. These regulatory RNAs can assist or interfere with other RNA, and affect various phases of gene expression, including chromatin organization, transcription machinery, messenger RNA (mRNA) processing and delivery to the cellular cytoplasm, mRNA alternative splicing, mRNA half-life, and facilitated or repressed translations of mRNA to proteins and post-protein synthesis processes [4, 5]. Regulatory RNAs can also affect chemokines and cytokines, their receptors, inflammation, innate and adaptive cellular immune functionality including antigen processing and presentation, cellular cycles and cellular death (e.g., apoptosis) [4, 5, 9].

Several pathogens utilize existing host cell regulatory RNAs, or synthesize their own regulatory RNAs, including miRNAs and/or lncRNAs, to further their replication and/or evade or disable cell defenses [4, 5, 10]. Pathogens utilizing regulatory RNA include *Borrelia burgdorferi*, *Campylobacter concisus*, *Escherichia coli*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Salmonella typhimurium*, the fungal pathogen *Crytococcus neoformans*; and the protozoans *Giardia lamblia, Leishmania major, Leishmania infantum, Plasmodium falciparum, Toxoplasma gondii, Trichomonas vaginalis* and *Trypanosoma brucei.* [4, 5]. Regulatory RNA are also utilized by viruses, including DNA viruses, such as EBV, KSHV, HCMV, HSV-1, HSV-2; and RNA viruses, such as Dengue virus-2, Ebola virus (EBOV), HIV, influenza viruses, West Nile virus, and the severe acute respiratory symptom corona viruses SARS-CoV and SARS-CoV-2 [4, 5, 9].

Regulatory RNA can modify several immune defense signaling pathways

Regulatory RNA can modify several immune defense signaling pathways for numerous purposes: (1) manipulating the signaling pathway of Toll-like receptors of the innate immune system for detection of pathogen-associated molecular patterns (PAMPs) [11], (2) manipulating expression of RIG-1-like receptors that normally detect PAMPs [12], (3) manipulating inflammasome priming and activation to block detection of cellular pathogens [9, 13, 14], (4) reducing cytokines (tumor-necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-12, IL-23) and chemokines (IL-8, CCL5, CXCL11) [4, 12, 15–17], (5) manipulating expression of cytokine receptors [9], (6) manipulating expression of chemokine receptors to impair signaling [18], (7) impairing interleukin-1β secretion [4, 13], (8) manipulating antigen processing and presentation to T-cells [19], (9) impairing NK-cell and T-cell attraction by MHC class I-related chain B (MICB) [20, 21] (10) manipulating transcription factor NF-κB signaling to control gene transcription, inflammation and apoptosis [4, 22], (11) regulating C-type lectin receptors (e.g., the glycan receptors for pathogens expressing mannose, fucose, β-1,3-glucan) to control major immune cell functions (e.g., inducing T_H1, T_H2 and T_H17 cell differentiation) [18], (12) manipulating cells by blocking the innate immune system Janus kinase (JAK)/signal transducer and activators of transcription (STAT) pathway [4, 7, 23], (13) manipulating cytokine signaling through the innate immune system mitogen-activated protein kinase (MAPK) pathways [24], (14) impairing synthesis of cellular cytosolic stimulator of interferon genes (STING) protein, which is involved in detecting cytosolic DNA viruses and other intracellular pathogen infections and inducing type I interferon production [25] and (15) delaying apoptotic host cell death [4, 5, 26].

For instance, 40 SARS-CoV-2 miRNAs and their associated regulated target genes were computationally predicted and reported [4]. This study indicated that the genes targeted by SARS-CoV-2 play important roles in NF-κB and JAK/STAT signaling pathways of the host immune system [4]. Several genes can be downregulated by miRNAs to assist SARS-CoV-2 cellular infections in escaping immune system defenses [4].

Table 1 tabulates several immune defense paths that can be targeted by pathogen usage of pathogenic or host cell regulatory RNA.

Pathogenic or human regulatory RNA recognition of target mRNA and degradation

Usually, mature miRNAs recognize their target mRNAs using six to eight nucleotides at the 5' end of the miRNA [27]. In this case, a full complementary match between the

Table 1 Cellular Immune Defenses That Can Be Targeted by Pathogen Regulatory RNA Usage

1. Toll-like receptors detection of pathogen-associated molecular patterns (PAMPs)
2. Expression of RIG-1-like receptors normally detecting PAMPs
3. Inflammasome priming and activation to block detection of cellular pathogens
4. Synthesis of cytokines (TNF-α, IL-6, IL-8, IL-12, IL-23) & chemokines (CXCL11)
5. Expression of cytokine receptors to impair signaling
6. Expression of chemokine receptors to impair signaling (NK-cell and T-cell migration)
7. Secretion of inflammatory cytokines interleukin-1β and interleukin-18
8. Processing and presentation of antigens to T-cells
9. MHC class I-related chain B (MICB) attraction of NK-cells & T-cells
10. NF-κB signaling to control gene transcription and inflammatory response
11. C-type lectin receptors (e.g., regulating T_H1, T_H2 and T_H17 cell differentiation)
12. Janus kinase (JAK)—signal transducers activators of transcription (STAT)
13. Cytokine signaling through mitogen-activated protein kinase (MAPK) pathways
14. Synthesis of cellular STING protein, which is involved in detecting cytosolic DNA virus infections
15. Cell death by apoptosis blocked to enable pathogen to complete life cycles for replication

References: [4, 5, 8–12, 14–17, 19–26]

miRNA and the untranslated 3' end of the target mRNA will start mRNA degradation, and a less perfect complementary match between the miRNA and mRNA will prevent the translation of the target mRNA into a protein [27]. A targeted mRNA is inactivated utilizing a host cell's defense against double-stranded RNA, a nuclease enzyme multiprotein complex in the cytoplasm called the RNA-induced silencing complex (RISC), which utilizes the miRNA as a guide strand to degrade the targeted mRNA [27]. A target mRNA may be regulated by multiple miRNAs, and a miRNA could have hundreds of separate mRNA targets [7]. LncRNA and miRNA can also interact—lncRNAs can bind to and sponge up miRNA, lncRNA can produce miRNA after cleavage by enzymes such as Dicer and/or Drosha, and lncRNA can compete with miRNA to bind with mRNA [5].

EBV, KSHV and HCMV can evade cellular immune defenses by synthesizing and secreting miRNAs [7, 23, 28], and HSV-1 can evade cellular defenses by utilizing normal cellular miRNA production [25]. Several miRNAs bind to infected host cell signal transducer and activator of transcription (STAT) transcription factors, including STAT3 and STAT5, or bind to mRNAs to manipulate the transcription and translation of interferon-stimulated genes [7, 29]. Pathogen usage of regulatory RNAs (miRNAs and lncRNAs) has a primary goal of impeding pathogen recognition by innate immune cells (NK-cells) and adaptive immune cells (T-cells) to allow pathogen replication [7].

Interactions by which regulatory RNA usage assists intracellular pathogen infections

Multiple pathogen infections of a host can result from immunodeficiencies caused by HIV [1, 2, 30–32]. Multiple pathogen infections of the same host cells have been discussed, including an intracellular protozoan parasite interfering with a second intracellular pathogen [33]. However, there has been relatively little consideration of the possible interactions of intracellular pathogens co-infecting the same cell [33].

Herpesviruses EBV, KSHV and HCMV utilize regulatory RNAs (e.g., miRNAs), which can decrease gene expression of interferon-stimulated genes (ISG) [7]. But ISG disruption would also interfere with ISG cellular defenses targeting other pathogens infecting the cell [7]. Herpesvirus cellular defense disablements would especially affect infected B-cells, endothelial cells and epithelial cells [7], and several other pathogen infections of these cells can also be facilitated by herpesvirus miRNAs. Impairment of cellular immune defenses, such as interferon-stimulated genes, by miRNAs and/or pathogen proteins, can also enable lytic reactivation of latent intracellular pathogens [7].

Pathogen utilization of regulatory RNA during infections manipulates numerous immune defenses. Table 2 tabulates several common pathogens that use regulatory RNA during cell infections, but this table is not comprehensive.

Extracellular effects of intracellular double pathogen interactions—potentially severe outcomes including accelerated T-cell exhaustion

As previously discussed, regulatory RNA usage by a pathogen, such as miRNAs and/or lncRNAs, can enable a pathogen to evade or manipulate cellular immune defenses of cells infected by the pathogen [4, 5, 10]. Therefore, successful evasion or manipulation of the applicable immune defenses that otherwise would have targeted an intracellular pathogen for suppression or elimination can enable an intracellular pathogen to avoid elimination, replicate extensively and become a long-duration chronic infection. A long-duration (30 days or more) chronic

Table 2 Pathogens Utilizing Regulatory RNA During Infections

Disease	Pathogen	MicroRNAs & LncRNAs Used	Comments
Lyme disease	*Borrelia burgdorferi*	miRNAs	In CNS, 38 + miRNAs
Campylobacteriosis	*Campylobacter concisus*	lncRNA	Gastrointestinal tract
Cryptococcosis	*Crytococcus neoformans*	lncRNA	HIV co-infection fatal
Escherichiosis	*Escherichia coli*	lncRNA	Some strains very lethal
Gastric ulcers	*Helicobacter pylori*	lncRNA	Gastrointestinal tract
Giardia	*Giardia lamblia*	lncRNA	Gastrointestinal tract
Leishmaniasis	*Leishmania amazonensis*	lncRNA	Can be lethal if visceral
Leishmaniasis	*Leishmania donovani*	lncRNA	Can be lethal if visceral
Leishmaniasis	*Leishmania infantum*	lncRNA	Can be lethal if visceral
Leishmaniasis	*Leishmania major*	lncRNA	Non-lethal, cutaneous
Salmonella	*Salmonella typhimurium*	lncRNA	Causes food poisoning
Toxoplasmosis	*Toxoplasma gondii*	lncRNA/miRNA	Infects > 30% population
Trichimoniasis/Trich	*Trichomonas vaginalis*	lncRNA	Sexually transmitted
Trypanosomiasis	*Trypanosoma brucei*	lncRNA	Sleeping sickness
Tuberculosis (TB)	*Mycobacterium tuberculosis*	lncRNA/miRNA	Kills 1.5 million/year
IM,BL,DLBCL,MS	EBV	lncRNA/miRNA	44 + miRNAs used
Karposi's sarcoma	KSHV	lncRNA/miRNA	Cuts interferons α/β
Cytomegalovirus	HCMV	lncRNA/miRNA	Infects 50–100% humans
Hepatitis C	HCV	lncRNA/miR-122	In 150,000,000
Herpes simplex 1	HSV-1	lncRNA/miRNA	Infects > 50% humans
Herpes simplex 2	HSV-2	lncRNA/miRNA	Globally prevalent
Dengue fever	Dengue virus-2	lncRNA/miRNA	Fatal if untreated
Influenza	Influenza A viruses	lncRNA/miRNA	Some strains can be lethal
West Nile fever	West Nile virus	lncRNA/miRNA	CNS cases can be fatal
AIDS	HIV-1	miRNA	Increases TB fatalities
Ebola virus	EBOV	lncRNA/miRNA	Can be very lethal
SARS	SARS-CoV	lncRNA/miRNA	Was lethally dangerous
COVID-19	SARS-CoV-2	lncRNA/miRNA	Variants keep miRNA

CNS central nervous system, *TB* tuberculosis; *IM* infectious mononucleosis, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, MS multiple sclerosis, *EBV* Epstein–Barr virus, *KSHV* Karposi sarcoma-associated herpesvirus, *HCMV* human cytomegalovirus, *HCV* Hepatitis C virus, *HSV*-1 Herpes simplex virus 1, *HSV*-2 Herpes simplex virus 2, *HIV* human immunodeficiency virus, *EBOV* Ebola virus, *SARS* severe acute respiratory syndrome, *CoV* coronavirus

References: [4, 5, 7, 10, 25, 28, 31, 32, 34–37]

intracellular pathogen infection that expresses significant pathogenic antigens can also create a long-duration chronic exposure of these pathogenic antigens to lymphocytes, such as T-cells, that are targeting these antigens [38–40]. Infected cells would express the pathogenic antigen on a major histocompatibility complex (MHC) for recognition by the T-cell's main receptor and also eventually express inhibitory ligands for the T-cell's inhibitory receptors [38–40]. T-cell exhaustion will ultimately result from the long-duration pathogenic antigen exposures to their targeting T-cells [38–40].

A first pathogen could assist a second pathogen with potentially severe outcomes by accelerating T-cell exhaustion of T-cell defenses that would normally target a second pathogen infection [41, 42]. Accelerated T-cell exhaustion with insufficient T-cell responses against the second

pathogen could enable a first time infection by the second pathogen to replicate extensively and dangerously in a host.

One already observed result of T-cell exhaustion may be the high mortality rates seen in some viral epidemics where the second pathogen infection is immunologically novel and can achieve continuous and long-duration high-antigen titers and T-cell exhaustion and/or T-cell suppression. Before considering accelerated T-cell exhaustion further, T-cell exhaustion will be summarized.

T-Cell exhaustion summarized

CD4^{+} and CD8^{+} T-cell exhaustion implies that essential T-cell functions are significantly reduced as a result of

chronic cancers or chronic and/or latent pathogen infections [40]. T-cell exhaustion occurs due to continuous long-duration antigen exposures [38–40]. T-cell exhaustion has been observed during latent infections by various protozoan, fungal, viral or bacterial pathogens, including *Toxoplasma gondii* [43], hepatitis B virus and hepatitis C virus [44, 45].

Even continuous low levels of antigens can cause T-cell exhaustion, which includes metabolic exhaustion and mitochondrial dysfunctions that impair T-cell effector functions and numerically decrease T-cells by inhibiting their proliferation [39, 46]. T-cell exhaustion severity increases with higher antigen titers and/or by longer time exposures to exposed antigens [39, 40].

T-Cell exhaustion effects on CD4^{+} T-Cells and/or CD8^{+} T-cells

T-cell exhaustion impairs pathogen suppression by CD4^{+} T-cells and CD8^{+} T-cells [45]. Several T-cell receptors contribute to T-cell exhaustion, such as co-stimulatory receptors and inhibitory receptors [45]. A larger number of multiple inhibitory receptors co-expressed during T-cell exhaustion correspond to a higher T-cell exhaustion severity [45]. T-cell exhaustion is made possible by several T-cell inhibitory receptors, such as the lymphocyte activation gene 3 protein (LAG-3), CD244, CD160, the T-cell immunoglobulin domain and mucin domain-containing protein 3 (TIM-3), the cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and frequently the programmed cell death protein 1 (PD-1) [45, 47, 48]. The severity of T-cell exhaustion corresponds to the numbers of inhibitory receptors expressed, where viral infections associated with severe T-cell exhaustion typically induce T-cells to express high numbers of inhibitory TIM-3 receptors [47].

It should also be noted that inhibitory receptors are also expressed during T-cell activation or differentiation states, and inhibitory receptor expressions are not exclusively associated with T-cell exhaustion caused by chronic infections, or even functional impairment, at least in the case of CD8^{+} T-cells [49]. It is also important to note that in T-cell activation or differentiation states or both states, the presence of certain stimulations, in CD8^{+} T-cell experiments, was able to produce increased expressions of T-cell inhibitory receptors within 24 h and greatly increase their expressions over 48 to 72 h [49].

SARS-CoV-2 effects depend on T-cell exhaustion of CD4^{+} T-cells and CD8^{+} T-cells

There have been assertions that SARS-CoV-2 induces both exhausted and senescent phenotypes of CD8^{+} T-cells and that an increased severity of COVID-19 is linked to the extent

of T-cell exhaustion and T-cell senescence in each patient [50]. However, the primary importance of T-cell exhaustion induced by SARS-CoV-2 was established by observations of CD4^{+} and CD8^{+} T-cell abnormalities having higher CD127 and PD-1 inhibitory receptor expressions, which were seen in surviving COVID-19 patients having long COVID [51]. CD8^{+} T-cells were extracted from the blood of COVID-19 patients, and antibody blockades of the PD-1 receptors on their in vitro CD8^{+} T-cells almost normalized the phenotype of these T-cells, and virtually restored normal effector T-cell functions, even against SARS-CoV-2 [51].

The blockade of the exhaustion-associated inhibitory PD-1 receptors, and the virtually normalized effector T-cell functions, suggests that T-cell exhaustion, especially PD-1 inhibitory receptor binding with its programmed cell death ligand 1 (PD-L1), is the main COVID-19 effect on T-cells, and T-cell exhaustion is a primary influence on severe COVID-19 outcomes and long COVID-19 [51]. Another effect seen in the COVID-19 patients was increased miRNA expressions (e.g., miR-15a-5p which targets PD-1 expression, miR-16a-5p, miR-28-5p) within their exhausted CD8^{+} T-cells and higher miRNA expressions (e.g., miR-15a-5p, miR-16a-5p, miR-28-5p) within their exhausted CD4^{+} T-cells [51].

T-Cell regulatory RNA usage and CD8^{+} T-cell exhaustion

T-cells have widespread regulatory RNA usage, and CD8^{+} T-cells have higher miRNA (e.g., miR-15a-5p, miR-155) expression during cancers and viral infections (e.g., HIV, SARS-CoV-2), which control CD8^{+} T-cell proliferation during cancers and infections and inhibit T-cell responses to inflammatory cytokines [51, 52]. CD8^{+} T-cell proliferation is controlled by transcription factor Fosl2, a member of the activator protein-1 (AP-1) transcription factors in T-cells [52]. Higher expression of miR-155 induces less transcription factor Fosl2 and results in increased expressions of inhibitory receptors on CD8^{+} T-cells, thereby controlling T-cell exhaustion development and maintenance during chronic infections or cancers [52]. Several T-cell miRNAs and lncRNAs control CD8^{+} T-cell survival and development genes, and CD8^{+} T-cell exhaustion is linked to a number of CD8^{+} T-cell miRNAs (e.g., miR-15, miR-17, miR-28, miR-29, miR-142, miR-150, miR155, miR198) and lncRNAs (e.g., lncRNA lnc-Tim3, lncRNAcd244) [51, 53].

T-cell exhaustion for a first pathogen can accelerate exhaustion in T-Cells targeting a second pathogen

T-cell exhaustion for one pathogen can assist creation of T-cell exhaustion in T-cells targeting a second pathogen [41, 54]. Direct and indirect pathways exist for double

pathogen infections to initiate T-cell exhaustion [53–57]. T-cell exhaustion can be caused by increased miRNAs (e.g., miR-155), by higher numbers of inhibitory receptors and by desensitization of T-cells' co-stimulatory receptors [46, 52, 53, 55, 56]. This has been observed in *T. gondii* infections, which result in increased expressions of inhibitory PD-1 receptors on T-cells and which also result in increased expressions of the ligand PD-L1 on cells infected by *T. gondii* [38]. Higher inhibitory receptor expressions on T-cells and elevated expressions of their corresponding ligands on infected cells can enable activation of the inhibitory receptors on T-cells. This could involve binding with ligands expressed on cells concurrently infected by pathogens such as *T. gondii* and another intracellular pathogen, causing exhaustion of CD8+ T-cells targeting either pathogen.

Accelerated T-cell exhaustion—severe outcomes for second pathogen infections

One possibility from T-cell exhaustion is that a chronic and/or latent first pathogen infection lasting several weeks can accelerate a severe T-cell exhaustion for a second pathogen. This could involve inducing T-cell expressions of numerous inhibitory receptors, such as PD-1, and by inducing infected host cell expressions of inhibitory ligands, such as PD-L1, for binding to the inhibitory receptors on the T-cells. A second distinct pathogen infection, such as a virulent pathogen that creates large antigen titers, can benefit from the pro-exhaustion cytokines, and/or expression of host cell inhibitory ligands by the same infected cell, and accelerate a T-cell exhaustion for the second pathogen [41, 42].

One practical consequence of accelerated T-cell exhaustion may be elevated mortality rates for specific viral epidemics, in which the second pathogen infection quickly achieves T-cell exhaustion, and fatally overwhelms an individual's immune system [51, 58, 59].

T-cell exhaustion has been repeatedly linked to COVID-19 cases with severe outcomes and/or mortality [51, 58, 59]. T-cell exhaustion can be considered a primary contributor to COVID-19 patient fatalities, particularly by CD8+ T-cell exhaustion [58–61]. But T-cell exhaustion can degrade the functions of both CD8+ and CD4+ T-cells. This also applies to follicular helper CD4+ T-cells, located primarily in lymph node and spleen germinal centers, where these CD4+ T-cells have essential roles in enabling antibody affinity maturation, isotype switching, generating memory B-cells and in enabling B-cell differentiation into immunoglobulin (antibody)-producing plasma cells [62]. Accelerated T-cell exhaustion would have an especially severe effect on novel first infections by the second pathogen. This would be particularly true if germinal center follicular helper CD4+ T-cell functions are impaired, and immunoglobulins (antibodies) from B-cells are numerically decreased or qualitatively inadequate

in affinity selection/maturation from somatic hypermutation to suppress the second pathogen [63].

Such inadequate B-cell populations have been extensively seen in severe cases of COVID-19. In these cases, patients have higher population fractions of the less-effective membrane-bound IgM immunoglobulin on B-cells, in contrast with higher population fractions of the more developed membrane-bound IgG immunoglobulins on B-cells seen in control patients or patients with mild cases [61]. These observations of isotype differences in the immunoglobulin expression by B-cells suggest follicular helper CD4+ T-cell interactions with B-cells in germinal centers did not promote adequate isotype switching and somatic hypermutation and affinity maturation of immunoglobulins targeting the SARS-CoV-2 virus. This could be the result of CD4+ T-cell exhaustion in these severe cases [63].

Accelerated T-cell exhaustion contribution to the initiation of the hyperinflammatory diseases and possibly autoimmune diseases

Some papers have linked hyperinflammatory disease initiation (e.g., the Kawasaki diseases, multisystem inflammatory syndrome) and several autoimmune disease initiation with abnormally high levels of antibodies secreted by B-cells and high titers of antigen–antibody immune complexes that could not be promptly phagocytized in some individuals [54, 64]. Major T-cell dysfunctions can also cause B-cell impairments which result in abnormally high numbers of ineffective antibodies [63]. Specifically, accelerated T-cell exhaustion by its inhibition of follicular helper T-cells needed by conventional B-cells can cause impaired B-cells and their production of abnormally high numbers of ineffective antibodies.

As explained, the hyperinflammatory diseases could be initiated by pathogens that evade T-cell control and thus require antigen neutralization by a very large number of antibodies. This could create a very large number of antigen–antibody immune complexes which cannot be quickly phagocytized by an individual's transient or permanent immuno-deficient immune system [54]. The steps by which antigen–antibody immune complexes can initiate hyperinflammatory diseases through a Type III hypersensitivity immune reaction in transiently or permanently immuno-deficient individuals having weak phagocytosis have already been outlined [54]. This is also supported by a 2020 study of intensive care cases of COVID-19, where it was observed that a T_H1 (cell-mediated immunity) response evolved into a T_H2 humoral immunity (antibody) response [65]. This response would then escalate into a Type III hypersensitivity immune reaction with deposition of antigen–antibody immune complexes in the walls of blood vessels to generate a severely inflammatory systemic vasculitis [65].
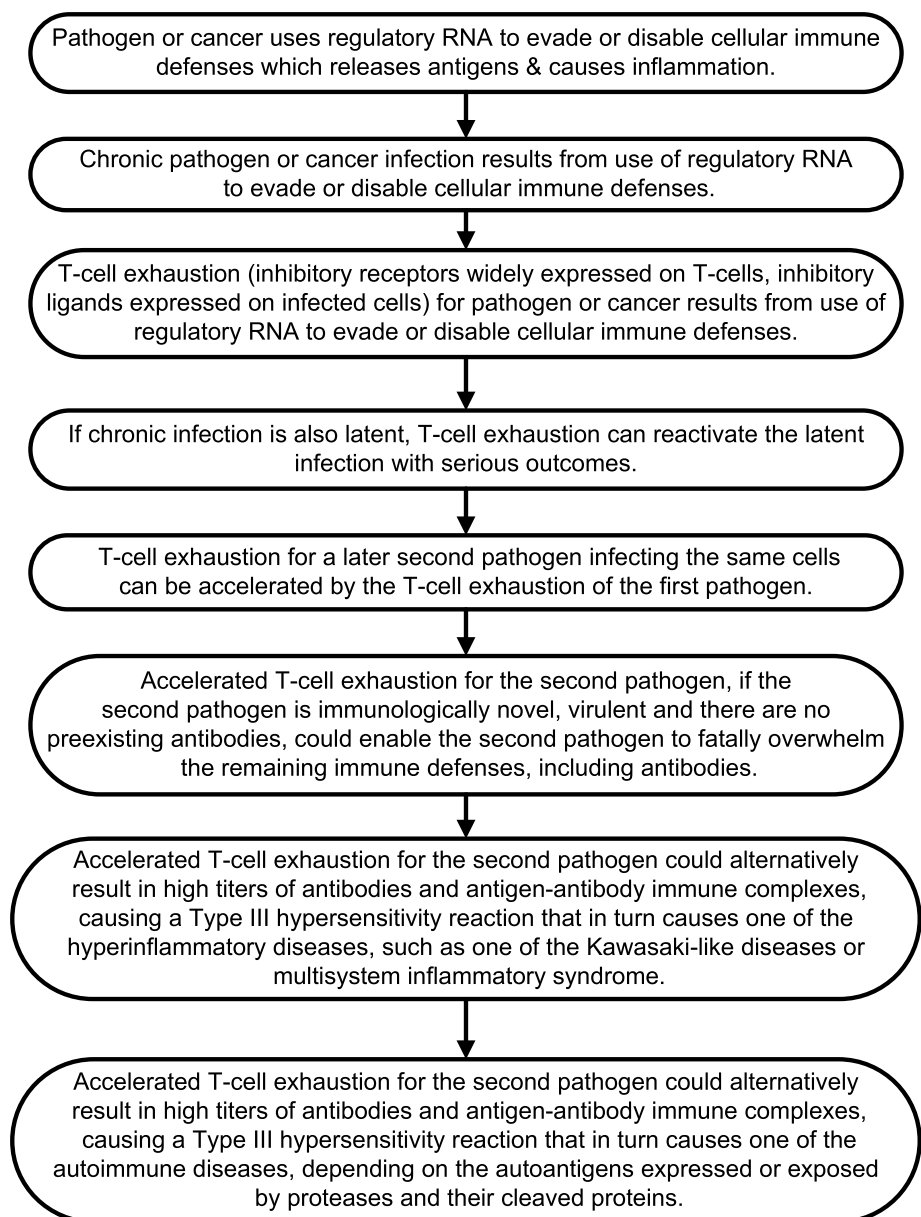
Furthermore, hyperinflammatory diseases including multisystem inflammatory syndrome (MIS) typically occur two to four weeks after a SARS-CoV-2 infection [66]. This delay could be due to the time required for antibody production, antigen–antibody immune complexes to become excessive and the time required for a Type III hypersensitivity reaction to initiate a hyperinflammatory disease [54].

The development of autoimmune diseases is an alternative outcome from a high titer of antigen–antibody immune complexes which cannot be quickly phagocytized in transiently or permanently immuno-deficient individuals [64, 67]. This can cause a Type III hypersensitivity immune reaction with proteinase (protease) creation of autoantigens [64, 67]. Therefore, it is quite plausible that accelerated T-cell exhaustion in immuno-deficient individuals can be a major factor in initiating acute hyperinflammatory diseases, including various types of Kawasaki disease or multisystem inflammatory syndrome, or a major factor in initiating a chronic autoimmune disease [54, 64, 67–70].

Accelerated T-cell exhaustion could potentially prevent an effective antibody defense to be implemented by B-cells and T-cells against the second pathogen, especially if the infection by the second pathogen is a first-time infection. Such a short time could be fatal or have a severe outcome, if an accelerated T-cell exhaustion for the second pathogen is too soon for follicular helper CD4$^+$ T-cells to assist B-cells in germinal centers in effectively targeting the second pathogen with antibodies using affinity maturation and antibody isotype switching [63].

Fig. 1 Flowchart showing the main steps in how pathogen or cancer usage of regulatory RNA can cause chronic infections and T-cell exhaustion, which in turn can cause reactivation of a latent chronic infection and/or cause accelerated T-cell exhaustion for a second pathogen that infects the same cells

Pathogen or cancer uses regulatory RNA to evade or disable cellular immune defenses which releases antigens & causes inflammation.

↓

Chronic pathogen or cancer infection results from use of regulatory RNA to evade or disable cellular immune defenses.

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T-cell exhaustion (inhibitory receptors widely expressed on T-cells, inhibitory ligands expressed on infected cells) for pathogen or cancer results from use of regulatory RNA to evade or disable cellular immune defenses.

↓

If chronic infection is also latent, T-cell exhaustion can reactivate the latent infection with serious outcomes.

↓

T-cell exhaustion for a later second pathogen infecting the same cells can be accelerated by the T-cell exhaustion of the first pathogen.

↓

Accelerated T-cell exhaustion for the second pathogen, if the second pathogen is immunologically novel, virulent and there are no preexisting antibodies, could enable the second pathogen to fatally overwhelm the remaining immune defenses, including antibodies.

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Accelerated T-cell exhaustion for the second pathogen could alternatively result in high titers of antibodies and antigen-antibody immune complexes, causing a Type III hypersensitivity reaction that in turn causes one of the hyperinflammatory diseases, such as one of the Kawasaki-like diseases or multisystem inflammatory syndrome.

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Accelerated T-cell exhaustion for the second pathogen could alternatively result in high titers of antibodies and antigen-antibody immune complexes, causing a Type III hypersensitivity reaction that in turn causes one of the autoimmune diseases, depending on the autoantigens expressed or exposed by proteases and their cleaved proteins.

In less severe cases, the host may be able to survive the accelerated T-cell exhaustion regarding the second pathogen and a faster-paced second pathogen infection from the weakened T-cell functionality, but the first pathogen infection remains. If the first pathogen creates a latent infection, T-cell exhaustion regarding the first pathogen can assist the first pathogen's reactivation [7, 38]. Such reactivations can potentially cause very severe symptoms, e.g., encephalitis, hepatitis or myocarditis, in the case of reactivated protozoan parasites, such as *T. gondii*, regardless of whether the second pathogen infection completely ends [41, 71].

Figure 1 illustrates a flowchart showing the main steps in how pathogen or cancer usage of regulatory RNA can cause chronic infections and T-cell exhaustion, which in turn can cause reactivation of a latent chronic infection and/or cause accelerated T-cell exhaustion for a second pathogen that infects the same cells. Accelerated T-cell exhaustion

for a novel first-time infection by the second pathogen can quickly produce high numbers of pathogens which can overwhelm the antibody defenses to kill the individual. However, if the individual's immune defenses are not overwhelmed and the individual survives, but the phagocytic capability of the host immune system is overwhelmed by a high number of antigen–antibody immune complexes, a Type III hypersensitivity immune reaction can occur in immuno-deficient individuals [54, 64, 68–70]. Depending on the second pathogen, this can either initiate a hyperinflammatory disease or alternatively develop into an autoimmune disease from the autoantigens expressed or exposed by the proteinases (proteases) released during the Type III hypersensitivity immune reaction [54, 64, 68–70].

Figure 2 illustrates a graphical time line comparison of conventional T-cell exhaustion for a first pathogen and accelerated T-cell exhaustion for a second pathogen. It shows

Fig. 2 Time line comparison of conventional T-cell exhaustion for a first pathogen and accelerated T-cell exhaustion for a second pathogen

Conventional T-cell Exhaustion Time Line (not drawn to scale)

|					
Time span from host infection by first pathogen until beginning of T-cell exhaustion for T-cells targeting first pathogen is ~ 15 days. Exhaustion fully developed in ~ 30 days.					
First pathogen infection of host cells begins	Antigens for the first pathogen are released or expressed by the pathogen, host cell or immune cells	Because of first pathogen, pro-exhaustion cytokines are secreted by the host cell and/or immune cells	In days, inhibitory receptors are expressed by T-cells targeting first pathogen	Infected host cells express ligands for the inhibitory receptors of T-cells	Ligands activate the T-cell inhibitory receptors - exhaustion of T-cells targeting the first pathogen begins

Second pathogen infection of the same host cells begins	Antigens for the second pathogen are released or expressed by the pathogen, host cell or immune cells	Because of first pathogen, pro-exhaustion cytokines were already secreted by host cell and/or immune cells (less time needed)	In days, inhibitory receptors are expressed by T-cells targeting the second pathogen	Infected host cells already express ligands for the inhibitory receptors of T-cells (less time needed)	Ligands activate the T-cell inhibitory receptors - exhaustion of T-cells targeting the second pathogen begins
Time span from host cell infection by second pathogen until beginning of T-cell exhaustion for T-cells targeting second pathogen is significantly less than 15 days. Exhaustion for second pathogen is fully developed in significantly less than 30 days.					

Accelerated T-cell Exhaustion Time Line (not drawn to scale)

Fig. 3 Conceptual graph of how pathogen or cancer usage of regulatory RNA can cause chronic infections and T-cell exhaustion, which in turn can cause reactivation of a latent chronic infection and/or cause accelerated T-cell exhaustion for a second pathogen
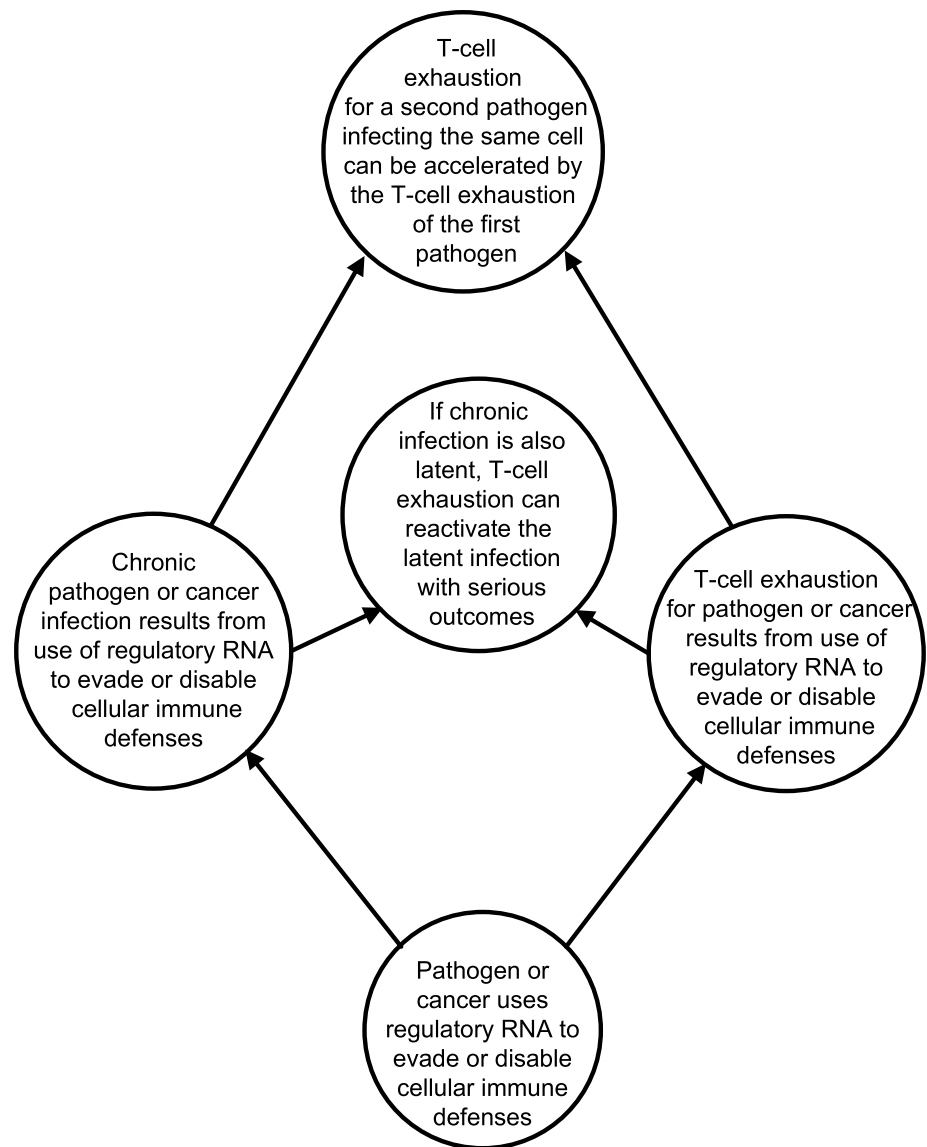
two steps that can contribute to a faster accelerated T-cell exhaustion for T-cells targeting the second pathogen, compared to the time required for conventional T-cell exhaustion for T-cells targeting the first pathogen.

Figure 3 is a conceptual graph of how pathogen or cancer usage of regulatory RNA can lead to chronic infections and T-cell exhaustion, which in turn can lead to reactivation of a latent chronic infection and/or lead to accelerated T-cell exhaustion for a second pathogen.

Conclusion

Pathogens use regulatory RNA, either their own or existing human regulatory RNA, including miRNA or lncRNA, for their own benefit, to assist replication in a host cell and/or host cell immune defense manipulation. Regulatory RNA use by intracellular pathogens can create chronic infections resulting in lymphocyte exhaustion including T-cell exhaustion regarding the pathogens. Regulatory RNA use by a pathogen can also assist a second pathogen infection of the same cell. Interactions between two intracellular pathogens can have significant consequences, such as an accelerated T-cell exhaustion for a second pathogen. T-cell exhaustion has the plausible consequence that a long-duration chronic and/or latent first pathogen infection can induce enough cytokine secretions to cause T-cells to express various inhibitory receptors and can induce infected cells to express several inhibitory ligands to bind with the T-cell inhibitory receptors. An immunologically novel second pathogen infection, especially a pathogen that produces large antigen titers, could then evade T-cell defenses if there was accelerated exhaustion of T-cells targeting the second pathogen. Accelerated T-cell exhaustion can occur when the first and second

pathogens infect the same cells and the second pathogen can reuse the infected cells' already expressed inhibitory ligands. Accelerated T-cell exhaustion may fundamentally explain the relatively short median and average times from diagnosis to mortality observed for viral epidemics, e.g., COVID-19, where in a significant number of fatal cases the second pathogen infection quickly overwhelms an individual's remaining immune defenses. It is also plausible that accelerated T-cell exhaustion is a major factor in the pathogenesis of several hyperinflammatory diseases and autoimmune diseases in immuno-deficient individuals. This could cause insufficient follicular helper CD4$^+$ T-cell assistance to germinal center B-cell somatic hypermutation, affinity maturation and isotype switching of antibodies. This could result in a Type III hypersensitivity immune reaction and a resulting proteinase creation of autoantigens.

Data availability Not applicable.

Declarations

Conflict of interest The author has no relevant financial or non-financial interests to disclose.

Ethical approval No ethical approval was required as this is a review article with no original research data.

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