Inflammation During Virus Infection: Swings and Roundabouts

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Abstract

Inflammation constitutes a concerted series of cellular and molecular responses that follow disturbance of systemic homeostasis, by either toxins or infectious organisms. Leukocytes modulate inflammation through production of secretory mediators, like cytokines and chemokines, which work in an autocrine and/or paracrine manner. These mediators can either promote or attenuate the inflammatory response and depending on differential temporal and spatial expression play a crucial role in the outcome of infection. Even though the objective is clearance of the pathogen with minimum damage to host, the pathogenesis of multiple human pathogenic viruses has been suggested to emanate from a dysregulation of the inflammatory response, sometimes with fatal consequences. This review discusses the nature and the outcome of inflammatory response, which is triggered in the human host subsequent to infection by single-sense plus-strand RNA viruses. In view of such harmful effects of a dysregulated inflammatory response, an exogenous regulation of these reactions by either interference or supplementation of critical regulators has been suggested. Currently multiple such factors are being tested for their beneficial and adverse effects. A successful use of such an approach in diseases of viral etiology can potentially protect the affected individual without directly affecting the virus life cycle. Further, such approaches whenever applicable would be useful in mitigating death and/or debility that is caused by the infection of those viruses which have proven particularly difficult to control by either prophylactic vaccines and/or therapeutic strategies using specific antiviral drugs.

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3.1 Introduction

The mammalian immune system has evolved arsenal and strategies to make a distinction between microbes that are either beneficial or benign or bad, an integral part of which is differential treatment of “self” and “non-self.” Whereas recognition of “self” as “non-self” can cause autoimmunity, the converse results in microbial colonization. In fact the human gut does harbor multiple variety of microbes as natural part of the biological ecosystem (Scarpellini et al. 2015). The recognized non-self are counteracted by adaptive and innate effectors of the immune system, using dedicated cells and biochemicals, which attempt to restrict the growth and impede colonization by the pathogen. The innate response is nonspecific, while the secondary adaptive response is specific for the pathogen or closely related species. The cellular component includes innate immune cells like the monocytes/macrophages, neutrophils, and natural killer (NK) cells and adaptive immune cells like B- and T-lymphocytes, which coordinate for an effective response. Cytokines are a dedicated group of biochemicals involved in this coordination and include interferons (IFNs), interleukins (ILs), and chemokines that are responsible for synchronizing the initiation, regulation, and termination of an immune response. A group (~100) of small polypeptides (<20 kDa) produced predominantly although not exclusively by immune cells like macrophages and lymphocytes, cytokines are secreted out exerting their function by engaging respective cell-surface receptors and depending on biological function are labeled as either pro-inflammatory (PIC) or anti-inflammatory (AIC) cytokines (Turner et al. 2014). On the one hand, several cytokines are functionally redundant, and on the other hand, some cells can express receptors for multiple cytokines.

3.2 The Positive-Sense Single-Stranded RNA Viruses

Viruses with positive-sense single-stranded RNA as genome can either be enveloped (Togaviridae, Flaviviridae, and Coronaviridae) or non-enveloped (Astroviridae, Caliciviridae, and Picornaviridae), and several from either group cause severe human pathology (Fields et al. 2013). Entry into human host can be by diverse means including mucosal contact (gut in enteroviruses) or vectorial inoculation (e.g., in dengue and JEV) or parenteral blood transfer (e.g., hepatitis C virus). Immobilization by interaction with extracellular matrix components like glycosaminoglycan is followed by tropism determinant cognate receptor-mediated entry (Chen et al. 1997; Olenina et al. 2005; Tan et al. 2013). In enveloped viruses, the envelope fuses with the endosomal membrane, while non-enveloped viruses breach the membrane of either the cell or the endosome using specific cofactors, ultimately
releasing viral genome into the host cytosol (Kumar et al. 2018; Plemper 2011). A culmination of the following steps results in direct translation of the genomic RNA to produce a polyprotein, which is cleaved by virus-derived and host-origin proteases to yield the multiple structural and nonstructural proteins (Fields et al. 2013). The structural features of the genomic RNA facilitating translation can be, e.g., a 5’ cap and a poly-A tail (Alphavirus, Togaviridae; Coronavirus, Coronaviridae) or a 5’ cap without a poly-A tail (Flavivirus, Flaviviridae) or an internal-ribosome entry site (IRES) serving for ribosome recruitment without a poly-A tail (hepatitis C virus) or an IRES with a poly-A tail (Picornaviridae, Astroviridae, Caliciviridae). After multiple rounds of translation, ribosome loading stops and the genomic RNA is replicated by virus-encoded RNA-dependent RNA polymerase (RdRp), in endoplasmic reticulum (ER) membrane-associated replication complexes (RCs) during which a double-stranded RNA intermediate is produced followed by its asymmetric transcription to produce multiple copies of plus-sense genomic RNA. The new genomic RNAs are packaged into virion particles that exit the cell by either secretory pathway or plasma-membrane budding (for enveloped viruses) or by cell lysis (for non-enveloped viruses) (Bird and Kirkegaard 2015; Pornillos et al. 2002).

### 3.3 Infection, Intimation, and Initiation of Inflammation

Although viruses can replicate in multiple types of cells, the pathological outcome manifests in only one or a few specific cell/tissue types. Independent of organismal entry site, the likeliest primary encounter of a virus is with mononuclear-phagocytic cells like monocytes, macrophages (Mφ), and dendritic cells (DCs). Mφ and DCs are tissue-localized cells constituting the first line of cellular defense, which when infected can undertake antiviral steps in addition to “informing” the other effectors of the innate and adaptive immune system (Pohl et al. 2007; Ginhoux and Jung 2014). Activated DCs shift to lymph nodes, process viral antigen, and “present” or display it for clonal expansion of cognate lymphocytes population. Mφ, which can be either tissue-resident or differentiated from afferent monocytes postinfection, play a more regulatory role and are important determinants of the outcome of the inflammatory response (Ginhoux and Jung 2014; Mercer and Greber 2013; Hou et al. 2012; Schulz et al. 2012). Tissue-resident Mφ, which are a distinct population from monocyte-derived ones, include microglial cells in CNS, liver Kupffer cells, skin Langerhans cells, etc. (Davies et al. 2013)

Monocytes/Mφ (and many other cell types) express molecular detector proteins called pattern recognition receptors (PRRs), specialized for interacting with signature motifs on microbe-derived molecules, termed as pathogen-associated molecular pattern (PAMP). Viral PAMPs include double-stranded (dsRNA) RNA (replication-intermediate formed during replication) and 5’-ppp (uncapped genomic RNA polymerized by de novo replication). Cellular PRRs specific for these include toll-like receptors (TLRs) like TLR3 (dsRNA) and RIG-I-like receptors (RLRs) like RIG-I, MDA5 (dsRNA, 5’-ppp end on RNA) (Jensen and Thomsen 2012). Nod-like receptors or NLRs form another class of cytosolic PRRs that can detect virus
infection, albeit in an indirect manner (Takeuchi and Akira 2010; Ichinohe et al. 2013). Physical engagement with PAMPs activates the respective PRRs, stimulating alterations in conformation of these sensors that allow them to interact with adapter molecules mediating the assembly of multi-protein complexes called inflammasome, in parallel to activating the expression of cytokine genes coding for type-1 interferons (IFNs) and NFκB target genes (Kawai et al. 2005; Pichlmair and Reis e Sousa 2007; Chen and Ichinohe 2015; Seth et al. 2005). Secreted type-I IFNs attach specific receptors, in a paracrine or autocrine manner, thereby activating the expression of many interferon-sensitive genes (ISGs) with diverse functions that confer antiviral property to their activity (Schneider et al. 2014; Schoggins and Rice 2011). ISGs include PRR-coding genes producing a feed-forward loop and aggravating inflammation. In parallel, NFκB enhances expression of pro-inflammatory genes like TNF-α, IL-1β, COX2, IL6, IL-12p40, or IL-12 besides components of NLRP3 (Tak and Firestein 2001; Bauernfeind et al. 2009). Upon assembly the NLRP3 inflammasome catalyzes caspase-1 activation, a protease which slices the precursor form of pleiotropic pro-inflammatory cytokines like IL-1β and IL-18 generating their active secreted forms (Garlanda et al. 2013; Biet et al. 2002). IL-1β potentiates the antiviral response by multiple ways in addition to inducing expression of type-I IFNs and ISGs in DCs (Ben-Sasson et al. 2011; Aarreberg et al. 2018). Chemokines (chemotactic cytokines) flag/point to the site of infection by a concentration gradient, attracting leukocytes like neutrophils, monocytes, and lymphocytes, subsequently activating them to release more cytokines thereby amplifying the inflammatory response (Sokol and Luster 2015; Ley 2014). Among these IL-12 and IL-2 (produced predominantly by DCs) have crucial immunomodulatory functions. IL-12 attracts CD4+ T-helper (Th) cells influencing their differentiation into IFN-γ secreting Th1 cells in addition to augmenting the cytotoxic activity of CD8+ T cells and NK cells (Athie-Morales et al. 2004; Henry et al. 2008). IL-2 on the other hand increases NK-cell sensitivity to IL-12 by receptor upregulation (Wang et al. 2000). IFN-γ which in contrast to type-I IFNs is produced exclusively by immune cells (T and NK cells) has pleiotropic antiviral effect including the capacity to polarize existing or newly recruited Mφ to M1 phenotype (Hu and Ivashkiv 2009; Verreck et al. 2004). Mφ either resident or monocyte-derived can acquire either an M1 or an M2 phenotype differing in ontology, phenotype, and secretome, with unidirectional plasticity from M1 to M2 (Halstead et al. 2010; Guiducci et al. 2005; Smith et al. 2016). M1-Mφ promotes a Th1 immune response which is necessary for resolution of infection, while the M2-Mφ endorses tissue repair following inflammation, suggesting that a premature skew in abundance of M2-Mφ at the expense of M1-Mφ would limit viral clearance leading to chronic infection and prolonged inflammatory response (Klenerman and Hill 2005). An emerging concept in modulation of inflammation involves the role of bacterial surface components like lipopolysaccharide on concurrent viral infection (Smith et al. 2016; Wilks and Golovkina 2012). Alterations in gut microbiome have been reported and potential influences this might have on disease outcome have been suggested (Preveden et al. 2017; Banks et al. 2015).

Though it is difficult to ascertain the number of asymptomatic infections for any given virus, the percentage of symptomatic infection vis-à-vis asymptomatic ones is
often a multivariate variable, being known for only a few. For example, only 1 among 4 individuals infected with DENV shows febrile symptoms. This suggests a success for the antiviral immune mechanisms in the majority of individuals. Animal studies using gene knockout models have given evidence of this efficacy for many viruses (Suthar et al. 2010; Samuel and Diamond 2005; Lazear et al. 2011; Deonarain et al. 2004; Burdeinick-Kerr et al. 2007). In case of humans, these information are complicated by differential efficacy of these pathways, protecting or predisposing individuals under the influence of genotype, environment, etc. (Paalani et al. 2011; Mitchell and Aneshensel 2016; Liu and Taioli 2015) Besides, there are few studies that indicate potential influence of medication or noninfectious ailments or societal stress on the outcome of infection through an influence on the immune system (Mehrbd et al. 2014; Gilbert et al. 2005; Htun et al. 2015; Jean et al. 2007).

3.3.1 Liver Damage Due to Hepatitis C Virus and Dengue Virus Infection

HCV and DENV infection can cause liver damage through a chronic and acute infection regime, respectively (Samanta and Sharma 2015; Axley et al. 2018). Liver as an organ is characterized by a high capacity to regenerate; however, chronic injury/scarring can lead to fibrosis, steatosis, or even hepatocellular carcinoma resulting in liver failure (Forbes and Newsome 2016). Hepatocytes constitute two-thirds of all liver cells and are associated with all major liver functions besides playing a crucial role in innate immune signaling (Kmiec 2001; Zhou et al. 2016). Hepatocytes are permissible to both HCV and DENV, the latter being reported to additionally infect Kupffer cells (Chang et al. 2003; Zehender et al. 1997; Boisvert et al. 2001; Caussin-Schwemling et al. 2001; Goutagny et al. 2003; Marianneau et al. 1999; de Macedo et al. 2006; Huerre et al. 2001). In acute infection, the major damage is through apoptosis following direct infection of these cells, whereas establishment of a chronic infection usually causes a sustained inflammation leading to infiltration of polymorphonuclear cells and lymphocytes (Huerre et al. 2001; Lim et al. 2014; Masalova et al. 2017; Deng et al. 2008; Bala et al. 2012; Sung et al. 2012). Irrespective of the virus, these infections augment PIC levels in the liver with drastic consequences. For example, hepatocyte apoptosis caused by either direct infection or effect of PICs like TNF-α generates apoptotic bodies which when engulfed by Kupffer cells induce the latter to release more PIC providing a positive loop toward inflammation (Canbay et al. 2003a; Burdette et al. 2012; Negash et al. 2013; Shimizu et al. 2005). Cytokines like TGFβ and PDGF thus released can “activate” hepatic stellate cells initiating a metabolic transformation in them to secrete more extracellular matrix that deposits as fibrotic tissue in addition to converting them into smooth muscle fibers (Canbay et al. 2003b; Hernandez-Gea and Friedman 2011). In addition to virus infection-induced changes, bacterial LPS can also potentially “activate” hepatic stellate cells (Brun et al. 2005). HCV infection skews macrophage population to M2 phenotype restraining virus clearance while promoting hepatic stellate cell activation mediated by TGFβ (Saha et al. 2016). Additionally, in
case of infection by both of these viruses, immune suppression mediated by AIC like IL10 is implicated for virus persistence and augmented pathology (MacDonald et al. 2002; Sugimoto et al. 2003). In fact higher levels of cytokines like IL10 and IL17 have shown positive correlation with liver damage (Fernando et al. 2016). Liver steatosis, a clinical feature common among HCV patients, is the result of intracellular ROS in hepatocytes (Okuda et al. 2002; Perlemuter et al. 2002). Irrespective of the stimulus, a continuous cycle of injury and repair involving hepatocytes strongly prognoses the growth of hepatocellular carcinoma, DNA damage by augmented levels of ROS and RNS level playing a critical role (Bishayee 2014; Capone et al. 2010).

3.3.2 CNS Damage Due to JEV, WNV, Zika Virus Infection, and Sometimes DENV Too

The central nervous system (CNS) is physiologically isolated from the rest of the body by a specialized selectively permeable barricade called as the blood–brain barrier (BBB), which allows passage to selected metabolites, respiratory gases, and an extremely limited repertoire of circulatory tissue cells. This isolation is necessary for protection of low regeneration capacity neuronal cells from systemic inflammation, which can also upset the structural and functional plasticity of neurons that is dependent on cytokine signaling (Arnett et al. 2001; Gougeon et al. 2013; Mason et al. 2001; Fischer et al. 2011; Brissoni et al. 2006). The CNS can have either neuronal or non-neuronal glial cells; the latter provide vital functional support and include microglia (macrophage-like immune cells), oligodendrocytes (which provide insulation for neurons), and astrocytes (responsible for repair of damaged neuronal tissue). Microglial cells have immunomodulatory function in suppressing a pathogenic inflammation (Seitz et al. 2018). Multiple viruses in the +ve-ssRNA genome group, including Coronavirus, Picornavirus, Flaviviridae, and Togaviridae, cause opportunistic infection of CNS (Bergmann et al. 2006; Koyuncu et al. 2013; Fletcher and McKeating 2012).

In the absence of a direct admission route, these viruses undergo limited replication in peripheral tissue, before entering through either peripheral nerves or BBB microvasculature or CNS infiltrating leukocytes (functioning as the proverbial “Trojan horse”) (Koyuncu et al. 2013; Jeha et al. 2003). A feature common here is a breach of the vascular endothelial barrier at varying locations, e.g., BBB for JEV/WNV, blood retinal barrier for ZIKV, and endothelial barriers in lungs/peritoneum for DENV. Breach in BBB is more common for some viruses (e.g., WNV, JEV, ZIKAV, poliovirus) correlating with fatality. Interestingly, WNV and JEV have been suggested to cause BBB disruption from inside the CNS (Li et al. 2015; Verma et al. 2009). Still other reports suggest infected endothelial cells to secrete PICs that disrupt the BBB (Chen et al. 2014; Chang et al. 2017; Roach and Alcendor 2017). The tissue damage is caused from a combination of either direct neuronal infection which activates intrinsic apoptosis or a hyperactive inflammatory response mediated by PICs or CD8+ cytotoxic T cells (CTLs) (Wang et al.
Infected neurons secrete chemokines that attract leukocytes like monocytes and lymphocytes (Klein et al. 2005; Shrestha and Diamond 2004; Glass et al. 2005; Kelley et al. 2003; Lim et al. 2011; Bardina et al. 2015; Durrant et al. 2015; Shrestha et al. 2008). The relation between a “good” and “bad” immune response is, however, very tricky when it comes to the CNS. Migration of CTLs expressing receptors for chemokines like CCL2, CCL3, CCL4, CCL5, CXCL9–11, as well as its timing with respect to establishment of infection, seems to play a crucial role in virus eradication and survival (Wang et al. 2003; Shrestha and Diamond 2004; Diamond et al. 2003; Sussman et al. 1989; Getts et al. 2010; Nansen et al. 2000; Chen et al. 2004; Liu et al. 2001; Zink et al. 2001; Winter et al. 2004). The CTLs exert their antiviral role by inducing cell death through either a perforin-dependent or Fas-FasL-mediated mechanism (Rossi et al. 1998; Shrestha and Diamond 2007). In addition to CTLs, other PICs might also induce direct cell death in neurons (Dhanwani et al. 2012; Olmo et al. 2017; Baer et al. 2016; Kumar et al. 2010).

### 3.3.3 Dengue Infection-Associated Vascular Leakage

Dengue virus causes a febrile illness with can turn fatal after a subsidence of the fever. The severity emanates from leakage of fluid from the blood vessels by a breach of the vascular endothelium. Circulating in four serotypes, severe disease is mostly associated with secondary infection by a serotype different from the one causing primary infection. Neutralizing antibodies generated during primary infection incompletely neutralize the secondary infection virus and instead promote their uptake by monocytes, by a phenomenon called antibody-dependent enhancement or ADE (Katzelnick et al. 2017; Dejnirattisai et al. 2016). Notwithstanding a primary or secondary infection, the pathological symptoms are considered to be the result of an unbridled host immune response (Basu and Chaturvedi 2008; Rothman 2011).

DENV infects a variety of cells including monocytes, dendritic cells (skin Langerhans cells), macrophages (Kupffer cells), and vascular endothelial cells, expectedly leading to PIC secretion (Wu et al. 2000; Jessie et al. 2004; Tolfvenstam et al. 2011). Different studies have reported a positive association of DHF/DSS development with extraordinarily augmented levels of different PICs that include macrophage migration inhibitory factor (MIF), IFN-α, TNF-α (Green et al. 1999; Kurane et al. 1993; Huang et al. 2000; Chen et al. 2006). Although multiple reports have suggested correlation between specific PIC level and plasma leakage, the mechanism is still elusive and limited to association studies (Priyadarshini et al. 2010; Her et al. 2017; Sehrawat et al. 2018; Malavige et al. 2012). Interestingly however, multiple similar association studies have suggested a positive association between levels of IL10 (an AIC) and severe/critical symptoms related to dengue infection (Malavige et al. 2013; Tsai et al. 2013; Flores-Mendoza et al. 2017). IL10, produced by multiple immune cells, suppresses immune response through upregulation of SOCS (suppressor of cytokine signaling) function and downregulation of IFN activity, the result being decreased T-cell cytotoxicity (Halstead et al. 2010;
Katzelnick et al. 2017; Tsai et al. 2013; Azeredo et al. 2001; Brasier et al. 2012. The augmentation of IL10 level has been suggested to emanate from monocytes infected by the ADE route with additional influence from high viremia (Tsai et al. 2014). IL10 is a dominant regulator of the immune system that can prolong pathogen clearance through a subversion of the immune response (Couper et al. 2008).

### 3.3.4 Lung Infection and Pathology by Coronaviruses

Coronavirus infections are usually benign causing self-limiting mild flu-like symptoms. However, recent outbreaks involving, e.g., severe acute respiratory syndrome coronavirus (SARS-CoV), which jumped species barrier through acquisition of minor genome mutations, have projected them as potentially severe human pathogens (Guan et al. 2004). Spread through aerosols, SARS-CoV primarily infect lung cells triggering an often fatal inflammatory response clinically called acute respiratory distress syndrome (ARDS) that starts with severe hypoxia, pulmonary edema progressing to systemic inflammation, and failure of multiple organs, culminating in high rate of mortality (Peiris et al. 2003; Lew et al. 2003; Tsushima et al. 2009; Farcas et al. 2005). Although evidence suggests that SARS-CoV can infect multiple cell types, lung type-II pneumocytes and ciliated epithelial cells constitute primary sites of virus replication, consequent to which these cells undergo apoptotic and/or necrotic death attracting innate immune cells and activating them to secrete PICs (Sims et al. 2005; Chow et al. 2004; Nicholls et al. 2003). The nature of inflammation following SARS-CoV infection is characterized by a prompt production of PICs through immediate NFκB activation and a delayed expression of type-I IFN genes (Shi et al. 2014; Kong et al. 2009; Wong et al. 2004). Severity of symptoms correlates positively with IL-6 levels while exhibiting negative correlation with that of IL-8 and TGFβ (Zhang et al. 2004). As observed with many other viral pathogenesis models, macrophage polarization culminating in preferential enrichment of M2-macrophages has been suggested to be responsible for SARS-CoV pathogenesis (Page et al. 2012). SARS-CoV infection is also associated with hemophagocytosis or engulfment of different types of blood cells by histiocytes (a class within macrophages), which is a clinical marker of immune system hyper-activation (Usmani et al. 2013).

### 3.4 Therapeutic Approaches Using Cytokine

Traditionally prophylactic or therapeutic strategies for combating viral pathogenesis are designed using vaccines or directly acting antivirals (DAA), respectively. But for many viruses there is no clinically approved product to serve in either approach. Since the etiology of critical pathogenic symptoms is often associated with an unbridled host inflammatory response, there have been suggestions and attempts to control the harmful effects through modulation of key inflammatory signaling (D’Elia et al. 2013). However, a holistic approach to complete “cure” should
probably involve investigations to provide support to both approaches simultaneously. Only ribavirin or the same combined with pegylated IFN-α was the therapeutic strategy for controlling HCV infection, before the advent of high efficacy DAAs. Similarly IFN-λ and glucocorticoids, both of which can consolidate the BBB, have been suggested as therapeutics for combating viral diseases that disrupt this barrier (Rhen and Cidlowski 2005; Daniels et al. 2014; Lazear et al. 2015; Wang et al. 2004; Blecharz et al. 2010; Fabene et al. 2008). Likewise, administration of PICs like CCL7 and IL17A has shown efficacy in increasing survival of mice experimentally infected with WNV (Bardina et al. 2015; Acharya et al. 2016). In dengue patients, however, meddling with either promoter or inhibitor of inflammation has been suggested as possible approaches (Tsai et al. 2013; Goh et al. 2014; Callaway et al. 2015; Ji et al. 2005; Dinarello 2011). Small molecules that can influence the function of the NLRP3 inflammasome have also been projected as potential therapies for CHIKV and can be tested against dengue as well (Chen et al. 2017; Coll et al. 2015; Hottz et al. 2013). Alternative approaches using pharmaceuticals that indirectly mitigate the pathological effect without interfering with inflammation have also been discussed (Olmo et al. 2017; Grip and Janciauskiene 2009; Reynolds and Miller 1989; Thomas and Grossberg 2009; Giguere and Tremblay 2004; Raemer et al. 2009).

3.5 Concluding Remarks

An ability to suppress innate immunity pathways is common among viruses that cause severe human diseases. Nonetheless modulating inflammation needs extreme caution, in order to reduce potential cytotoxicity of the administered therapeutic. Therefore, there is a need to go beyond association studies to generate a clearer picture of the exact role that inflammation plays in viral pathology, which can then assist in developing therapeutic strategies that tinker with inflammation.

Conflict of Interest The author declares that they have no competing interests.

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