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**Phantom of the inflammasome in the gut: Cytomegalovirus**

Arslan F *et al*. Cytomegalovirus in the gut

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**Abstract**

Cytomegalovirus (CMV) is frequently detected in inflammatory bowel tissue, especially in corticosteroid-refractory patients, and it has been blamed for adverse outcomes. However, the first acquisition of CMV does not involve the colon. In particular in the colonic mucosa, which evolved due to the gut microbial relationship, CMV promotes inflammation *via* recruited monocytes and not through replication in resident macrophages. Whether CMV is the last straw in the process of mucosal inflammation, a doomed agent, or an innocent bystander is a difficult question that remains elusive. With this work, we will try to review the relationship between intestinal mucosa and CMV in the framework of basic virological principles.

**Key words:** Cytomegalovirus; Ulcerative colitis; Gancyclovir; Inflammatory bowel disease

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**Core tip:** We will here draw an analogy between the cytomegalovirus and the hero of the Gaston Leroux’s “The Phantom of the Opera” novel, with the intestinal mucosa as the opera building. We aimed to emphasize the viral pathogenesis process to understand the elusive character of cytomegalovirus in the inflammatory bowel diseases.

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**INTRODUCTION**

Gaston Leroux’s “The Phantom of the Opera” novel features a Paris opera building haunted by a phantom, an ugly genius of a man who had devoted his life to music and desperate love. The dungeons and tunnels that he created led to dynamic movements, enabling him to appear and disappear like a phantom all over the opera building. The protagonist may be interpreted as creative or destructive throughout the novel. He is a great composer and he makes clever devices, while strangling people with a Punjab lasso at the same time. What circumstances push the protagonist to lash out with violence and destruction? While that question is of interest to literary critics, we will here draw an analogy between the cytomegalovirus (CMV) and the hero of the aforementioned novel, with the intestinal mucosa as the opera building. For that, however, we must look at the basic viral pathogenesis before any deeper analysis.

**VIRUSES**

Viruses are nonliving particles, and their replication is entirely dependent on the ability to infect the cells of their hosts[1]. This obligate dependence should suggest that every conditional change must be of some interest to the host as well as the virus. The first step in viral infection is entry into the target cell *via* specific receptors that provide tropism and fusion to the cells. Glycoprotein complexes act as an entry and fusion activator[2]. The second step in viral infection is replication and the production of new virions to spread[3]. After this step, there is another important component to complete infection: the immune response. A nonspecific role is played by the host cell’s intrinsic defenses: apoptosis, autophagy, RNA silencing, and antiviral proteins, while pathogen-specific responses harness the innate and adaptive immunity process[4]. Intracellular detection of viral infection occurs *via* receptors (Toll-like receptors, RIG, MDA) on cellular compartments (cytoplasm, plasma, and endosomal membranes)[5-7]. Following recognition, virus-infected cells and uninfected sentinel cells (dendritic cells, macrophages, natural killer cells) produce interferons in response to cellular products. Cytokines, both proinflammatory and anti-inflammatory, and chemokines are complementary elements in the ongoing inflammation[8]. Encoding cytokine homologs to block receptors and soluble cytokine receptors to neutralize cytokines, or altering the cytokine signaling pathway, are the preferred targets in herpesvirus survival strategies[9]. This diversity in the virus-host interaction causes different inflammatory stimulations that differ in clinical presentation. In particular, non-cytopathic viruses do not stimulate inflammation and may persist over a long duration. However, encoding at least one regulator of intrinsic/innate defenses is an essential component of viral pathogenesis.

**CYTOMEGALOVIRUS**

CMV is a member of the β-herpesvirus subfamily. The virion consists of a 235-kb double-stranded linear DNA core in an icosahedral nucleocapsid, enveloped by a proteinaceous matrix. Nearly 200 of its genes encode proteins, but some express only noncoding RNAs, including approximately 14 microRNAs[10]. The genes with functions beyond transcription and proliferation necessitate a look at the human-CMV interaction from a co-evolutionary point of view. For instance, some virally encoded proteins show homology with the human chemokine receptor family[9]. Thus, this lifelong interaction may have a positive effect on our immunity, which can be revealed through animal studies[11].

Worldwide CMV seroprevalence has increased from 40% to 99%, and population-based studies have shown that young children are an important source of CMV for childbearing women[12,13]. A survey has also demonstrated that primary school-age children continue to shed CMV in urine and live viremia at higher rates when compared with older children[14]. Moreover, 18-30 year-old college students shed CMV in saliva and urine without antibody response[15]. Notably, neither children nor college students experienced any clinical conditions. In contrast, mother-to-child transmission can occur even in the womb or during birth, as well as through breastfeeding. The association between fetal infection or frailty and human-CMV interactions from the beginning to the end of life is being investigated by researchers[16].

In light of the latest data, platelet-derived growth factor receptor alpha (PDGFR-α) has been identified as an entry receptor that forms a heterotrimeric complex with gH/gL/gO in fibroblasts[17]. Additionally, while cell line-based in vitro studies show some proteins, such as neuropilin 2, act as epithelial/endothelial receptors, in real life most of these receptors are found inside the immune cells[18,19]. Fibroblasts, a type of stromal cells, endogenously express PDGFR. In a previous report, perivascular stromal cells were found to be susceptible to CMV infection in an ulcerative colitis murine model *via* PDGFR-β and CXC chemokine ligand 12[20]. Additionally, in another investigation, more PDGFRα+ cells (smooth muscle cells) were found in the distal than in the proximal colon, which may be related to the frequency of CMV colitis rather than cell involvement[21]. If the inflammasome affects stromal and not epithelial cells, it may be inferred that CMV participates in the ongoing process at least *via* its immunomodulatory effect. In contrast, it is interesting to think that the lifelong persistence of the virus and the protective and dormant structure of the epithelial/endothelial cells may interact in terms of the infectious process.

CMV persists (latency) over the host’s lifetime in specific progenitor cells that undergo reprogramming from hemopoietic stem cells[22,23]. This latency is broken intermittently through viral reactivation that is controlled by the adaptive immunity[24]. Moreover, monocyte recruitment to the relevant locations is the main mechanism in clinical manifestations of CMV[25]. In particular in the colonic mucosa, which evolved due to the gut microbial relationship, CMV promotes inflammation *via* recruited monocytes and not through replication in resident macrophages[26]. Although monocyte recruitment is essential in the effective control and elimination of viral, bacterial, fungal, and protozoal infections, it is worth questioning whether the intruder, here CMV, can alter the infection dynamics on its own. As mentioned before, we postulate that CMV plays a role akin to “The Phantom of the Opera” in the mucosa, with a balance between creative and destructive behaviors. Like the Phantom, CMV has gained a bad reputation, especially where inflammatory diseases are concerned, whereas a viral genome study revealed a higher ebola virus (EBV) load in mucosal samples[27]. Both the CMV and EBV encode a viral ortholog of cellular interleukin-10 that impedes inflammatory responses and modulates host immunity[28].

The rumors about the tortures inflicted by the Phantom show similarities with the existence of CMV and inflammations flaring in the mucosa. Be they a sign of direct or indirect pathogenicity, the first acquisition of CMV does not involve the colon. Whether CMV is the last straw in the process of mucosal inflammation, a doomed agent, or an innocent bystander is a difficult question that remains elusive. Thus, another important question follows on: to treat or not to treat?

CMV is frequently detected in inflammatory bowel tissue, especially in corticosteroid-refractory patients, and it has been blamed for adverse outcomes. Ganciclovir treatment is preferred by some clinicians, with or without other immunomodulatory drugs. Since clinical relevance and treatment efficacy have not been determined precisely, an accepted approach is not available. Many observational studies and a few metanalyses have been carried out on the effect that ganciclovir treatment has on CMV reactivation in inflammatory bowel diseases[29]. Unfortunately, these uncontrolled and selection bias studies have not delivered adequate conclusions. Colectomy rates show high variability in both ganciclovir-treated and untreated groups.

**CONCLUSION**

Researchers should focus the novel basic scientific data about the host and CMV interaction and re-review the clinical definitions, and treatment effectiveness of antivirals in the light of the evolutionary perspective.

**REFERENCES**

1 **Sun X**, Ilca SL, Huiskonen JT, Poranen MM. Dual Role of a Viral Polymerase in Viral Genome Replication and Particle Self-Assembly. *MBio* 2018; **9**: pii: e01242-18 [PMID: 30279282 DOI: 10.1128/mBio.01242-18]

2 **Sathiyamoorthy K**, Chen J, Longnecker R, Jardetzky TS. The COMPLEXity in herpesvirus entry. *Curr Opin Virol* 2017; **24**: 97-104 [PMID: 28538165 DOI: 10.1016/j.coviro.2017.04.006]

3 **Morrison KM**, Beucler MJ, Campbell EO, White MA, Boody RE, Wilson KC, Miller WE. Development of a Primary Human Cell Model for the Study of Human Cytomegalovirus Replication and Spread within Salivary Epithelium. *J Virol* 2019; **93**: pii: e01608-18 [PMID: 30404806 DOI: 10.1128/JVI.01608-18]

4 **Landolfo S**, De Andrea M, Dell'Oste V, Gugliesi F. Intrinsic host restriction factors of human cytomegalovirus replication and mechanisms of viral escape. *World J Virol* 2016; **5**: 87-96 [PMID: 27563536 DOI: 10.5501/wjv.v5.i3.87]

5 **Lee N**, Wong CK, Hui DS, Lee SK, Wong RY, Ngai KL, Chan MC, Chu YJ, Ho AW, Lui GC, Wong BC, Wong SH, Yip SP, Chan PK. Role of human Toll-like receptors in naturally occurring influenza A infections. *Influenza Other Respir Viruses* 2013; **7**: 666-675 [PMID: 23552014 DOI: 10.1111/irv.12109]

6 **Luangsay S**, Ait-Goughoulte M, Michelet M, Floriot O, Bonnin M, Gruffaz M, Rivoire M, Fletcher S, Javanbakht H, Lucifora J, Zoulim F, Durantel D. Expression and functionality of Toll- and RIG-like receptors in HepaRG cells. *J Hepatol* 2015; **63**: 1077-1085 [PMID: 26144659 DOI: 10.1016/j.jhep.2015.06.022]

7 **Tengroth L**, Millrud CR, Kvarnhammar AM, Kumlien Georén S, Latif L, Cardell LO. Functional effects of Toll-like receptor (TLR)3, 7, 9, RIG-I and MDA-5 stimulation in nasal epithelial cells. *PLoS One* 2014; **9**: e98239 [PMID: 24886842 DOI: 10.1371/journal.pone.0098239]

8 **Chaaitanya IK**, Muruganandam N, Sundaram SG, Kawalekar O, Sugunan AP, Manimunda SP, Ghosal SR, Muthumani K, Vijayachari P. Role of proinflammatory cytokines and chemokines in chronic arthropathy in CHIKV infection. *Viral Immunol* 2011; **24**: 265-271 [PMID: 21830898 DOI: 10.1089/vim.2010.0123]

9 **Scarborough JA**, Paul JR, Spencer JV. Evolution of the ability to modulate host chemokine networks via gene duplication in human cytomegalovirus (HCMV). *Infect Genet Evol* 2017; **51**: 46-53 [PMID: 28315475 DOI: 10.1016/j.meegid.2017.03.013]

10 **Crough T**, Khanna R. Immunobiology of human cytomegalovirus: From bench to bedside. *Clin Microbiol Rev* 2009; **22**: 76-98, Table of Contents [PMID: 19136435 DOI: 10.1128/CMR.00034-08]

11 **Smithey MJ**, Venturi V, Davenport MP, Buntzman AS, Vincent BG, Frelinger JA, Nikolich-Žugich J. Lifelong CMV infection improves immune defense in old mice by broadening the mobilized TCR repertoire against third-party infection. *Proc Natl Acad Sci U S A* 2018; **115**: E6817-E6825 [PMID: 29967140 DOI: 10.1073/pnas.1719451115]

12 **Staras SA**, Flanders WD, Dollard SC, Pass RF, McGowan JE Jr, Cannon MJ. Cytomegalovirus seroprevalence and childhood sources of infection: A population-based study among pre-adolescents in the United States. *J Clin Virol* 2008; **43**: 266-271 [PMID: 18778968 DOI: 10.1016/j.jcv.2008.07.012]

13 **Mussi-Pinhata MM**, Yamamoto AY, Aragon DC, Duarte G, Fowler KB, Boppana S, Britt WJ. Seroconversion for Cytomegalovirus Infection During Pregnancy and Fetal Infection in a Highly Seropositive Population: "The BraCHS Study". *J Infect Dis* 2018; **218**: 1200-1204 [PMID: 29868783 DOI: 10.1093/infdis/jiy321]

14 **Amin MM**, Bialek SR, Dollard SC, Wang C. Urinary Cytomegalovirus Shedding in the United States: The National Health and Nutrition Examination Surveys, 1999-2004. *Clin Infect Dis* 2018; **67**: 587-592 [PMID: 29471326 DOI: 10.1093/cid/ciy143]

15 **Huang Y**, Guo X, Song Q, Wang H, Yu H, Zhang Y, Qiao E, Xue W, Li X, Zhuang S, Wei F, Li T, Ge S, Wu T, Xia N, Zhang J. Cytomegalovirus Shedding in Healthy Seropositive Female College Students: A 6-Month Longitudinal Study. *J Infect Dis* 2018; **217**: 1069-1073 [PMID: 29294037 DOI: 10.1093/infdis/jix679]

16 **Araújo Carvalho AC**, Tavares Mendes ML, Santos VS, Tanajura DM, Prado Nunes MA, Martins-Filho PRS. Association between human herpes virus seropositivity and frailty in the elderly: A systematic review and meta-analysis. *Ageing Res Rev* 2018; **48**: 145-152 [PMID: 30391341 DOI: 10.1016/j.arr.2018.10.009]

17 **Wu K**, Oberstein A, Wang W, Shenk T. Role of PDGF receptor-α during human cytomegalovirus entry into fibroblasts. *Proc Natl Acad Sci U S A* 2018; **115**: E9889-E9898 [PMID: 30275317 DOI: 10.1073/pnas.1806305115]

18 **Martinez-Martin N**, Marcandalli J, Huang CS, Arthur CP, Perotti M, Foglierini M, Ho H, Dosey AM, Shriver S, Payandeh J, Leitner A, Lanzavecchia A, Perez L, Ciferri C. An Unbiased Screen for Human Cytomegalovirus Identifies Neuropilin-2 as a Central Viral Receptor. *Cell* 2018; **174**: 1158-1171.e19 [PMID: 30057110 DOI: 10.1016/j.cell.2018.06.028]

19 **Schellenburg S**, Schulz A, Poitz DM, Muders MH. Role of neuropilin-2 in the immune system. *Mol Immunol* 2017; **90**: 239-244 [PMID: 28843905 DOI: 10.1016/j.molimm.2017.08.010]

20 **Matsumura K**, Nakase H, Kosugi I, Honzawa Y, Yoshino T, Matsuura M, Kawasaki H, Arai Y, Iwashita T, Nagasawa T, Chiba T. Establishment of a novel mouse model of ulcerative colitis with concomitant cytomegalovirus infection: in vivo identification of cytomegalovirus persistent infected cells. *Inflamm Bowel Dis* 2013; **19**: 1951-1963 [PMID: 23839229 DOI: 10.1097/MIB.0b013e318293c5bf]

21 **Lu C**, Huang X, Lu HL, Liu SH, Zang JY, Li YJ, Chen J, Xu WX. Different distributions of interstitial cells of Cajal and platelet-derived growth factor receptor-α positive cells in colonic smooth muscle cell/interstitial cell of Cajal/platelet-derived growth factor receptor-α positive cell syncytium in mice. *World J Gastroenterol* 2018; **24**: 4989-5004 [PMID: 30510374 DOI: 10.3748/wjg.v24.i44.4989]

22 **Zhu D**, Pan C, Sheng J, Liang H, Bian Z, Liu Y, Trang P, Wu J, Liu F, Zhang CY, Zen K. Human cytomegalovirus reprogrammes haematopoietic progenitor cells into immunosuppressive monocytes to achieve latency. *Nat Microbiol* 2018; **3**: 503-513 [PMID: 29588542 DOI: 10.1038/s41564-018-0131-9]

23 **Krishna BA**, Poole EL, Jackson SE, Smit MJ, Wills MR, Sinclair JH. Latency-Associated Expression of Human Cytomegalovirus US28 Attenuates Cell Signaling Pathways To Maintain Latent Infection. *MBio* 2017; **8**: pii: e01754-17 [PMID: 29208743 DOI: 10.1128/mBio.01754-17]

24 **Goodrum F**. Human Cytomegalovirus Latency: Approaching the Gordian Knot. *Annu Rev Virol* 2016; **3**: 333-357 [PMID: 27501258 DOI: 10.1146/annurev-virology-110615-042422]

25 **Shi C**, Pamer EG. Monocyte recruitment during infection and inflammation. *Nat Rev Immunol* 2011; **11**: 762-774 [PMID: 21984070 DOI: 10.1038/nri3070]

26 **Dennis EA**, Smythies LE, Grabski R, Li M, Ballestas ME, Shimamura M, Sun JJ, Grams J, Stahl R, Niederweis ME, Britt WJ, Smith PD. Cytomegalovirus promotes intestinal macrophage-mediated mucosal inflammation through induction of Smad7. *Mucosal Immunol* 2018; **11**: 1694-1704 [PMID: 30076393 DOI: 10.1038/s41385-018-0041-4]

27 **Lopes S**, Andrade P, Conde S, Liberal R, Dias CC, Fernandes S, Pinheiro J, Simões JS, Carneiro F, Magro F, Macedo G. Looking into Enteric Virome in Patients with IBD: Defining Guilty or Innocence? *Inflamm Bowel Dis* 2017; **23**: 1278-1284 [PMID: 28617757 DOI: 10.1097/MIB.0000000000001167]

28 **Young VP**, Mariano MC, Tu CC, Allaire KM, Avdic S, Slobedman B, Spencer JV. Modulation of the Host Environment by Human Cytomegalovirus with Viral Interleukin 10 in Peripheral Blood. *J Infect Dis* 2017; **215**: 874-882 [PMID: 28453840 DOI: 10.1093/infdis/jix043]

29 **Pillet S**, Pozzetto B, Roblin X. Cytomegalovirus and ulcerative colitis: Place of antiviral therapy. *World J Gastroenterol* 2016; **22**: 2030-2045 [PMID: 26877608 DOI: 10.3748/wjg.v22.i6.2030]

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