

HSHV-HIV, not just molecular interaction, but also interfere with the fate-Re “Claudin-2 downregulation by KSHV infection is involved in the regulation of endothelial barrier function”

Chunhong Di¹, Xiaobo Wang¹, Yutao Yan²✉, Lei Yang²✉

1. Affiliated Hospital, Hangzhou Normal University, 126 Wenzhou St., Hangzhou 310015, Zhejiang, China;
2. School of Medicine, Hangzhou Normal University, 16 Xuelin St. Hangzhou 310018, Zhejiang, China.

✉ Corresponding authors: **Yutao Yan, M.D., Ph.D.**, School of Medicine, Hangzhou Normal University, 16 Xuelin St. Hangzhou Zhejiang 310018. Email: 20130070@hznu.edu.cn Tel: (86)571-28867302 **Lei Yang, M.D., Ph.D.**, School of Medicine, Hangzhou Normal University, 16 Xuelin St. Hangzhou Zhejiang 310018. Email: yanglei62@hznu.edu.cn Tel: (86)571-28865010

© Ivyspring International Publisher. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY-NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>). See <http://ivyspring.com/terms> for full terms and conditions.

Received: 2017.04.13; Accepted: 2017.07.10; Published: 2017.07.18

Abstract

Co-infection of Kaposi sarcoma-associated herpesvirus (KSHV) and human immunodeficiency virus (HIV) was able to prolong the survival of patients with AIDS, but the underlying mechanisms are still elusive. Different from previous hypothesis such as the role of KSHV on cell transformation, Tan *et al* (J Cutan Pathol 2014; 41: 630–639. doi:10.1111/cup.12332) pointed out a novel insight that claudin-2 is involved in the prolonged survival of KSHV-HIV infected patients by increasing the transendothelial barrier function. Further, this report identified new model to study molecular interactions, especially DNA-RNA interaction.

Key words: Kaposi sarcoma-associated herpesvirus, human immunodeficiency virus

Introduction

Kaposi sarcoma (KS), manifested mainly by dark purple skin and mouth nodules, is caused by the infection of Kaposi sarcoma-associated herpesvirus (KSHV) [1]. KS, designated as an AIDS-defining cancer, has been one of the first recognized HIV-related diseases since early 1980s [2]. Epidemiologic and skin cancer care studies indicate that co-infection of KSHV and HIV interfere with the prognosis of aids patients in comparison with patients infected solely with KSHV or HIV, in which KS patients infected successively with HIV will have a prolonged survival than other AIDS patients (HIV mono-infection). For example, without highly active antiretroviral therapy (HAART), 93% of KSHV-HIV co-infected patients can survive longer than 3 years, while less than 28% of AIDS patients survive longer

than 2 years [3-5], the involved mechanisms may be interesting to be defined. Previous studies were focused on the roles of KSHV in transformation of host cells roughly by interactions between components of KSHV and host cells. Flore *et al.*, for the first time, identified the KSHV-induced transformation, in which infection of KSHV in human primary endothelial cells stimulates long-term proliferation and survival, this transformation is also evidence by KSHV related Multicentric Castleman disease (MCD) [6-8]. Another possibility regarding the prolonged survival in concurrent KSHV-HIV patients is about the T cell response as what Dr. Tan characterized [9]. Featured Th2 response in KS patients synergizes with predominant Th1-Th2 switch in AIDS patients, which will ameliorate the pathologic

impact of the individual infections [10, 11].

Tan *et al.* [9] investigated the potential underlying mechanisms by microarray, and identified three hundred and forty-three differentially expressed genes, including claudin-2 [9]. Further investigation demonstrated that knockdown of claudin-2 in cultured endothelial cells enhances barrier function by altering the charge selectivity, but not the size selectivity. This study may shed some novel mechanistic insights underlying the prolonged survival of KSHV-AIDS patients. Claudin-2 was the first channel-forming claudin identified with important roles in cation permeability (especially cation Na⁺ permeability), by thus, regulates epithelial barrier function or endothelial barrier function, which is the featured marker for related inflammation [12]. For example, intensive investigations identified the role of claudin-2 in the onset and development of inflammatory bowel diseases (mainly gut microbe related diseases) by compromising the transepithelial barrier function [13] and pulmonary inflammation by regulating alveolar cell permeability [14]. On the contrary, the enhanced barrier by claudin-2 deficiency may limit further bacterial or viral penetration and infection [15].

In vivo, endothelial monolayers override on the extracellular matrix (ECM), and ECM is made up of very thin basement membrane on thick interstitial matrix. The interactions between monolayers and ECM are crucial for the homeostasis in vascular endothelium and endothelial barrier function [16]. Many different molecules are involved in the regulation of endothelium-ECM interactions, for example, integrins play important roles for the interaction of endothelial cells with the matrix, therefore, for endothelial barrier function [17], evidenced by the study in which treatment of cells with the synthetic peptide Gly-Arg-Gly-Asp-Ser (GRGDS), which competes with the integrin RGD binding domain of laminin, vitronectin, collagen and fibronectin, caused cell rounding and cell detachment from the matrix [18]. Besides integrins, the claudin family is composed of more than 20 molecules and endothelial cells are particularly rich in claudins 4, 5 and 16 [19, 20]. Tight junction permeability is significantly influenced by the type(s) of claudin present or absent in the endothelial cells, for example, pore-forming claudin2 is normally very low expressed in endothelial cells, which is important for the maintenance of endothelial barrier function [21]. Further, by the interaction with ECM, claudin-2 overexpression can facilitate the metastasis of breast cancer [22].

To make the data from Dr. Tan's lab more valuable, it may be better to construct the KSHV-HIV

co-infection cellular and animal model, then to specify the function of claudin-2 in biological process. Further, the study of the effect of KSHV-HIV co-infection on the fate of infected cells, or of patients, in the meantime, provided a novel model to study KSHV-HIV interaction, or DNA-RNA interaction. KSHV decreases the expression of toll-like receptor 4 (TLR4) [23], however, HIV infection stimulates its expression [24]. Infection of KSHV can interfere with the expression of TLR4 induced by HIV infection, further sensing the presence of LPS [25]. Plus, KSHV can inhibit the recruitment of mononuclear leukocyte [26], which can be induced by HIV [27]. However, synergistic biological functions also stay in the corner. The KSHV ORF50-encoded reactivation and transcriptional activator (RTA) interacts synergistically with HIV-1 Tat protein in the transactivation of HIV-1 LTR, leading to increased cellular susceptibility to HIV infection [28]. In short, the study of KSHV-HIV interaction may reveal many other biological phenomena and functions.

The research of Dr. Tan opened a novel niche to study the prolonged survival in KSHV-HIV concurrent infection, but there are still many challenges to draw a conclusion. For example, Dr. Tan should study how claudin-2 determines the cell fate during KSHV-HIV co-infection? What are the interactions between claudin-2 and other factors such as T cell responses? Further, it will be of significance to explore the potential of claudin-2 as an interventional target.

Acknowledgments

This work was supported by Grants from the Natural Science Foundation of China (81570479) and the Climbing Program in Hangzhou Normal University-Phase II (PF14002004021).

Competing Interests

The authors have declared that no competing interest exists.

References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;266(5192):1865-9. PubMed PMID: 7997879.
2. Friedman-Kien AE, Laubenstein LJ, Rubinstein P, Buimovici-Klein E, Marmor M, Stahl R, et al. Disseminated Kaposi's sarcoma in homosexual men. *Ann Intern Med*. 1982;96(6 Pt 1):693-700. PubMed PMID: 6283973.
3. Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B. Survival with the acquired immunodeficiency syndrome. Experience with 5833 cases in New York City. *N Engl J Med*. 1987;317(21):1297-302. doi: 10.1056/NEJM198711193172101. PubMed PMID: 3500409.
4. Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science*. 1996;274(5293):1739-44. PubMed PMID: 8939871.
5. Dezube BJ. Clinical presentation and natural history of AIDS-related Kaposi's sarcoma. *Hematol Oncol Clin North Am*. 1996;10(5):1023-9. PubMed PMID: 8880194.

6. Flore O, Rafii S, Ely S, O'Leary JJ, Hyjek EM, Cesarman E. Transformation of primary human endothelial cells by Kaposi's sarcoma-associated herpesvirus. *Nature*. 1998;394(6693):588-92. doi: 10.1038/29093. PubMed PMID: 9707121.
7. Ablashi DV, Chatlynne LG, Whitman JE, Jr., Cesarman E. Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases. *Clin Microbiol Rev*. 2002;15(3):439-64. PubMed PMID: 12097251; PubMed Central PMCID: PMCPCMC118087.
8. Cesarman E. Gammaherpesvirus and lymphoproliferative disorders in immunocompromised patients. *Cancer Lett*. 2011;305(2):163-74. doi: 10.1016/j.canlet.2011.03.003. PubMed PMID: 21493001; PubMed Central PMCID: PMCPCMC3742547.
9. Tan X, Li D, Wang X, Zeng Y, Yan Y, Yang L. Claudin-2 downregulation by KSHV infection is involved in the regulation of endothelial barrier function. *J Cutan Pathol*. 2014;41(8):630-9. doi: 10.1111/cup.12332. PubMed PMID: 24995964.
10. Bahbouhi B, Landay A, Al-Harthi L. Dynamics of cytokine expression in HIV productively infected primary CD4+ T cells. *Blood*. 2004;103(12):4581-7. doi: 10.1182/blood-2003-12-4172. PubMed PMID: 14764521.
11. Rezaee SA, Cunningham C, Davison AJ, Blackburn DJ. Kaposi's sarcoma-associated herpesvirus immune modulation: an overview. *J Gen Virol*. 2006;87(Pt 7):1781-804. doi: 10.1099/vir.0.81919-0. PubMed PMID: 16760382.
12. Rosenthal R, Gunzel D, Krug SM, Schulzke JD, Fromm M, Yu AS. Claudin-2-mediated cation and water transport share a common pore. *Acta Physiol (Oxf)*. 2016. doi: 10.1111/apha.12742. PubMed PMID: 27359349.
13. Luettig J, Rosenthal R, Barmeyer C, Schulzke JD. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation. *Tissue Barriers*. 2015;3(1-2):e977176. doi: 10.4161/21688370.2014.977176. PubMed PMID: 25838982; PubMed Central PMCID: PMCPCMC4372021.
14. Ikari A, Sato T, Watanabe R, Yamazaki Y, Sugatani J. Increase in claudin-2 expression by an EGFR/MEK/ERK/c-Fos pathway in lung adenocarcinoma A549 cells. *Biochim Biophys Acta*. 2012;1823(6):1110-8. doi: 10.1016/j.bbamer.2012.04.005. PubMed PMID: 22546605.
15. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, et al. Intestinal permeability--a new target for disease prevention and therapy. *BMC Gastroenterol*. 2014;14:189. doi: 10.1186/s12876-014-0189-7. PubMed PMID: 25407511; PubMed Central PMCID: PMCPCMC4253991.
16. Yuan SY, Rigor RR. Regulation of Endothelial Barrier Function. *Integrated Systems Physiology: From Molecule to Function to Disease*. San Rafael (CA)2010.
17. Dejana E, Colella S, Languino LR, Balconi G, Corbascio GC, Marchisio PC. Fibrinogen induces adhesion, spreading, and microfilament organization of human endothelial cells in vitro. *J Cell Biol*. 1987;104(5):1403-11. PubMed PMID: 2437130; PubMed Central PMCID: PMCPCMC2114477.
18. Stickel SK, Wang YL. Alpha-actinin-containing aggregates in transformed cells are highly dynamic structures. *J Cell Biol*. 1987;104(6):1521-6. PubMed PMID: 3034916; PubMed Central PMCID: PMCPCMC2114522.
19. Anderson JM, Van Itallie CM. Physiology and function of the tight junction. *Cold Spring Harb Perspect Biol*. 2009;1(2):a002584. doi: 10.1101/cshperspect.a002584. PubMed PMID: 20066090; PubMed Central PMCID: PMCPCMC2742087.
20. Kratzer I, Vasiljevic A, Rey C, Fevre-Montange M, Saunders N, Strazielle N, et al. Complexity and developmental changes in the expression pattern of claudins at the blood-CSF barrier. *Histochem Cell Biol*. 2012;138(6):861-79. doi: 10.1007/s00418-012-1001-9. PubMed PMID: 22886143; PubMed Central PMCID: PMCPCMC3483103.
21. Steinemann A, Galm I, Chip S, Nitsch C, Maly IP. Claudin-1, -2 and -3 Are Selectively Expressed in the Epithelia of the Choroid Plexus of the Mouse from Early Development and into Adulthood While Claudin-5 is Restricted to Endothelial Cells. *Front Neuroanat*. 2016;10:16. doi: 10.3389/fnana.2016.00016. PubMed PMID: 26941614; PubMed Central PMCID: PMCPCMC4761916.
22. Tabaries S, Dupuy F, Dong Z, Monast A, Annis MG, Spicer J, et al. Claudin-2 promotes breast cancer liver metastasis by facilitating tumor cell interactions with hepatocytes. *Mol Cell Biol*. 2012;32(15):2979-91. doi: 10.1128/MCB.00299-12. PubMed PMID: 22645303; PubMed Central PMCID: PMCPCMC3434516.
23. Lagos D, Vart RJ, Gratrix F, Westrop SJ, Emuss V, Wong PP, et al. Toll-like receptor 4 mediates innate immunity to Kaposi sarcoma herpesvirus. *Cell Host Microbe*. 2008;4(5):470-83. doi: 10.1016/j.chom.2008.09.012. PubMed PMID: 18996347; PubMed Central PMCID: PMCPCMC2698447.
24. Nicol MQ, Mathys JM, Pereira A, Ollington K, Jeong MH, Skolnik PR. Human immunodeficiency virus infection alters tumor necrosis factor alpha production via Toll-like receptor-dependent pathways in alveolar macrophages and U1 cells. *J Virol*. 2008;82(16):7790-8. doi: 10.1128/JVI.00362-08. PubMed PMID: 18524817; PubMed Central PMCID: PMCPCMC2519548.
25. Equils O, Faure E, Thomas L, Bulut Y, Trushin S, Ardit M. Bacterial lipopolysaccharide activates HIV long terminal repeat through Toll-like receptor 4. *J Immunol*. 2001;166(4):2342-7. PubMed PMID: 11160291.
26. Butler LM, Jeffery HC, Wheat RL, Rae PC, Townsend K, Alkharsah KR, et al. Kaposi's sarcoma-associated herpesvirus infection of endothelial cells inhibits neutrophil recruitment through an interleukin-6-dependent mechanism: a new paradigm for viral immune evasion. *J Virol*. 2011;85(14):7321-32. doi: 10.1128/JVI.00021-11. PubMed PMID: 21543487; PubMed Central PMCID: PMCPCMC3126554.
27. Koedel U, Kohleisen B, Sporer B, Lahrtz F, Ovod V, Fontana A, et al. HIV type 1 Nef protein is a viral factor for leukocyte recruitment into the central nervous system. *J Immunol*. 1999;163(3):1237-45. PubMed PMID: 10415019.
28. Karijolic J, Zhao Y, Peterson B, Zhou Q, Glaunsinger B. Kaposi's sarcoma-associated herpesvirus ORF45 mediates transcriptional activation of the HIV-1 long terminal repeat via RSK2. *J Virol*. 2014;88(12):7024-35. doi: 10.1128/JVI.00931-14. PubMed PMID: 24719417; PubMed Central PMCID: PMCPCMC4054375.