The growing evidence behind the connection between infections and cancer (Part 1)

AONM webinar 28th July 2022

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A growing body of research suggests that a number of viruses, bacteria, and parasites cause cancer in humans

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ARTICLES | VOLUME 13, ISSUE 6, P607-615, JUNE 01, 2012

Global burden of cancers attributable to infections in 2008: a review and synthetic analysis

Catherine de Martel, MD • Jacques Ferlay, ME • Silvia Franceschi, MD • Jérôme Vignat, MSc • Freddie Bray, PhD • David Forman, PhD • et al. Show all authors

Published: May 09, 2012 • DOI: https://doi.org/10.1016/S1470-2045(12)70137-7

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Linked Articles

Summary

Background

Infections with certain viruses, bacteria, and parasites have been identified as strong risk factors for specific cancers. An update of their respective contribution to the global burden of cancer is warranted.

"It is estimated that about 20% of human cancer cases worldwide are caused by infection with bacteria, parasites or viruses"[4]

Source: *1.* https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents*, 2022; 2.* Vandeven N, Nghiem P. Pathogen-driven cancers and emerging immune therapeutic strategies. Cancer Immunol Res. 2014 Jan;2(1):9-14; 3. *Emerging Infectious Diseases. Vol. 4 No. 3 / Jul. – Sept.1998: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640277/pdf/9716980.pdf ; 4.* https://www.frontiersin.org/articles/10.3389/fmicb.2018.00081/full#B37*; 5.* https://www.microbiologyresearch.org/content/journal/jgv/10.1099/vir.0.80737-0*; 6.* https://www.cancer.org/healthy/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer/intro.html

What cancers have pathogens been associated with?

Part 1:

- Breast cancer
- Blood cancers
- Monoclonal Gammopathy
- Glioblastoma
- Prostate

Part 2:

- Lung
- Colorectal/gastric/oesophageal cancer
- Cervical cancer

What cancers have pathogens been associated with?

- **Breast cancer**
- Blood cancers
- Monoclonal Gammopathy
- Glioblastoma
- Prostate

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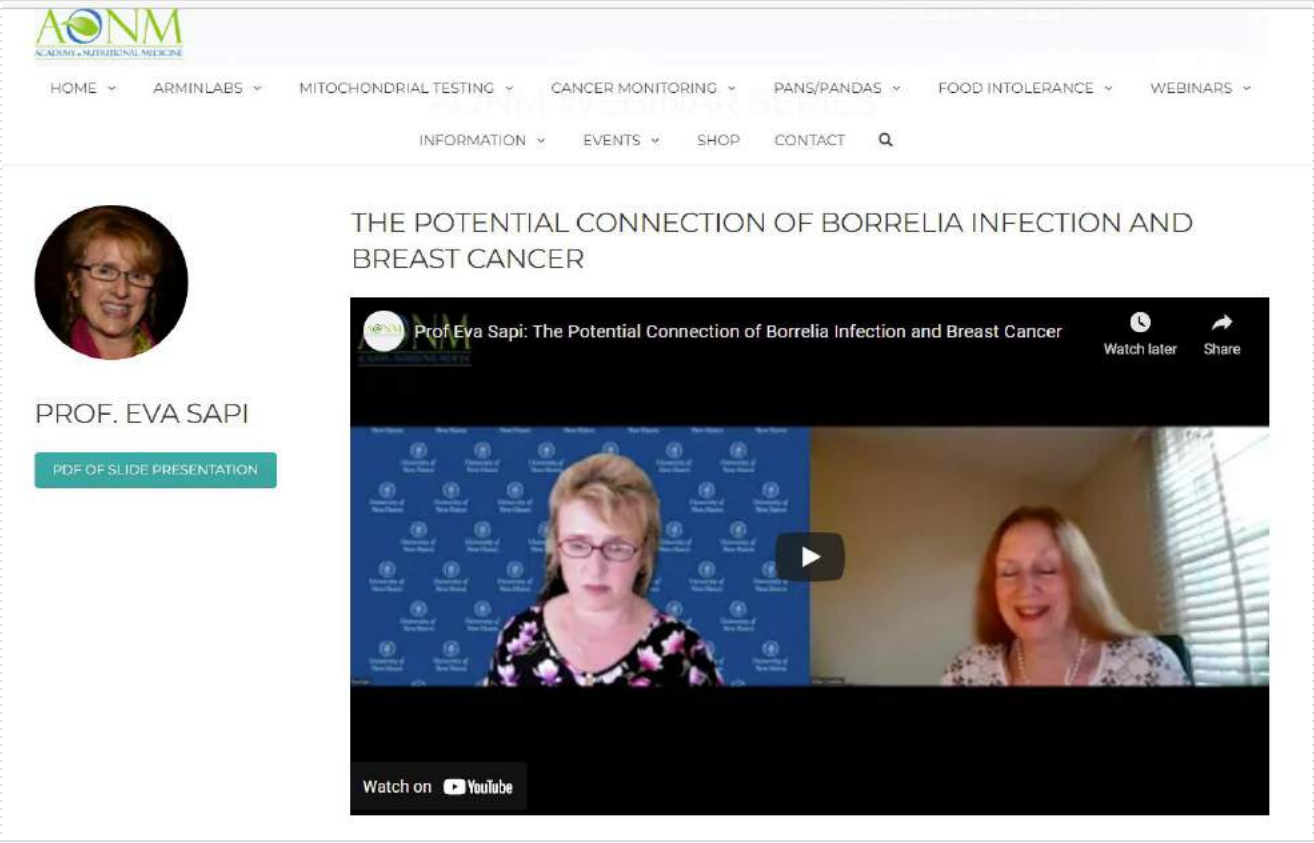

https://aonm.org/view-past-webinars/

British Journal of Cancer 2011: EBV "a marker of biological aggressiveness in breast cancer"

British Journal of Cancer (2011) 104, 332 – 337

www.bjcancer.com

Epstein-Barr virus as a marker of biological aggressiveness in breast cancer

C Mazouni*[,1,2,6], F Fina[1,6], S Romain[1], L Ouafik[3], P Bonnier[4], J-M Brandone[5] and P-M Martin[1]

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PURPOSE: Although a potential role of the Epstein-Barr virus (EBV) in the pathogenesis of breast cancer (BC) has been underlined, results remain conflicting. Particularly, the impact of EBV infection on biological markers of BC has received little investigation.
METHODS: In this study, we established the frequency of EBV-infected BC using real-time quantitative PCR (RT–PCR) in 196 BC specimens. Biological and pathological characteristics according to EBV status were evaluated.
RESULTS: EBV DNA was present in 65 of the 196 (33.2%) cases studied. EBV-positive BCs tended to be tumours with a more aggressive phenotype, more frequently oestrogen receptor negative ($P=0.05$) and with high histological grade ($P=0.01$). Overexpression of thymidine kinase activity was higher in EBV-infected BC ($P=0.007$). The presence of EBV was weakly associated with *HER2* gene amplification ($P=0.08$).
CONCLUSION: Our study provides evidence for EBV-associated BC undergoing distinct carcinogenic processes, with more aggressive features.

British Journal of Cancer (2011) **104,** 332–337. doi:10.1038/sj.bjc.6606048 www.bjcancer.com
Published online 21 December 2010

Keywords: breast cancer; Epstein-Barr virus; HER2; real-time quantitative PCR; thymidine kinase

A viral aetiology is one recently evocated theory behind the physiopathology of breast cancer (BC) (Glaser *et al*, 2004; de Villiers *et al*, 2005; zur Hausen, 2009). Even though, the mechanistic aspects of cancer induction by infectious agents sound multiples, that is, immunosuppressive, linked to animal–human

For instance, although Murray *et al* (2003)could detect EBV nuclear antigen-1 by immunochemistry using 2B4-1 monoclonal antibody, they failed to detect the EBV genome by quantitative PCR. The reasons behind these apparently conflicting results remain to be clarified: however, technical limitations of the assays,

Molecular Diagn

"EBV DNA was present in 65 of the 196 (33.2%) cases studied. EBV-positive BCs tended to be tumours with a more aggressive phenotype, more frequently oestrogen receptor negative (P ¼ 0.05) and **with high histological grade** (P ¼ 0.01). Overexpression of thymidine kinase activity was higher in EBV-infected BC (P ¼ 0.007). The presence of EBV was weakly associated with HER2 gene amplification (P ¼ 0.08)"

"CONCLUSION: Our study provides evidence for EBV-associated BC undergoing distinct carcinogenic processes, with more aggressive features."

Source: *Mazouni C, Fina F, Romain S, Ouafik L, Bonnier P, Brandone JM, Martin PM. Epstein-Barr virus as a marker of biological aggressiveness in breast cancer. Br J Cancer. 2011 Jan 18;104(2):332-7.*

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A 2012 study showed a statistical association of EBV with increased breast carcinoma risk after analysis of 1,535 cases

Breast

OPEN ACCESS Freely available online

PLoS one

Epstein-Barr Virus Infection and Sporadic Breast Cancer Risk: A Meta-Analysis

Qiang Huo, Ning Zhang, Qifeng Yang*

Department of Breast Surgery, School of Medicine, Shandong University, Qilu Hospital, Ji'nan, Shandong, People's Republic of China

Abstract

Background: A large number of epidemiological studies have evaluated the association between Epstein-Barr virus infection and breast carcinoma risk but results have been inconsistent.

Methodology: Research using the polymerase chain reaction technique for detecting the Epstein-Barr virus was selected; 24 studies and 1535 cases were reviewed. Information on the study populations, sample types, publication calendar period and histological types of breast carcinoma were collected. An unconditional logistic regression model was used to analyze potential parameters related to the Epstein-Barr virus prevalence. A Kappa test was used to evaluate the consistency in detecting different Epstein-Barr virus DNA regions. Nine studies that included control groups and 1045 breast cancer cases were adopted in this meta-analysis.

Conclusions: We found that 29.32% of the patients with breast carcinoma were infected with the Epstein-Barr virus. The prevalence of Epstein-Barr was highest in Asia (35.25%) and lowest in the USA (18.27%). Statistical analysis revealed a trend that showed lobular breast carcinoma might have the strongest association with Epstein-Barr virus infection. This meta-analysis showed a significant increase in breast malignancy risk in patients testing positive for the Epstein-Barr virus (OR = 6.29, 95% CI = 2.13–18.59). This result suggests that an Epstein-Barr virus infection is statistically associated with increased breast carcinoma risk.

Citation: Huo Q, Zhang N, Yang Q (2012) Epstein-Barr Virus Infection and Sporadic Breast Cancer Risk: A Meta-Analysis. PLoS ONE 7(2): e31656. doi:10.1371/journal.pone.0031656

Editor: Syed A. Aziz, Health Canada, Canada

Received November 13, 2011; **Accepted** January 17, 2012; **Published** February 21, 2012

Funding: Dr. Yang is supported by Program for New Century Excellent Talents in University, Key Project of Chinese Ministry of Education (No. 108080) (http://www.moe.edu.cn/), National Natural Science Foundation of China (No. 30772133; No. 81072150) (http://www.nsfc.gov.cn) and Independent Innovation Foundation of Shandong University (IIFSDU, No. 2009JQ007) (http://www.sdu.edu.cn/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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"This meta-analysis showed a significant increase in breast malignancy risk in patients testing positive for the Epstein-Barr virus (OR = 6.29, 95% CI = 2.13–18.59). This result suggests that an Epstein-Barr virus infection is **statistically associated with increased breast carcinoma risk.**"

Breast cancer and EBV: Multiple peer-reviewed studies

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2019 review: increased expression of CMV gene products found to correlate with a more aggressive BC phenotype

Harkins *et al. Herpesviridae* 2010, **1**:8
http://www.herpesviridae.org/content/1/1/8

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RESEARCH Open Access

Detection of human cytomegalovirus in normal and neoplastic breast epithelium

Lualhati E Harkins[1], Lisa A Matlaf[2], Liliana Soroceanu[2], Katrin Klemm[1], William J Britt[3], Wenquan Wang[4], Kirby I Bland[5], Charles S Cobbs[2*]

Abstract

Introduction: Human cytomegalovirus (HCMV) establishes a persistent life-long infection, and can cause severe pathology in the fetus and the immunocompromised host[1]. Breast milk is the primary route of transmission in humans worldwide, and breast epithelium is thus a likely site of persistent infection and/or reactivation, though this phenomenon has not previously been demonstrated. Increasing evidence indicates HCMV infection can modulate signaling pathways associated with oncogenesis. We hypothesized that persistent HCMV infection occurs in normal adult breast epithelium and that persistent viral expression might be associated with normal and neoplastic ductal epithelium.

Methods: Surgical biopsy specimens of normal b
from breast cancer patients (n = 21) were obtain
hybridization, PCR and DNA sequencing for evid

Results: We detected HCMV expression specifica
cases evaluated. In contrast, HCMV expression wa
with ductal carcinoma in situ (DCIS) and infiltrati

Conclusions: These findings are the first to dem
epithelium in a significant percentage of normal
breast epithelium in a high percentage of norma
patients, raising the possibility that viral infection

Introduction

Environmental and epidemiological factors that

HCMV expression was .. evident in neoplastic breast epithelium in a high percentage of normal and neoplastic breast tissues obtained from breast cancer patients, raising the possibility that viral infection may be involved in the neoplastic process

2019 review

cancers MDPI

Review

A Review of the Potential Role of Human Cytomegalovirus (HCMV) Infections in Breast Cancer Carcinogenesis and Abnormal Immunity

Jürgen Geisler [1,2], Joel Touma [1,2,3], Afsar Rahbar [4,5], Cecilia Söderberg-Nauclér [4,5] and Katja Vetvik [2,3,*]

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Received: 25 October 2019; Accepted: 19 November 2019; Published: 22 November 2019

check for updates

Abstract: Previously recognized classical human onco-viruses can regulate complex neoplastic events, and are estimated to play a role during carcinogenesis in 15–20% of cancer cases. Although the DNA and gene products of several viruses have been found in breast tumors, none of the classical onco-viruses have definitely been linked to the initiation of breast cancer. However, recent evidence shows that human cytomegalovirus (HCMV) gene products are found in >90% of tumors and metastases of breast cancers, and their increased expression can be correlated to a more aggressive breast cancer phenotype. Supporting the active role of HCMV in breast cancer, a specific HCMV strain,

"… recent evidence shows that human cytomegalovirus (HCMV) gene products are **found in >90%** of tumors and metastases of breast cancers, and **their increased expression can be correlated to a more aggressive breast cancer phenotype**."

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Mycoplasma found to be positive in almost 40% of breast cancer cases (2001 study)

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E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol, 2001;7(2):266 - 269
World Journal of Gastroenterology
Copyright©2001 by the WJG Press ISSN 1007 - 9327

Mycoplasma infections and different human carcinomas

Su Huang, Ji You Li, Jan Wu, Lin Meng and Cheng Chao Shou

Subject headings Gastrointestinal neoplasms/ microbiology; mycoplasma infections; antibodies, monoclonal; immunohistochemistry

Huang S, Li JY, Wu J, Meng L, Shou CC. Mycoplasma infections and different human carcinomas. *World J Gastroenterol*, 2001;7(2):266-269

Abstract

AIM **To explore relationships between human carcinomas and mycoplasma infection.**

METHODS **Monoclonal antibody PD4, which specifically recognizes a distinct protein from mycoplasma hyorhinis, was used to detect mycoplasma infection in different paraffin embedded carcinoma tissues with immunohistochemistry. PCR was applied to amplify the mycoplasma DNA from the positive samples for confirming immunohistochemistry.**

RESULTS **Fifty of 90 cases (56%) of gastric carcinoma were positive for mycoplasma hyorhinis. In other gastric diseases, the mycoplasma infection ratio was 28% (18/49) in chronic superficial gastritis, 30% (14/46) in gastric ulcer and 37%**

CONCLUSION **There was high correlation between mycoplasma in… suggests the p… the two. The m… by mycoplasma**

INTRODUCTION

Mycoplasma is… isolated from na… medium. Myco… membrane of m… can enter these … organism, myco… many diseases[4]… some mycoplas… cell transforma… chromosomal l… association be… remains unclear… was prepared w… MGC803 as imm…

Mycoplasma infection was found to be positive in 39.7% of breast cancer cases via immunohistochemistry assays (25/63)

Mycoplasma infection in other carcinoma tissues

Beside the gastriointestinal carcinomas, other cancer tissues from human esophagus, lung, breast and brain were also analyzed (Table 4).

Table 4 Mycoplasma infection in other carcinoma tissues

Types of carcinoma	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
Esophagus	53	26	21	6	27	50.9
Lung	59	28	23	8	31	52.6
Breast	63	38	17	8	25	39.7
Glioma	91	53	27	11	38	41.0
Total	266	145	88	33	121	45.5

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Bartonella-infected endothelium may contribute to initiating inflammatory breast cancer and rapid spread

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Poster Session Abstracts

Abstract P3-10-03: *Bartonella henselae* Infection Detected in Patients with Inflammatory Breast Cancer.

SV Fernandez, L Aburto, R Maggi, EB Breitschwerdt, and M Cristofanilli

DOI: 10.1158/0008-5472.SABCS12-P3-10-03 Published December 2012

Article Info & Metrics

Abstracts: Thirty-Fifth Annual CTRC-AACR San Antonio Breast Cancer Symposium-- Dec 4-8, 2012; San Antonio, TX

Abstract

Inflammatory breast cancer (IBC) is a very aggressive type of advanced breast cancer with a poor prognosis. Clinical symptoms involve a rapid onset of changes in the skin overlying the breast, including edema, redness and swelling including a wrinkled and orange peel appearance in the skin. This particular presentation is due to the invasion of the skin dermal lymphatics by breast cancer cells that obstructed the lymph channels producing the characteristic skin changes that mimic an inflammatory process. Mouse Mammary Tumor-associated Virus (MMTV) and other infectious agents have been consider as possible etiological agents of IBC particularly related to the initial description of higher incidence in women living in rural areas in North Africa. Although, the etiopathological role of bacteria in this disease has never been explored in spite of the evidence that chronic infections with certain bacteria can facilitate tumors development.

December 2012
Volume 72, Issue 24
Supplement
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Source: Cancer Res 2012;72(24 Suppl):Abstract no. P3-10-03.

"An acute inflammatory reaction triggered by the Bartonella infected endothelium may be crucial for initiating the chronic inflammation in inflammatory breast cancer patients and the rapid spread of tumor cells."

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What cancers have pathogens been associated with?

- Breast cancer
- **Blood cancers: Lymphoma (Burkitt's, Hodgkin's and Non-Hodgkin's, mantle cell, B-cell), myelodysplastic syndrome and leukaemia (both acute lymphoblastic and chronic lymphocytic leukaemia: ALL & CLL)**
- Monoclonal Gammopathy
- Glioblastoma
- Prostate

Link of EBV to lymphoma was discovered by Burkitt in the 1950s

biology

MDPI

Review

Pathogens and Carcinogenesis: A Review

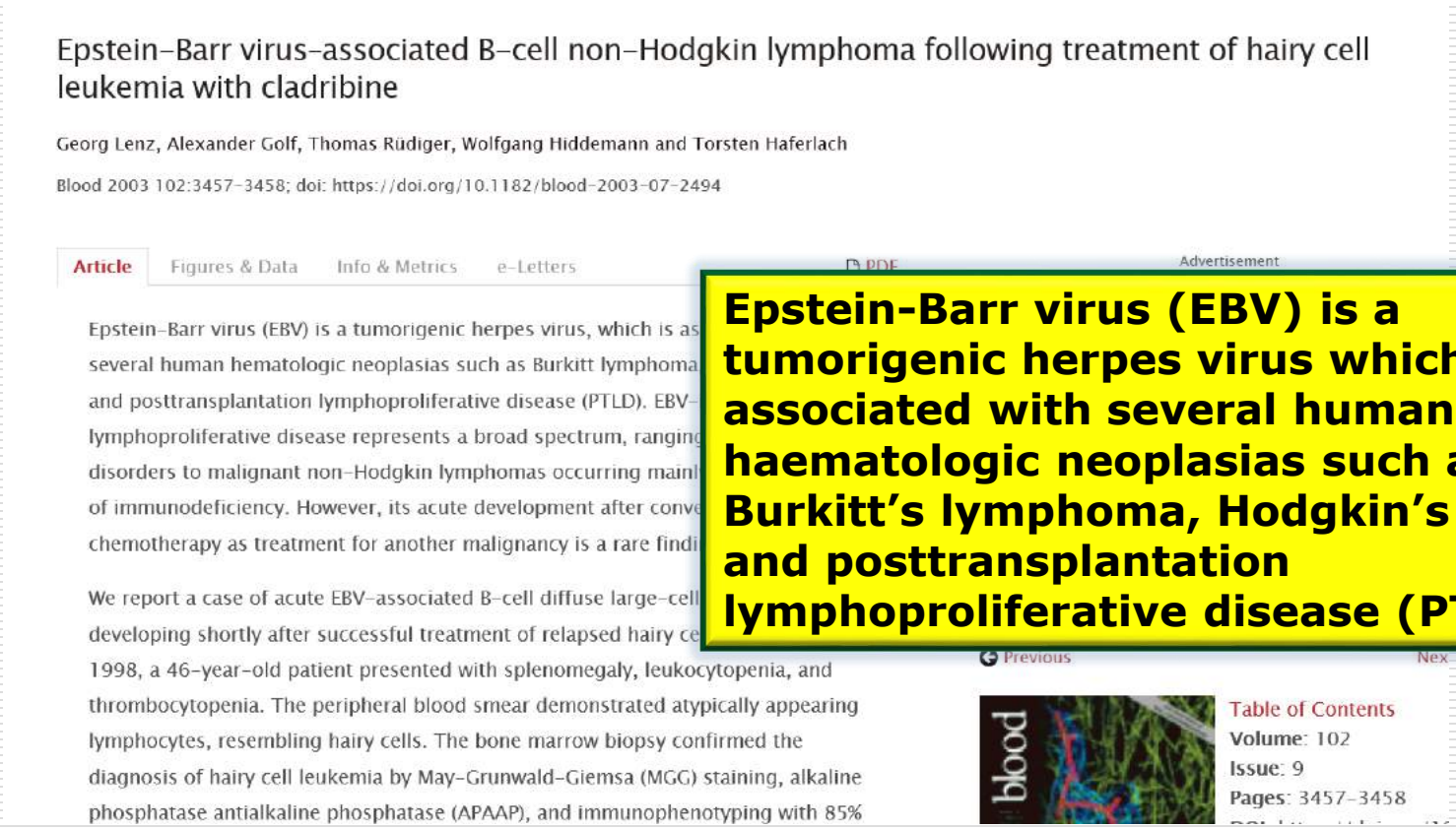
Muhammad Nur Adam Hatta, Ezanee Azlina Mohamad Hanif, Siok-Fong Chin and Hui-min Neoh *

UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, Jalan Ya'acob Latiff, Cheras, Kuala Lumpur 56000, Malaysia; P98904@siswa.ukm.edu.my (M.N.A.H.);

Epstein-Barr Virus (EBV)	Lymphoma	**Burkitt's Lymphoma** • Apoptosis inhibition via p53 mutations • Genetic instability due to ROS and NOX2 production via EBNA1 • Lymphocyte immortalization regulation via EBNA2 • B to lymphoblastic cell line generation due to chronic infection **Hodgkin's Lymphoma** • Formation of multinucleated HRS cells from B lymphocytes • Cell signal disruptions due to defective HRS cells • Increased HRS cell survival due to LMP-1 and -2 expression • Lymph node structure disruption and cytokine activity increment due to CIITA mutagenesis	• Avoid body fluid transfer from infected patients • Small molecule inhibitor (EBNA1 inhibitor, HDAC inhibitors, butyrate and GCV, bortezomib, CDKs inhibitors, PI3K inhibitors, BCL-2 inhibitors, mTOR inhibitors, ixazomib) • Immunotherapy (immune checkpoint inhibitors) • Cell therapy (monoclonal antibodies, T-cell therapy)

Source: *https://pubmed.ncbi.nlm.nih.gov/34203649/*

EBV is associated with various human haematological neoplasias



Epstein–Barr virus–associated B–cell non–Hodgkin lymphoma following treatment of hairy cell leukemia with cladribine

Georg Lenz, Alexander Golf, Thomas Rüdiger, Wolfgang Hiddemann and Torsten Haferlach

Blood 2003 102:3457–3458; doi: https://doi.org/10.1182/blood-2003-07-2494

Article Figures & Data Info & Metrics e-Letters PDF

Epstein–Barr virus (EBV) is a tumorigenic herpes virus, which is as
several human hematologic neoplasias such as Burkitt lymphoma
and posttransplantation lymphoproliferative disease (PTLD). EBV–
lymphoproliferative disease represents a broad spectrum, ranging
disorders to malignant non–Hodgkin lymphomas occurring mainl
of immunodeficiency. However, its acute development after conve
chemotherapy as treatment for another malignancy is a rare findi

We report a case of acute EBV–associated B–cell diffuse large–cell
developing shortly after successful treatment of relapsed hairy ce
1998, a 46–year–old patient presented with splenomegaly, leukocytopenia, and
thrombocytopenia. The peripheral blood smear demonstrated atypically appearing
lymphocytes, resembling hairy cells. The bone marrow biopsy confirmed the
diagnosis of hairy cell leukemia by May–Grunwald–Giemsa (MGG) staining, alkaline
phosphatase antialkaline phosphatase (APAAP), and immunophenotyping with 85%

Advertisement

Epstein-Barr virus (EBV) is a tumorigenic herpes virus which is associated with several human haematologic neoplasias such as Burkitt's lymphoma, Hodgkin's disease, and posttransplantation lymphoproliferative disease (PTLD)

Previous Nex

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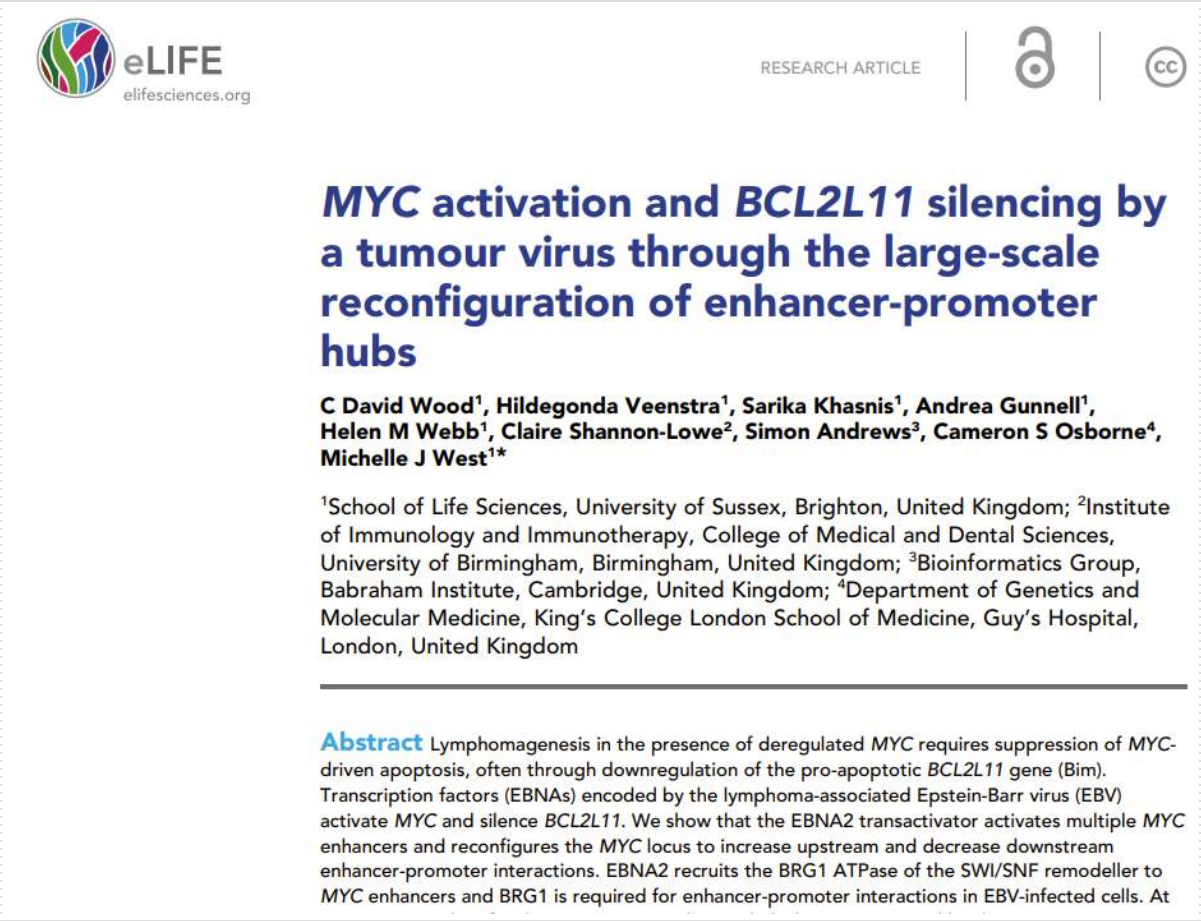
Volume: 102
Issue: 9
Pages: 3457–3458

Source: *Ramesh G et al. Interaction of the Lyme Disease Spirochete Borrelia burgdorferi with Brain Parenchyma Elicits Inflammatory Mediators from Glial Cells as Well as Glial and Neuronal Apoptosis. Am J Pathol. 2008 Nov; 173(5): 1415–1427*

Blood cancers and EBV: Seminal research at the University of Sussex – important genetic implications



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RESEARCH ARTICLE

MYC activation and *BCL2L11* silencing by a tumour virus through the large-scale reconfiguration of enhancer-promoter hubs

C David Wood[1], Hildegonda Veenstra[1], Sarika Khasnis[1], Andrea Gunnell[1], Helen M Webb[1], Claire Shannon-Lowe[2], Simon Andrews[3], Cameron S Osborne[4], Michelle J West[1]*

[1]School of Life Sciences, University of Sussex, Brighton, United Kingdom; [2]Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom; [3]Bioinformatics Group, Babraham Institute, Cambridge, United Kingdom; [4]Department of Genetics and Molecular Medicine, King's College London School of Medicine, Guy's Hospital, London, United Kingdom

Abstract Lymphomagenesis in the presence of deregulated *MYC* requires suppression of *MYC*-driven apoptosis, often through downregulation of the pro-apoptotic *BCL2L11* gene (Bim). Transcription factors (EBNAs) encoded by the lymphoma-associated Epstein-Barr virus (EBV) activate *MYC* and silence *BCL2L11*. We show that the EBNA2 transactivator activates multiple *MYC* enhancers and reconfigures the *MYC* locus to increase upstream and decrease downstream enhancer-promoter interactions. EBNA2 recruits the BRG1 ATPase of the SWI/SNF remodeller to *MYC* enhancers and BRG1 is required for enhancer-promoter interactions in EBV-infected cells. At

Epstein-Barr virus (EBV) is associated with the development of numerous lymphomas including Burkitt's (BL), post-transplant, Hodgkin's and certain NK and T-cell lymphomas

Professor West said: "This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer."

Source: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5005034/pdf/elife-18270.pdf*

Patients with Hodgkin's disease have greatly increased cells with HHV-6 DNA

Human herpesvirus-6 (HHV-6) in Hodgkin's disease: Cellular expression of viral antigens as compared to oncogenes met and fes, tumor suppressor gene product p53, and interleukins 2 and 6

Article *in* In vivo (Athens, Greece) 8(4):501-16 · July 1994 *with* 9 Reads
Source: PubMed

Gerhard Richard Krueger
43.68 · University of Texas Health Science Center at Houston

A Gue

R Knuefermann

+ 5

Hans
48.8

"Patients with Hodgkin's disease (HD) frequently show elevated serum titers against human herpersvirus-6 (HHV-6) and their tissues contain significantly increased numbers of cells with HHV-6 DNA."

Abstract

Patients with Hodgkin's disease (HD) frequently show elevated serum titers against human herpersvirus-6 (HHV-6) and their tissues contain significantly increased numbers of cells with HHV-6 DNA. This may coincide with similar data of Epstein-Barr virus (EBV) infections. According to in vitro studies, Hodgkin- and Reed-Sternberg (RS) cells can be infected by HHV-6 and may be coinfected by HHV-6 and EBV. Both viruses are potentially oncogenic and also may interfere with the production of various cytokines. We now demonstrate by using immunohistological methods that HHV-6 antigens are present in 77.3% of the HD lymphomas, 37% of which contain the replication-associated p41 "early-late" antigen and 63% the late membrane antigen complex gp116/64/54. Monocytic cell populations including HD and RS cells are most frequently antigen-positive, while lymphoid cells are less frequently. These cells also express IL-6 and IL-6 receptors as well as the IL-2 receptor a chain (CD25), while only occasionally the IL-2 receptor beta chain (p70). IL-6 receptors are significantly more frequently expressed than IL-6 itself. HD and RS cells constitute a significant pool of proliferating cells as reflected by their 95% positivity for PCNA, yet tumor suppressor genes are found in only 21% and the proto-oncogenes fes and met are expressed in various types of cells. The data may indicate that both viruses possibly contribute to the course of the disease through polyclonal stimulations of cell proliferation and coincident dysregulation of the cytokine network control of cell function and proliferation. A direct oncogenic effect of EBV and HHV-6 in HD appears less probable.

Source: *Krueger et al. Human herpesvirus-6 (HHV-6) in Hodgkin's disease: cellular expression of viral antigens as compared to oncogenes met and fes, tumor suppressor gene product p53, and interleukins 2 and 6. In Vivo. 1994 Jul-Aug;8(4):501-16*

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Association betwen Borrelia and non-Hodgkin's/ mantle cell lymphoma

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Blood. 2008 Jun 15; 111(12): 5524–5529. PMCID: PMC2972577
Prepublished online 2008 Apr 18. doi: 10.1182/blood-2007-08-109611
Clinical Trials and Observations

Borrelia infection and risk of non-Hodgkin lymphoma

Claudia Schöllkopf,[✉1] Mads Melbye,[1] Lars Munksgaard,[2] Karin Ekström Smedby,[3] Klaus Rostgaard,[1] Bengt Glimelius,[4,5] Ellen T. Chang,[6,7] Göran Roos,[8] Mads Hansen,[2] Hans-Olov Adami,[3,9] and Henrik Hjalgrim[1]

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Abstract

Reports of the presence of *Borrelia burgdorfe*
that infection with *B burgdorferi* may be caus
We conducted a Danish-Swedish case-control
controls. History of tick bite or *Borrelia* infec
and through enzyme-linked immunosorbent a
subset of 1579 patients and 1358 controls. Sta
subtypes, were assessed by logistic regression
history of tick bite (odds ratio [OR] = 1.0; 95% confidence interval: 0.9-1.1), *Borrelia* infection (OR = 1.3
[0.96-1.8]) or the presence of anti-*Borrelia* antibodies (OR = 1.3 [0.9-2.0]). However, in analyses of NHL subtypes, self-reported history of *B burgdorferi* infection (OR = 2.5 [1.2-5.1]) and seropositivity for anti-*Borrelia* antibodies (OR = 3.6 [1.8-7.4]) were both associated with risk of mantle cell lymphoma. Notably, this specific association was also observed in persons who did not recall *Borrelia* infection yet tested positive for anti-*Borrelia* antibodies (OR = 4.2 [2.0-8.9]). Our observations suggest a previously unreported association between *B burgdorferi* infection and risk of mantle cell lymphoma.

"Schoellkopf et al conducted a Danish-Swedish case-control study of 3,055 patients with non-Hodgkin's lymphoma and 3,187 population controls to evaluate the association of lymphoma subtypes with Borrelia burgdorferi. Self-reported history of B burgdorferi infection (OR = 2.5) and seropositivity for anti-Borrelia antibodies (OR – 3.6) were both found to increase the risk of mantle cell lymphoma"
Epidemiology of Chronic Disease: Global Perspectives (book), Randall E. Harris MD PhD, 2013.

"Our observations suggest a previously unreported association between *B burgdorferi* infection and risk of mantle cell lymphoma."

"Moreover, regression of lymphomas upon treatment of the Borrelia infection has also been reported"

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Babesia and B-cell lymphoma

Infect Dis Clin North Am. Author manuscript; available in PMC 2014 Apr 24.
Published in final edited form as:
Infect Dis Clin North Am. 2008 Sep; 22(3): 469–ix.
doi: 10.1016/j.idc.2008.03.010

PMCID: PMC3998201
NIHMSID: NIHMS70263

Human Babesiosis

Edouard Vannier, PhD,[a] Benjamin E. Gewurz, MD, PhD,[b] and Peter J. Krause, MD[c,d]

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Introduction

Go to:

Human babesiosis is an emerging tick-borne infectious disease caused by protozoa of the genus *Babesia* that are obligate parasites of red blood cells. Long recognized as pathogens imposing a significant health burden on domesticated animals, *Babesia* spp. increasingly have been identified over the last 50 years as a cause of infection in people throughout the world.

The first reference to babesiosis is probably in Exodus 9:3, which describes the plague visited upon the cattle of Pharaoh Rameses II. Viktor Babes, a Hungarian pathologist who investigated the cause of febrile hemoglobinuria in cattle grazing in the Danube region of Romania, was the microorganism residing in red blood cells.[1] Shortly thereafter, Smith and organism in Texas cattle.[2] Named *Pyrosoma bigeminum* after its pear sha recognized as *Babesia bigemina*. The cattle tick, *Boophilus annulatus*, was transmission of Texas cattle fever. By making this seminal observation, Sm concept that hematophagous arthropods can transmit an infectious agent to species of babesia subsequently have been identified in wild and domestic animals.[3]

The majority of patients with Babesiosis in a 2008 case study had underlying B-cell lymphoma[1]

Source: *1. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis. 2008; 46(3):370–6.*

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Ehrlichia/Anaplasma associated with myelodysplastic disease and leukaemia

ELSEVIER

Medical Hypotheses

Volume 85, Issue 6, December 2015, Pages 891-893

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?

Charles A. Kallick[a], Daniel A. Friedman[b], Mramba B.A. Nyindo[c]

Show more

https://doi.org/10.1016/j.mehy.2015.09.015

Abstract

We hypothesize that a large group of medical conditions of unknown etiology including leukemia, multiple myeloma, myelodysplastic and autoimmune disorders, may be associated with or caused by an obscure group of intracellular obligate parasitic bacteria named Ehrlichia/Anaplasma (EA). Ensconced in the stem cells of the bone marrow, EA may disrupt the normal development and function of many of the cells of immunity, manifesting itself as different syndromes. Recent studies of the activity of EA suggest direct effects on the immune system consistent with the manifestations of leukemia. We reference here three leukemia patients with direct or indirect evidence of EA infection. Moreover, EA have been

"Recent studies of the activity of EA [Ehrlichia/Anaplasma] suggest direct effects on the immune system consistent with the manifestations of leukaemia"

"It is further hypothesized, moreover, that treatment of leukaemia with antibiotics effective against EA would also result in beneficial impact. This has been tried. The results, cited below, hint at proof of EA infection as a cause of leukaemia as well as a potentially important course of treatment."

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Coxiella lymphadenitis may lead to lymphomagenesis and then to Non-Hodgkin's Lymphoma

Regular Article

LYMPHOID NEOPLASIA

B-cell non-Hodgkin lymphoma linked to *Coxiella burnetii*

Cléa Melenotte,[1,*] Matthieu Million,[1,*] Gilles Audoly,[1] Audrey Gorse,[2] Hervé Dutronc,[3] Gauthier Roland,[4] Michal Dekel,[5] Asuncion Moreno,[6] Serge Cammilleri,[7] Maria Patrizia Carrieri,[8,9] Camelia Protopopescu,[8,9] Philippe Ruminy,[10] Hubert Lepidi,[1,11] Bertrand Nadel,[12] Jean-Louis Mege,[1] Luc Xerri,[13,14] and Didier Raoult[1]

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Key Points

- *Coxiella burnetii* is associated with an increased risk of lymphoma; its presence in the tumor microenvironment may favor lymphomagenesis.
- Lymphoma has to be considered in patients with Q fever and lymphoid disorders, especially those with persistent focalized infections.

Bacteria can induce human lymphomas, whereas lymphoproliferative disorders have been described in patients with Q fever. We observed a lymphoma in a patient with Q fever that prompted us to investigate the association between the 2 diseases. We screened 1468 consecutive patients of the 2004 to 2014 French National Referral Center for Q fever database. The standardized incidence ratios (SIRs) of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) were calculated comparatively to the 2012 Francim Registry. The presence of *Coxiella burnetii* was tested using immunofluorescence and fluorescence in situ hybridization using a specific 16S ribosomal RNA probe and genomic DNA probe. Seven patients (0.48%) presented mature B-cell lymphoma consisting of 6 DLBCL and 1 FL. An excess risk of DLBCL and FL was found in Q fever patients compared with the general population (SIR [95% confidence interval], 25.4 [11.4-56.4] and 6.7 [0.9-47.9], respectively). *C burnetii* was detected in CD68$^+$ macrophages within both lymphoma and lymphadenitis tissues but localization in CD123$^+$ plasmacytoid dendritic cells (pDCs) was found only in lymphoma tissues. Q fever patients with persistent focalized infection were found more at risk of lymphoma (hazard ratio, 9.35 [1.10-79.4]). Interleukin-10 (IL10) overproduction (P = .0003) was found in patients developing

Coxiella: An intracellular bacterium that typically resides in macrophages. Ticks are the most common reservoir for *C burnetii* , and most human infections are transmitted from farm animals, such as cows, sheep, or goats.

PLOS ONE

RESEARCH ARTICLE

A transcriptional signature associated with non-Hodgkin lymphoma in the blood of patients with Q fever

Cléa Melenotte[1☯], Soraya Mezouar[1☯], Amira Ben Amara[1], Simon Benatti[2], Jacques Chiaroni[3,4], Christian Devaux[1], Régis Costello[5], Guido Kroemer[6,7,8,9,10,11,12,13], Jean-Louis Mege[1], Didier Raoult[1]*

1 Aix-Marseille Univ, IRD, APHM, MEPHI, IHU-Méditerranée Infection, Marseille, France, **2** Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy, **3** Établissement Français du Sang Alpes Méditerranée, Marseille, France, **4** Aix-Marseille University, CNRS, ADES, "Biologie des Groupes Sanguins", Marseille, France, **5** Service d'hématologie de la Conception, Assistance publique des hôpitaux de Marseille, Marseille, France, **6** Gustave Roussy Cancer Campus, Villejuif, France, **7** INSERM, U1138, Paris, France, **8** Equipe **11** labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers, Paris, France, **9** Université Paris Descartes, Sorbonne Paris Cité, Paris, France, **10** Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France, **11** Université Pierre et Marie Curie, Paris, France, **12** Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France, **13** Karolinska

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Citation: M
Benatti S, C
transcriptio
Hodgkin ly
fever. PLoS
10.1371/jo

"… we have identified a transcriptomic signature from PBMC of patients with C. burnetii-associated lymphoma that consists of the overexpression of several genes including MIR17HG, REL and SP100. Patients with C. burnetii lymphadenitis presented high level of BCL2 mRNA in blood, shared a similar transcriptomic signature with patients infected with C. burnetii and were diagnosed with lymphoma. This argues in favor of the hypothesis that C. burnetii lymphadenitis may facilitate subsequent lymphomagenesis leading to NHL."

Source: https://ashpublications.org/blood/article/127/1/113/34853/B-cell-non-Hodgkin-lymphoma-linked-to-Coxiella; https://academic.oup.com/cid/article-abstract/20/3/489/321561?redirectedFrom=fulltext

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"Children treated for acute leukaemia … at risk of severe Varicella Zoster Virus"

Pediatr Blood Cancer 2014;61:2077–2079

BRIEF REPORT

Varicella Zoster Immune Status in Children Treated for Acute Leukemia

Soonie R. Patel, MBChB, MRCPCH, MD,[1]* Jessica Bate, MBBS, MA, MRCPCH,[2] Peter A.C. Maple, BSc(Hons), MSc, PhD, FIBMS,[3] Kevin Brown, MD, MRCP FRCPath,[3] Judith Breuer, MBBS, MD, FRCPath,[4] and Paul T. Heath, MBBS(Hons), FRACP, MRCPCH[2]

Children treated for acute leukemia are at increased risk of severe infection with varicella zoster virus (VZV). We studied the VZV sero-status of children with acute leukemia prior to starting chemotherapy and after completion of chemotherapy. VZV sero-status was assessed using time resolved fluorescence immunoassay (TRFIA) before starting treatment and 6 months after completion of treatment. Prior to starting treatment for acute leukemia, a significant proportion of children (35%) are VZV seronegative. On completion of treatment most patients maintained protective VZV antibody levels; however, 35% had reduced/loss VZV antibody to a level considered non-protective and susceptible to VZV infection. Pediatr Blood Cancer 2014;61:2077–2079. © 2014 Wiley Periodicals, Inc.

Key words: acute leukemia; children; immunity; varicella zoster virus

INTRODUCTION

Varicella zoster virus (VZV) is a human alphaherpesvirus, which causes Varicella (chicken pox) as the primary infection. As with other alphaherpesviruses VZV establishes latency and re-activates to cause Herpes zoster (shingles). VZV is lymphotropic (for CD4 and CD8 lymphocytes) and also induces production of cytotoxic T cells that recognize and destroy virus-infected cells [1]. Varicella in lymphopenic individuals however, can result in severe disease with increased risk of dissemination and death [2,3].

Leukemia is the most common form of childhood malignancy; acute lymphoblastic leukemia (ALL) represents about 80% of cases, acute myeloid leukemia (AML) about 15% [4]. Both the disease and the treatment are immune suppressive; leukemia has an effect on the adaptive immune system [5,6], and chemotherapy causes reductions of B-lymphocyte [7], T-lymphocyte [8] and total immunoglobulin (Ig) levels [6,9]. B- and T-lymphocyte function

We studied the VZV sero-status of children prior to starting chemotherapy and after completion of chemotherapy for acute leukemia.

METHODS

Patient Population

The study was conducted over a 2-year period, from 1st October 2002 to 30th September 2004. Patients were recruited from the Paediatric Department at The Royal Marsden Hospital (RMH), Sutton, UK. Patients were recruited as part of a re-vaccination study that entailed measurement of specific antibody concentrations against vaccine preventable infections. Eligible patients were aged 1–18 years, diagnosed with ALL or AML and starting chemotherapy according to the Medical Research Council of United Kingdom ALL (MRC UKALL97 modified UKALL99, and for disease relapsed patients UKALL R2) and UKAML (UKAML10 or

> Pediatr Blood Cancer. 2014 Nov;61(11):2077-9. doi: 10.1002/pbc.25086. Epub 2014 May 2.

Varicella zoster immune status in children treated for acute leukemia

Soonie R Patel [1], Jessica Bate, Peter A C Maple, Kevin Brown, Judith Breuer, Paul T Heath

Affiliations + expand

PMID: 24789692 DOI: 10.1002/pbc.25086

Abstract

Children treated for acute leukemia are at increased risk of severe infection with varicella zoster virus (VZV). We studied the VZV sero-status of children with acute leukemia prior to starting chemotherapy and after completion of chemotherapy. VZV sero-status was assessed using time resolved fluorescence immunoassay (TRFIA) before starting treatment and 6 months after completion of treatment. Prior to starting treatment for acute leukemia, a significant proportion of children (35%)

> Pediatr Hematol Oncol. 1996 May-Jun;13(3):231-8. doi: 10.3109/08880019609030821.

Varicella zoster infections in children with acute lymphoblastic leukemia

A Poulsen [1], K Schmiegelow, M Yssing

Affiliations + expand

PMID: 8735338 DOI: 10.3109/08880019609030821

Abstract

During the period July 1986 through December 1991, 67 children were treated for non-B-cell acute lymphoblastic leukemia at The Juliane Marie Centre, GGK, The University Hospital Rigshospitalet, Copenhagen. Twenty-five children were susceptible to varicella zoster (VZ) virus at diagnosis. For these patients the cumulated risk of VZ exposure was 90% after 32 months. Five patients developed varicella (two of whom had pneumonitis) during the period of antileukemic treatment. Two of these

"VZV is lymphotropic (for CD4 and CD8 lymphocytes) and also induces production of cytotoxic T cells that recognize and destroy virus-infected cells [1]. Varicella in lymphopenic individuals, however, can result in severe disease"

Source: *Patel SR, Bate J, Maple PA, Brown K, Breuer J, Heath PT. Varicella zoster immune status in children treated for acute leukemia. Pediatr Blood Cancer. 2014 Nov;61(11):2077-9.*

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Chronic lymphocytic leukaemia is highly sensitive to infection by HSV1

Cancer. 1999 Oct 1;86(7):1210-5.

Herpes lymphadenitis in association with chronic lymphocytic leukemia

J P Higgins [1], R A Warnke

Affiliations + expand

PMID: 10506706

Abstract

Background: Herpes simplex virus (HSV) infections range in severity from common cutaneous outbreaks to life-threatening central nervous system and deep organ involvement. HSV lymphadenitis is extremely rare but occurs both as a component of widely disseminated disease and as a localized, mild illness.

Methods: Five patients with chronic lymphocytic leukemia (CLL) underwent lymph node biopsy and were found to have histologic and immunophenotypic evidence of HSV infection in association with CLL.

Gene Ther. 2000 Jul;7(14):1210-6. doi: 10.1038/sj.gt.3301241.

Chronic lymphocytic leukemia B cells are highly sensitive to infection by herpes simplex virus-1 via herpesvirus-entry-mediator A

D J Eling [1], P A Johnson, S Sharma, F Tufaro, T J Kipps

Affiliations + expand

PMID: 10918489 DOI: 10.1038/sj.gt.3301241

Abstract

We found that chronic lymphocytic leukemic (CLL) B cells are highly sensitive to infection with vectors derived from replication-defective herpes simplex virus-1 (rdHSV-1). CLL B cells were found to express high levels of herpes virus entry mediator (Hve) A, but not HveC, the other known receptor for HSV-1. An HveA cDNA from CLL cells was found to encode Arg-->Lys and Val-->Iso substitutions at amino acids 17 and 241, respectively. Nevertheless, this cDNA encoded a functional receptor for HSV-1 when transfected into Chinese hamster ovarian (CHO) cells. Antibodies to HveA could block rdHSV-1 infection of CLL cells and HveA-transfected CHO cells with similar efficiencies in vitro. In contrast to B cells of normal donors, CLL B cells were resistant to the cytopathic effects of infection by rdHSV-1 and maintained high-level expression of the transgene for several days in vitro. We propose that this is due to the expression by CLL cells of the anti-apoptotic protein, bcl-2. Consistent with this, we found

Journal of Hematology, Vol. 8, No. 2, Jun 2019

Journal of Hematology, ISSN 1927-1212 print, 1927-1220 online, Open Access

Journal website http://www.thejh.org

Case Report

Volume 8, Number 2, June 2019, pages 79-82

Herpes Simplex Necrotic Lymphadenitis Masquerading as Richter's Transformation in Treatment-Naive Patients With Chronic Lymphocytic Leukemia

Yan Amber Hodgson[a, d], Stephen Gareth Jones[b], Helen Knight[a], Vishakha Sovani[c], Christopher Paul Fox[a]

There are reports of Herpes Simplex Virus masquerading as Chronic Lymphocytic Leukaemia

Source: *Higgins JP, Warnke RA. Herpes lymphadenitis in association with chronic lymphocytic leukemia. Cancer. 1999 Oct 1;86(7):1210-5; https://pubmed.ncbi.nlm.nih.gov/10506706/; Eling DJ, Johnson PA, Sharma S, Tufaro F, Kipps TJ. Chronic lymphocytic leukemia B cells are highly sensitive to infection by herpes simplex virus-1 via herpesvirus-entry-mediator A. Gene Ther. 2000 Jul;7(14):1210-6.https://pubmed.ncbi.nlm.nih.gov/10918489/*

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What cancers have pathogens been associated with?

- Breast cancer
- Blood cancers
- **Monoclonal Gammopathy (MGUS)**
- Glioblastoma
- Prostate

Bartonella and MGUS (Monoclonal Gammopathy of Undetermined Significance)

Am J Hematol. 2006 Feb;81(2):115-7.

Transient monoclonal gammopathy in a patient with Bartonella quintana endocarditis.

Sève P[1], Turner R, Stankovic K, Perard L, Broussolle C.

Author information

Abstract

Monoclonal gammopathy has been reported rarely in association with infectious diseases. Viral infection has been the most frequently reported. We report a case of Bartonella quintana endocarditis in a 45-year-old homeless male associated with a monoclonal IgG kappa gammopathy. The gammopathy disappeared after 8 months of antibiotics while the Bartonella antibody titre was decreasing. This correlation suggests a causative role for B. quintana for the monoclonal gammopathy. To the best of our knowledge, this the first report of monoclonal gammopathy in the course of B. quintana infection.

PMID: 16432867 DOI: 10.1002/ajh.20499

[Indexed for MEDLINE] Free full text

"This correlation suggests a causative role for B. quintana for the monoclonal gammopathy."

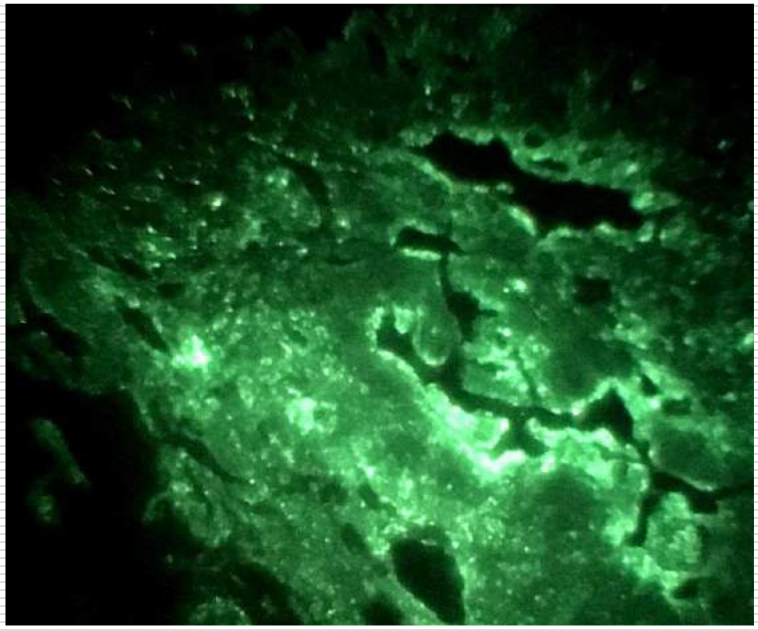
"The gammopathy disappeared after 8 months of antibiotics"

Source: Am J Hematol. 2006 Feb;81(2):115-7

What cancers have pathogens been associated with?

- Breast cancer
- Blood cancers
- Monoclonal Gammopathy
- **Glioblastoma**
- Prostate

Borrelia in Glioblastoma Multiformae



Glioblastoma Multiformae Brain Biopsies - Formalin fixed- with Immunohistochemical Full Panel evaluation and Confirmation of Diagnosis by neuropathologist- ---
Images (3 per case) of FISH DNA probe for detection of Burgdorferi Borrelia DNA with DNA probes specific for gene of Inner cell membrane of Burgdorferi Borrelia Gene bbo 0740- Validated DNA probe and all Controls acceptable

Alan MacDonald, M.D., FCAP, Copyright, year 2016 January, all rights reserved

"In the case of neurons, glial cells and Borrelia, there is evidence from co-incubation of cells in tissue culture with living Borrelia in pure cultures that Borrelia first binds to the tissue cultured cells, and then, stepwise, inserts the entire spirochete into the cytoplasm and then into the nucleus of glial cells. Liposomes from Borrelia's outer surface membrane contain DNA. Transmission electron micrographs have imaged the transit of Borrelia liposomes from the external cellular milieu, to penetrate the cytoplasm of eukaryotic cells, and next to penetrate the nucleus."

Source: *Alan MacDonald, M.D., FCAP, Copyright, Jan. 2016, https://durayresearch.files.wordpress.com/2016/01/report-for-gbm-cases-five-with-fish-probes.pdf; https://www.lymeneteurope.org/forum/viewtopic.php?t=6048*

"In Glioblastoma patients, Cytomegalovirus activity is higher than in healthy controls"

OncoImmunology

Taylor & Francis

ISSN: (Print) 2162-402X (Online) Journal homepage: https://www.tandfonline.com/loi/koni20

Discordant humoral and cellular immune responses to *Cytomegalovirus* (CMV) in glioblastoma patients whose tumors are positive for CMV

Afsar Rahbar, Inti Peredo, Nina Wolmer Solberg, Chato Taher, Mensur Dzabic, Xinling Xu, Petra Skarman, Olesja Fornara, Charlotte Tammik, Koon Yaiw, Vanessa Wilhelmi, Alice Assinger, Giuseppe Stragliotto & Cecilia Söderberg-Naucler

To cite this article: Afsar Rahbar, Inti Peredo, Nina Wolmer Solberg, Chato Taher, Mensur Dzabic, Xinling Xu, Petra Skarman, Olesja Fornara, Charlotte Tammik, Koon Yaiw, Vanessa Wilhelmi, Alice Assinger, Giuseppe Stragliotto & Cecilia Söderberg-Naucler (2015) Discordant humoral and cellular immune responses to *Cytomegalovirus* (CMV) in glioblastoma patients whose tumors are positive for CMV, OncoImmunology, 4:2, e982391, DOI: 10.4161/2162402X.2014.982391

To link to this article: https://doi.org/10.4161/2162402X.2014.982391

"Emerging evidence suggests that human Cytomegalovirus (HCMV) is present in 90–100% of GBMs and that add-on antiviral treatment for HCMV shows promise to improve survival."

Neuro-Oncology 14(3):246–255, 2012.
doi:10.1093/neuonc/nor227
Advance Access publication February 8, 2012

NEURO-ONCOLOGY

Consensus on the role of human cytomegalovirus in glioblastoma

Kristine Dziurzynski, Susan M. Chang, Amy B. Heimberger, Robert F. Kalejta, Stuart R. McGregor Dallas, Martine Smit, Liliana Soroceanu, and Charles S. Cobbs, the HCMV and Gliomas Symposium†

Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas (K.D., A.B.H.); Neurological Surgery, the University of California at San Francisco, San Francisco, California (S.M.C., C.S.C.); Institute for Molecular Virology and McArdle Laboratory for Cancer Research, the University of Wisconsin-Madison, Madison, Wisconsin (R.F.K.); Molecular Biology, Lewis Thomas Laboratory, Princeton University, Princeton, New Jersey (S.R.M.D.); Department of Medicinal Chemistry, Faculty of Sciences, VU University Amsterdam, The Netherlands (M.J.S.); and California Pacific Medical Center Research Institute, San Francisco, California (C.S.C., L.S.)

"… there is sufficient evidence to conclude that HCMV could modulate the malignant phenotype in glioblastomas by interacting with key signaling pathways"

Source: *Rahbar A, Peredo I, Solberg NW, Taher C, Dzabic M, Xu X, Skarman P, Fornara O, Tammik C, Yaiw K, Wilhelmi V, Assinger A, Stragliotto G, Söderberg-Naucler C. Discordant humoral and cellular immune responses to Cytomegalovirus (CMV) in glioblastoma patients whose tumors are positive for CMV. Oncoimmunology. 2015 Feb 25;4(2):e982391.https://pubmed.ncbi.nlm.nih.gov/25949880/*

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Glioblastoma and Toxoplasmosis, Cancer Epidemiology 2021

Received: 17 July 2020 | Revised: 12 November 2020 | Accepted: 3 December 2020
DOI: 10.1002/ijc.33443

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Toxoplasma gondii infection and the risk of adult glioma in two prospective studies

James M. Hodge[1] | Anna E. Coghill[2] | Youngchul Kim[3] | Noemi Bender[4] | Stephanie A. Smith-Warner[5] | Susan Gapstur[1] | Lauren R. Teras[1] | Tom K. Grimsrud[6] | Tim Waterboer[4] | Kathleen M. Egan[2]

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[2]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida
[3]Department of Biostatistics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida
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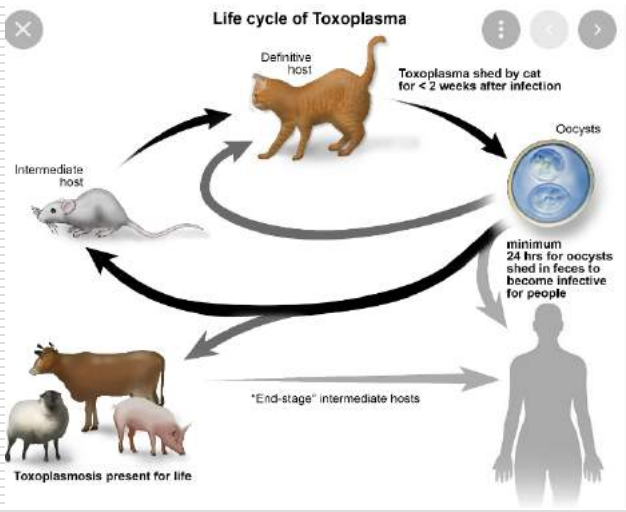
[5]Department of Nutrition and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
[6]Department of Research, Cancer Registry of Norway, Oslo, Norway

Correspondence

Abstract

Toxoplasma gondii (*T gondii*) is a common parasite that shows affinity to neural tissue and may lead to the formation of cysts in the brain. Previous epidemiologic studies have suggested an association between glioma and increased prevalence of *T gondii* infection, but prospective studies are lacking. Therefore, we examined the association between prediagnostic *T gondii* antibodies and risk of glioma in two prospective cohorts using a nested case-control study design. Cases and matched controls were selected from the American Cancer Society's Cancer Prevention Study-II Nutrition Cohort (CPSII-NC) (n = 37 cases and 74 controls) and the Norwegian Cancer Registry's Janus Serum Bank (Janus) (n = 323 cases and 323 controls). Blood samples collected prior to diagnosis were analyzed for antibodies to two *T gondii* surface antigens (p22 and sag-1), with individuals considered seropositive if antibodies to either antigen were detected. Conditional logistic regression was used to calculate odds

"Our findings provide the first prospective evidence of an association between T gondii infection and risk of glioma."
"The findings do suggest that individuals with higher exposure to the *T gondii* parasite are more likely to go on to develop glioma," (Study author, Anna Coghill, PhD), "though further research is needed."



Source: *https://onlinelibrary.wiley.com/doi/10.1002/ijc.33443; https://ascopost.com/news/january-2021/association-between-toxoplasma-gondii-infection-and-risk-of-glioma/#:~:text=A%20new%20study%20published%20by,group%20that%20was%20cancer%2Dfree; https://www.vet.cornell.edu/departments-centers-and-institutes/cornell-feline-health-center/health-information/feline-health-topics/toxoplasmosis-cats*

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T. gondii inhibits glioblastoma apoptosis by targeting a purinergic signalling pathway (finding in 2019)

Zhou et al. Parasites Vectors (2019) 12:284
https://doi.org/10.1186/s13071-019-3529-1

Parasites & Vectors

RESEARCH Open Access

Toxoplasma gondii ROP18 inhibits human glioblastoma cell apoptosis through a mitochondrial pathway by targeting host cell P2X1

Li-Juan Zhou[1], Min Chen[1], Santhosh Puthiyakunnon[1], Cheng He[1], Jing Xia[1], Cynthia Y. He[2], Sheng-Qun Deng[1] and Hong-Juan Peng[1*]

Abstract

Background: Apoptosis plays a critical role in the embryonic development, homeostasis of immune system and host defense against intracellular microbial pathogens. Infection by the obligate intracellular pathogen *Toxoplasma gondii* can both inhibit and induce host cell apoptosis; however, the parasitic factors involved remain unclear. The *T. gondii* virulence factor ROP18 (*Tg*ROP18) has been reported to regulate host cell apoptosis; nevertheless, results for this regulation have been rarely reported or have provided contradictory findings. Human purinergic receptor 1 (P2X1) is an ATP-gated ion channel that responds to ATP stimulation and functions in cell apoptosis mediation. The precise roles of *Tg*ROP18 in *T. gondii* pathogenesis, and the relationship between *Tg*ROP18 and host P2X1 in host cell apoptosis are yet to be revealed.

Methods: Apoptosis rates were determined by flow cytometry (FCM) and TUNEL assay. The interaction between *Tg*ROP18 and the host P2X1 was measured by fluorescence resonance energy transfer (FRET) and co-immunoprecipitation (co-IP) assay. Calcium influx and mitochondrial membrane depolarization were determined by FCM after JC-1 staining. The translocation of cytochrome C (Cyt C), Bax and Bcl2 proteins, expression of the apoptotic proteins PARP and caspase activation were detected by western blotting.

Results: The apoptosis rates of glial or immune cells (human SF268, mouse RAW264.7 and human THP-1 cells) infected by any *T. gondii* strain (RH-type I, ME49-type II and VEG-type III) were significantly inhibited compared with their uninfected controls. *Tg*ROP18 inhibited ATP-induced apoptosis of SF268 with P2X1 expression, but had no effect on RAW264.7 or THP-1 cells without detectable P2X1 expression. It was further identified that *Tg*ROP18 interacted with P2X1, and overexpression of ROP18 in COS7 cells significantly inhibited cell apoptosis mediated by P2X1. Moreover, *Tg*ROP18 also inhibited P2X1-mediated Ca^{2+} influx, translocation of cytochrome C from the mitochondria to the

"Here, individuals who were seropositive for exposure to antigens from the tachyzoite stage of the parasite life cycle were more likely to be diagnosed with glioma in the 13 years following blood collection."

NB: Toxoplasmosis may masquerade as a glioma ↓

ELSEVIER

Interdisciplinary Neurosurgery
Volume 17, September 2019, Pages 57-59

Case Reports & Case Series

Case of cerebral toxoplasmosis masquerading as high-grade glioma

Kathleen P. McKenzie [a], Winnifred M. Wong [b], Shane B. Patterson [c], Joseph H. McDermott [d], Narayana K. Swamy [e], Claire L. Hiles [f]

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Source: *1. https://parasitesandvectors.biomedcentral.com/track/pdf/10.1186/s13071-019-3529-1.pdf;*
2. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X%2814%2962509-X/fulltext

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The role of mycoplasma and glioblastoma

Infectious Agents and Cancer
BMC

Role of infectious agents in the carcinogenesis of brain and head and neck cancers

Kenneth Alibek, Ainur Kakpenova, and Yeldar Baiken

"Mycoplasma infections have been found in different types of carcinoma tissue, including glioma" The association appears primarily indirect so far, due to cytokine-mediated damage and inflammatory lesions

Biochim Biophys Acta Bioenerg. 2018 Sep;1859(9):975-983. doi: 10.1016/j.bbabio.2018.03.012. Epub 2018 Mar 23.

Mycoplasma infection and hypoxia initiate succinate accumulation and release in the VM-M3 cancer cells

Roberto E Flores [1], Ashley K Brown [1], Luke Taus [1], Julianna Khoury [1], Frank Glover [1], Kenjiro Kami [2], Rangaprasad Sarangarajan [3], Tony E Walshe [3], Niven R Narain [3], Michael A Kiebish [3], Laura M Shelton [2], Christos Chinopoulos [4], Thomas N Seyfried [5]

Affiliations + expand

PMID: 29580805 DOI: 10.1016/j.bbabio.2018.03.012
Free article

Abstract

Succinate is known to act as an inflammatory signal in classically activated macrophages through stabilization of HIF-1α leading to IL-1β production. Relevant to this, hypoxia is known to drive succinate accumulation and release into the extracellular milieu. The metabolic alterations associated

Metabolic pathways linked to Mycoplasma are responsible for succinate accumulation and release in cancer cells, thus identifying potential targets involved in both inflammation and hypoxia.

Source: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573938/pdf/1750-9378-8-7.pdf;* Huang S, Li JY, Wu J, Meng L, Shou CC: Mycoplasma infections and different human carcinomas. World J Gastroenterol 2001, 7:266–269; https://pubmed.ncbi.nlm.nih.gov/29580805/

What cancers have pathogens been associated with?

- Breast cancer
- Blood cancers
- Monoclonal Gammopathy
- Glioblastoma
- **Prostate**

Strong mycoplasma link with prostate cancer, too …

Journal List › Oncotarget › v.2(4); 2011 Apr › PMC3248169

Oncotarget
Open Access Impact Journal

Oncotarget. 2011 Apr; 2(4): 289–297. PMCID: PMC3248169
Published online 2011 Apr 4. doi: 10.18632/oncotarget.256

Association of *Mycoplasma hominis* infection with prostate cancer

Yulia A. Barykova,[1] Denis Yu. Logunov,[1] Maxim M. Shmarov,[1] Andrei Z. Vinarov,[2] Dmitry N. Fiev,[2] Natalia A. Vinarova,[2] Irina V. Rakovskaya,[1] Patricia Stanhope Baker,[3] Inna Shyshynova,[3,5] Andrew J. Stephenson,[4] Eric A. Klein,[4] Boris S. Naroditsky,[1] Alexander L. Gintsburg,[1] and Andrei V. Gudkov[3,5]

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See commentary "Mycoplasma and cancer: in search of the link" on page 271.
See commentary "The "Infectious" Nature of Human Prostate Cancer: A Cautionary Note" on page 281.

This article has been cited by other articles in PMC.

Abstract

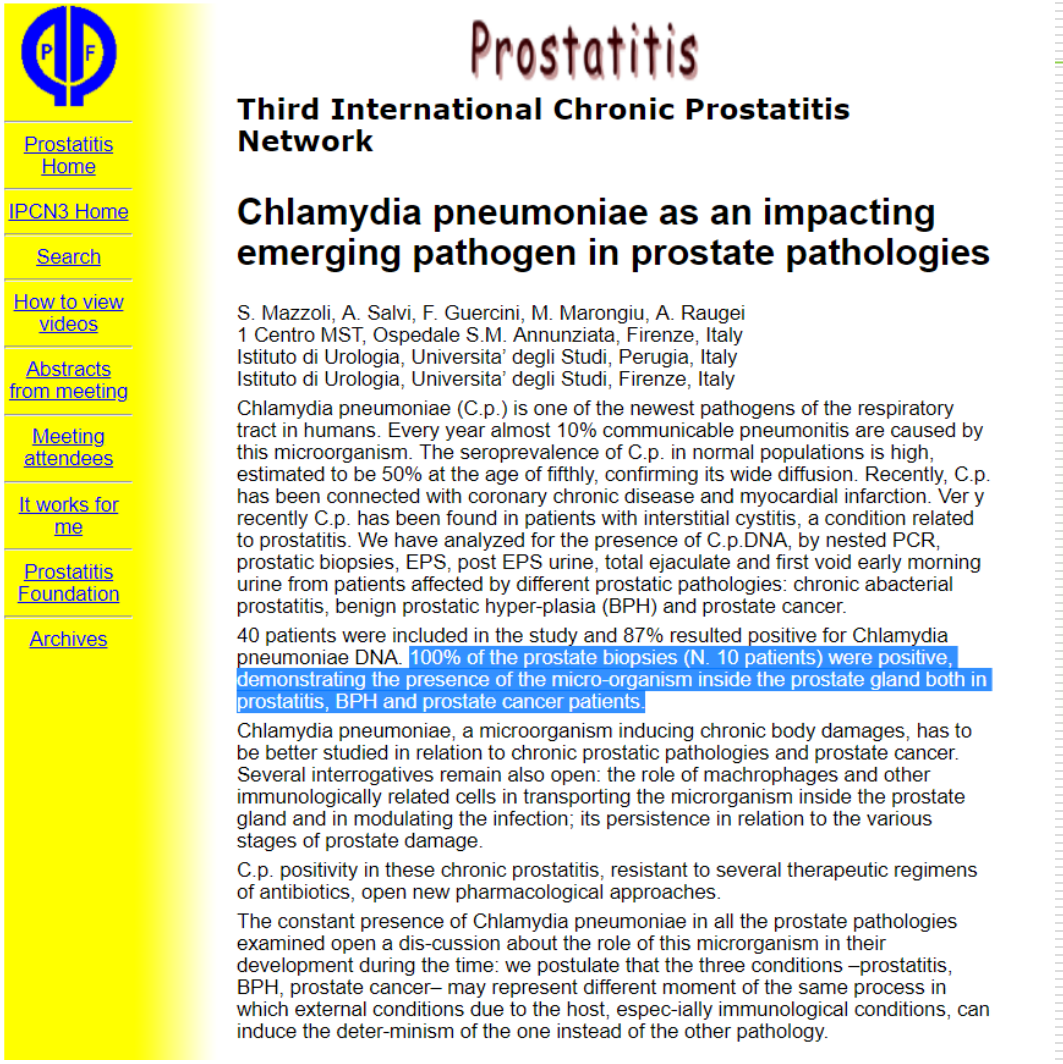
Go to:

The origin of chronic inflammation preceding the development of prostate cancer (PCa) remains unknown. We investigated possible involvement of mycoplasma infection in PCa by screening prostate biopsies from two groups of Russian men undergoing PCa diagnosis. *M. hominis* was detected by standard PCR in 15% of the 125 patients in the first group and by quantitative real-time PCR in 37.4% of the 123 men in the second group. In both groups, stratification of patients according to diagnosis showed that *M. hominis* was present at three times higher frequency in patients with PCa than in those with benign prostatic hyperplasia. No *M. hominis* was detected in the prostates of 27 men without detectable prostate disease. In addition, PCa-positive men had higher titers of antibodies against *M. hominis* and average PSA levels were higher in *M. hominis*-positive men. These data, together with previous observations linking mycoplasma infection with cell transformation, genomic instability and resistance to apoptosis, suggest that *M. hominis* infection may be involved in PCa development and may, therefore, be a potential PCa marker and/or target for improved prevention and treatment of this disease.

"This study by Barykova *et al*. [7] is the latest of several that indicate **a strong link between mycoplasma species and prostate cancer**"

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248167/

Chlamydia pneumoniae in prostate cancer



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Chlamydia pneumoniae as an impacting emerging pathogen in prostate pathologies

S. Mazzoli, A. Salvi, F. Guercini, M. Marongiu, A. Raugei
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Istituto di Urologia, Universita' degli Studi, Perugia, Italy
Istituto di Urologia, Universita' degli Studi, Firenze, Italy

Chlamydia pneumoniae (C.p.) is one of the newest pathogens of the respiratory tract in humans. Every year almost 10% communicable pneumonitis are caused by this microorganism. The seroprevalence of C.p. in normal populations is high, estimated to be 50% at the age of fifthly, confirming its wide diffusion. Recently, C.p. has been connected with coronary chronic disease and myocardial infarction. Ver y recently C.p. has been found in patients with interstitial cystitis, a condition related to prostatitis. We have analyzed for the presence of C.p.DNA, by nested PCR, prostatic biopsies, EPS, post EPS urine, total ejaculate and first void early morning urine from patients affected by different prostatic pathologies: chronic abacterial prostatitis, benign prostatic hyper-plasia (BPH) and prostate cancer.

40 patients were included in the study and 87% resulted positive for Chlamydia pneumoniae DNA. 100% of the prostate biopsies (N. 10 patients) were positive, demonstrating the presence of the micro-organism inside the prostate gland both in prostatitis, BPH and prostate cancer patients.

Chlamydia pneumoniae, a microorganism inducing chronic body damages, has to be better studied in relation to chronic prostatic pathologies and prostate cancer. Several interrogatives remain also open: the role of machrophages and other immunologically related cells in transporting the microrganism inside the prostate gland and in modulating the infection; its persistence in relation to the various stages of prostate damage.

C.p. positivity in these chronic prostatitis, resistant to several therapeutic regimens of antibiotics, open new pharmacological approaches.

The constant presence of Chlamydia pneumoniae in all the prostate pathologies examined open a dis-cussion about the role of this microrganism in their development during the time: we postulate that the three conditions –prostatitis, BPH, prostate cancer– may represent different moment of the same process in which external conditions due to the host, espec-ially immunological conditions, can induce the deter-minism of the one instead of the other pathology.

"100% of the prostate biopsies (N. 10 patients) **were positive**, **demonstrating the presence of the micro-organism inside the prostate** gland both in prostatitis, benign prostate hyperplasia and **prostate cancer patients**."

Source: https://www.prostatitis.org/a212000.html

A 2013 meta-analysis showed that HSV-2 is associated with elevated prostate cancer risk

"HSV-2 infection was associated with increased prostate cancer risk (OR=1.209; 95% CI, 1.003–1.456). Results of the stratified analysis suggested that such an association existed among participants from North and South America (OR=1.226; 95% CI, 1.000–1.503)."[1]

"… preceding herpes zoster infection is a suggestive risk marker for subsequent PCa after controlling for potential confounders …
It is suggested that herpes zoster could be **an early manifestation of immune impairment** associated with occult malignancy. Second, the **herpes zoster may weaken the immune system, which allows tumor cells to escape from immune surveillance**"[2]

Source: 1. Ge X, Wang X, Shen P. Herpes simplex virus type 2 or human herpesvirus 8 infection and prostate cancer risk: A meta-analysis. Biomed Rep. 2013 May;1(3):433-439; https://pubmed.ncbi.nlm.nih.gov/24648964/; 2. Tsao, Yao-Hsuan et al. Herpes zoster and the subsequent risk of prostate cancer in an Asian population, Medicine: October 02, 2020 - Volume 99 - Issue 40 https://journals.lww.com/md-journal/fulltext/2020/10020/ herpes_zoster_ and_the_subsequent_risk_of_prostate.49.aspx

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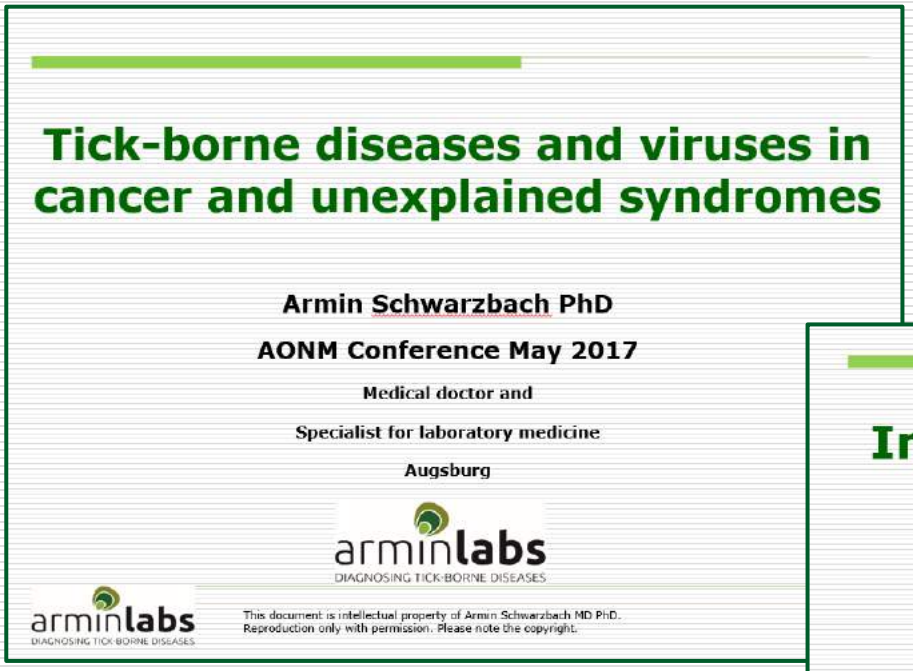
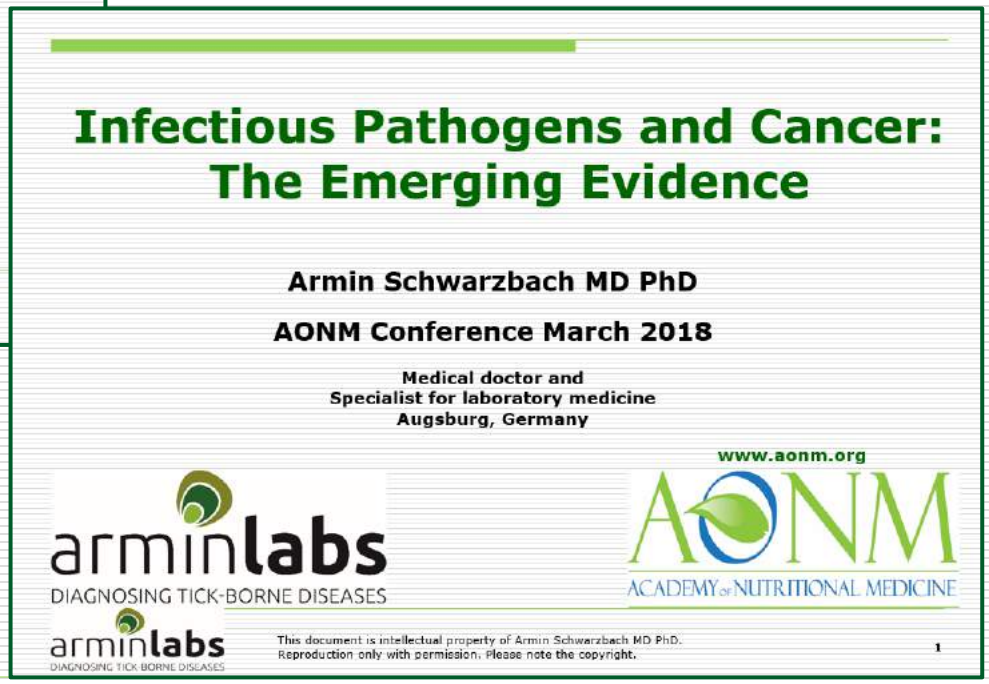
Further presentations on the links between pathogens and cancer available from AONM





See https://aonm.org/cancer-webinar-series/

Tailored testing protocols available for all the types of cancer mentioned

Please request from AONM (0333 121 0305)

Test panels in different cancers

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Breast cancer

Borrelia: EliSpot, Tickplex Basic
EBV: EliSpot, Immunoarray
CMV: EliSpot
Mycoplasma: EliSpot, IgG/IgA
Bartonella: EliSpot

Blood cancers

EBV: EliSpot, Immunoarray
HHV6: EliSpot
Ehrlichia/Anaplasma
Borrelia: EliSpot, Tickplex Basic
CMV: EliSpot
Babesia: EliSpot
Coxiella/Q Fever: IgG/IgM
Varicella Zoster Virus: EliSpot, IgG/IgA
HSV1: EliSpot, IgG/IgM/IgA

Monoclonal Gammopathy (MGUS)

Bartonella: EliSpot

Glioblastoma

Borrelia: EliSpot, Tickplex Basic
CMV: EliSpot
Toxoplasma: IgG/IgM
Mycoplasma: EliSpot, IgG/IgA

Prostate cancer

Mycoplasma: EliSpot, IgG/IgA
Chlamydia pneumoniae: EliSpot, IgG/IgA
HSV 2: EliSpot, IgG/IgM/IgA

Part 2 on September 6th, 7.00 pm

The connection between infections and cancer:

Part 2:

- **Lung**
- **Colorectal**
- **Gastric**
- **Oesophageal**
- **Cervical cancer**

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Thank you very much for your attention!

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SARS-CoV-2 and cancer: associations evident, but too early for long-term studies

Review | Open Access | Published: 17 May 2021

The intersection of COVID-19 and cancer: signaling pathways and treatment implications

Zhi Zong, Yujun Wei, Jiang Ren, Long Zhang & Fangfang Zhou

Molecular Cancer **20**, Article number: 76 (2021) | Cite this article

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Abstract

The outbreak of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a serious public healt concern. Patients with cancer have been disproportionately affected by this pandemic. Increasing evidence has documented that patients with malignancies are highly susceptil severe infections and mortality from COVID-19. Recent studies have also elucidated the molecular relationship between the two diseases, which may not only help optimize canc care during the pandemic but also expand the treatment for COVID-19. In this review, we highlight the clinical and molecular similarities between cancer and COVID-19 and summ the four major signaling pathways at the intersection of COVID-19 and cancer, namely, cytokine, type I interferon (IFN-I), androgen receptor (AR), and immune checkpoint sign In addition, we discuss the advantages and disadvantages of repurposing anticancer treat for the treatment of COVID-19.

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In this review, we highlight the clinical and molecular similarities between cancer and COVID-19 and summarize the four major signaling pathways at the intersection of COVID-19 and cancer, namely, cytokine, type I interferon (IFN-I), androgen receptor (AR), and immune checkpoint signaling. In addition, we discuss the advantages and disadvantages of repurposing anticancer treatment for the treatment of COVID-19."

Source: *https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-021-01363-1*

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