Infectious Pathogens and Cancer: The Emerging Evidence

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Armin Schwarzbach MD PhD
Medical doctor and
Specialist for laboratory medicine
Augsburg, Germany

ArminLabs
Laboratory for tick-borne diseases

www.aonm.org

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WHO, 1997: “Up to 84% of cases of some cancers are attributable to viruses, bacteria, and parasites”

“A growing body of research suggests that a number of viruses, bacteria, and parasites cause cancer in humans, thus providing new possibilities for treatment and prevention of cancer. In 1997, the World Health Organization estimated that up to 84% of cases of some cancers are attributable to viruses, bacteria and parasites, and that more than 1.5 million (15%) new cases each year could be avoided by preventing the infectious disease associated with them. ... The pathogenic mechanisms by which infectious agents cause cancer have not been resolved but they appear to be diverse. ... This finding not only suggests a causal role but that treatment of a bacterial infection can actually result in regression of cancer.”

Cassell, GH. Infectious Causes of Chronic Inflammatory Diseases and Cancer Emerging Infectious Diseases. National Center for Infectious Diseases. Centers for Disease Control and Prevention, Atlanta, GA.

“... since the discovery of links between H. pylori and gastric lymphomas and adenocarcinomas, and HPV-induced neoplasias from mouth to anal domains, chronic infections have provided a model to explain the transit of a benign cell into a malignant cell.”

Alan B. MacDonald, M.D., Fellow, College of American Pathologists, January 2016

Infectious Pathogens and Cancer: The Emerging Evidence

1. Stealth bacteria involvement
2. Viral involvement
3. Indirect involvement
Infectious Pathogens and Cancer: The Emerging Evidence

1. Stealth bacteria involvement
   ► Borrelia
   ► Bartonella
   ► Babesia
   ► Chlamydia pneumoniae
   ► Mycoplasma
   ► Chlamydia trachomatis
   ► Ehrlichia
   ► Toxoplasma

2. Viral involvement

3. Indirect involvement
Borrelia and non-Hodgkin/mantle cell lymphoma

“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”
Borrelia in Glioblastoma Multiformae

Glioblastoma Multiformae Brain Biopsies - Formalin fixed- with Immunohistochemical Full Pam=nelPane 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.”

Bartonella is able to produce tumours

Current Knowledge of Bartonella Species

M. Maurin, R. Birtles, D. Raoult*

Bartonella species are now considered emerging pathogens. Of the 11 currently recognized species, four have been implicated in human disease, although only two have been encountered in Europe. Bartonella quintana infections are now being diagnosed among the urban homeless and deprived, manifesting as trench fever, and Bartonella henselae has been shown to be the causative agent of cat scratch disease. Both species also cause a variety of HIV-associated infections, including bacillary angiomatosis. However, perhaps the most significant presentation of bartonellae infection is culture-negative endocarditis. The epidemiologies of Bartonella infections are poorly understood; most Bartonella henselae infections are probably acquired from infected cats, either directly by contact with a cat or indirectly via fleas. No animal reservoir has been implicated for Bartonella quintana; however, infection can be transmitted via the human body louse. Diagnosis of Bartonella infections can be made using histological or microbiological methods. The demonstration of specific antibodies may be useful in some instances, although certainly not in all. Cultivation of Bartonella is difficult, as the bacteria are extremely fastidious. Polymerase chain reaction-based or immunological methods for the detection of bartonellae in infected tissues have proven useful. Clinical relapse is often associated with Bartonella infections despite a wide range of prescribed regimens. Only aminoglycosides display in vitro bactericidal activity against intracellular Bartonella species; therefore, they are recommended for treatment of Bartonella infections.

Human infections due to Bartonella species are widely considered emerging diseases. They include long-recognized diseases such as Carrion’s disease (classic bartonellosis), trench fever, and cat-scratch disease and newer clinical manifestations such as bacillary angiomatosis, peliosis hepaticis, septicemia, endocarditis, chronic lymphadenopathy, and neurologic disorders. New molecular biology techniques, mainly based on 16S rRNA gene amplification and analysis, have allowed recognition of the role of Bartonella (formerly Rochalimaea) species in a number of these illnesses. The most striking pathological feature of Bartonella infection is the apparent ability of these bacteria to produce angioproliferative lesions in immunocompromised patients, such as those infected with HIV. Capillary and endothelial cell proliferations are characteristic histologic findings of bacillary angiomatosis, peliosis hepaticis, and classic bartonellosis.


“Bartonellae are the only known bacteria with the ability to produce angiogenic tumors in humans”
In Vitro Model of *Bartonella henselae*-Induced Angiogenesis

James E. Kirby

**ABSTRACT**

*Bartonella henselae* is a gram-negative pathogen that causes angiogenesis. Here, I establish in vitro models to study *Bartonella*-induced blood vessel formation. I found that *B. henselae* induces long-term endothelial survival and tubular differentiation within type I collagen matrix.

*Bartonella henselae* is an emerging bacterial pathogen that causes disease (endocarditis, and angioproliferative lesions in AIDS patient). Angioproliferative lesions are the most unique and defining feature of proliferating endothelial cells, these aggregates of immature vas abnormal form of angiogenesis. They differ from the less exuberant stimulation by vascular endothelial growth factor (VEGF), a critical produced by tumors or introduced experimentally.
Bartonella and MGUS (Monoclonal Gammopathy of Undetermined Significance)

Transient monoclonal gammopathy in a patient with Bartonella quintana endocarditis.

Sève P¹, Turner R, Stankovic K, Perard L, Broussolle C.

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.

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

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

“The gammopathy disappeared after 8 months of antibiotics”
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.
Babesia and B-cell lymphoma

Human Babesiosis

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

Introduction

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 discovered hemoglobinuria in cattle grazing in the Dambe region of Romania, was the first to recognize this microorganism residing in red blood cells.[1] Shortly thereafter, Smith named a microorganism in Texas cattle.[2] Named Pyrosemia bigemina after its peculiar hemoglobinuria, Babesia bigemina was an early example of transmission by a tick. The cattle tick, Boophilus annulatus, was identified as the vector for transmission of Texas cattle fever. By making this seminal observation, Smith and Kilborne established the concept that hematophagous arthropods can transmit an infectious agent to vertebrate hosts. More than 100 species of Babesia have been identified in wild and domestic animals.[3]

Interestingly, the majority of case patients in the study had underlying B-cell lymphoma
Chlamydia pneumoniae associated with lung cancer

"CHSP-60 seropositivity and elevated antibody titers were associated with significantly increased risk for subsequent lung cancer, supporting an etiologic role for C. pneumoniae infection in lung carcinogenesis."

"Higher titre may be a better predictor of lung cancer risk"

Source: http://cebp.aacrjournals.org/content/19/6/1498.long; https://www.ncbi.nlm.nih.gov/pubmed/21194924

Cancer Epidemiology, Biomarkers & Prevention

Chlamydia pneumoniae Infection and Risk for Lung Cancer

Abstract

Chlamydia pneumoniae (C. pneumoniae) is a common cause of acute respiratory infection and has been hypothesized to cause several chronic diseases, including lung cancer. Numbers of studies were conducted to analyse the association between C. pneumoniae infection and risk of lung cancer, but no clear consensus had been found. To assess this relationship more precisely, a meta-analysis was performed. The electronic databases PubMed, Embase, Web of Science, and CNKI were searched. Data were extracted and analysed independently by two investigators. Ultimately, 12 studies, involving 2585 lung cancer cases and 2585 controls from four prospective studies and eight retrospective studies, were included. Overall, people exposed to C. pneumoniae infection had an odds ratio (OR) of 1.48 (95% confidence interval: 1.24-1.77) for lung cancer risk, relative to those not exposed. C. pneumoniae infection was clearly identified as a risk factor for prospective studies (OR: 1.16, 95% CI: 1.00-1.36) and retrospective studies (OR: 2.17, 95% CI: 1.79-2.63) and in both IgG and IgA cutoff groups (OR: 1.22, 95% CI: 1.06-1.41) and the IgA ≥ 64 cutoff group (OR: 2.35; 95% CI: 1.88-2.93). In conclusion, C. pneumoniae infection is associated with an increased risk for lung cancer, higher titre may be a better predictor of lung cancer risk.
Chlamydia pneumoniae in prostate cancer

Third International Chronic Prostatitis Network

Chlamydia pneumoniae as an impacting emerging pathogen in prostate pathologies

S. Mazzoli, A. Salvi, F. Guercini, M. Marongiu, A. Ruggeri
1 Centro MST, Ospedale S.M. Annunziata, Firenze, Italy
Istituto di Urologia, Universita' degli Studi, Porugia, 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% communicate 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. Very 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 hyperplasia (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, benign prostate hyperplasia 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 macrophages and other immunologically related cells in transporting the microorganism 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 discussion about the role of this microorganism 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, especially immunological conditions, can induce the determinism of the one instead of the other pathology.

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

“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.”
High level of Mycoplasma in various cancers

**Table 1** Mycoplasma infection in different grades of gastric carcinoma.

<table>
<thead>
<tr>
<th>Grades of differentiation</th>
<th>Total number of cases</th>
<th>Negative cases (−)</th>
<th>Positive cases (+)</th>
<th>Total positive cases</th>
<th>Ratio of positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>23</td>
<td>3</td>
<td>12</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>II-III</td>
<td>18</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>61</td>
</tr>
<tr>
<td>III</td>
<td>49</td>
<td>30</td>
<td>14</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>40</td>
<td>35</td>
<td>50</td>
<td>56</td>
</tr>
</tbody>
</table>

**Table 3** Mycoplasma infection in different grades of colon carcinoma.

<table>
<thead>
<tr>
<th>Grades of differentiation</th>
<th>Total number of cases</th>
<th>Negative cases (−)</th>
<th>Positive cases (+)</th>
<th>Total positive cases</th>
<th>Ratio of positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>42</td>
<td>15</td>
<td>15</td>
<td>27</td>
<td>64</td>
</tr>
<tr>
<td>II-III</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>26</td>
<td>19</td>
<td>32</td>
<td>55 (mean)</td>
</tr>
</tbody>
</table>

"There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two."

Source: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/)
Strong link with prostate cancer ...

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

Association of *Mycoplasma hominis* infection with prostate cancer


Abstract

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.

Source: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248167/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248167/)
Mycoplasma infection transforms normal lung cells and induces bone morphogenetic protein 2 expression by post-transcriptional mechanisms.

Jiang S1, Zhang S, Langenfeld J, Lo SC, Rogers MB.

Abstract
Bone morphogenetic protein 2 (BMP2) is an essential growth factor and morphogen, whose pathological expression and dysregulation influence development and physiology. We present the novel finding that mycoplasma infection of diverse types (mesenchymal, epithelial, and myeloid) triggers BMP2 protein in BEAS-2B cells (immortalized human bronchial epithelial cells), which normally do not express BMP2 production in A549 cells (lung adenocarcinoma cells). Indeed, mycoplasma is as strong an activator of BMP2 and retinoic acid. Second, we showed that post-transcriptional mechanisms including regulation of BMP2 mechanisms, contributed to the increased BMP2 expression in mycoplasma-infected cells. Furthermore, AS1411 that binds the post-transcriptional regulator nucleolin induced BMP2 exclusively in infected BEAS-2B cells transformed by chronic mycoplasma infection, as demonstrated by qRT-PCR. These findings have important implications regarding the effects of mycoplasma on BMP2-regulated proliferation, differentiation, and apoptosis.

Mycoplasma pneumoniae Infection Induces Reactive Oxygen Species and DNA Damage in A549 Human Lung Carcinoma Cells

Gongping Sun1, Xuefeng Xu2, Yingshuo Wang2, Xiaoyun Shen1, Zhimin Chen2,* and Jun Yang1,3,4,.*

ABSTRACT
Mycoplasma pneumoniae is a frequent cause of community-acquired bacterial respiratory infections in children and adults. In the present study, using a proteomic approach, we studied the effects of M. pneumoniae infection on the protein expression profile of A549 human lung carcinoma cells. M. pneumoniae infection induced changes in the expression of cellular proteins, in particular a group of proteins involved in the oxidative stress response, such as glucose-6-phosphate 1-dehydrogenase, NADH dehydrogenase (ubiquinone) Fe-S protein 2, and ubiquinol-cytochrome c reductase complex core protein 1 mitochondrial precursor. The oxidative status of M. pneumoniae-infected cells was evaluated,
Detection of mycoplasma infection in circulating tumor cells in patients with hepatocellular carcinoma.

Choi HS¹, Lee HM¹, Kim WT¹, Kim MK¹, Chang HJ², Lee HR³, Joh JW⁴, Kim DS⁵, Ryu CJ⁶.

Abstract

Many studies have shown that persistent infections of bacteria promote carcinogenesis and metastasis. Infectious agents and their products can modulate cancer progression through the induction of host inflammatory and immune responses. The presence of circulating tumor cells (CTCs) is considered as an important indicator in the metastatic cascade. We unintentionally produced a monoclonal antibody (MAb) CA27 against the mycoplasmal p37 protein in mycoplasma-infected cancer cells during the searching process of novel surface markers of CTCs. Mycoplasma-infected cells were enriched by CA27-conjugated magnetic beads in the peripheral blood mononuclear cells in patients with hepatocellular carcinoma (HCC) and analyzed by confocal microscopy with anti-CD45 and CA27 antibodies. CD45-negative and CA27-positive cells were readily detected in three out of seven patients (range 12-30/8.5 ml blood), indicating that they are mycoplasma-infected circulating epithelial cells. CA27-positive cells had larger size than CD45-positive hematological lineage cells, high nuclear to cytoplasmic ratios and irregular nuclear morphology, which identified them as CTCs. The results show for the first time the existence of mycoplasma-infected CTCs in patients with HCC and suggest a possible correlation between mycoplasma infection and the development of cancer metastasis.

KEYWORDS: Circulating tumor cell; Hepatocellular carcinoma; Metastasis; Monoclonal antibody; Mycoplasma.

“The results show for the first time the existence of mycoplasma-infected CTCs in patients with HCC and suggest a possible correlation between mycoplasma infection and the development of cancer metastasis.”
Chlamydia trachomatis blocks apoptosis by destroying the p53 tumour suppressor gene

A research team at the Max Planck Institute for Infection Biology in Berlin has now observed the breakdown of an important endogenous protective factor in the course of chlamydial infection. By activating the destruction of p53 protein, the bacterium blocks a key protective mechanism of infected cells, the initiation of programmed cell death. This protective function of p53 is also impaired in many forms of cancer.


Chlamydia trachomatis is associated with a greater risk of invasive cervical cancer

“This study, based on data from 1,238 case and 1,100 control participants in 7 countries worldwide, shows that C. trachomatis serum antibodies were associated with a 1.8-fold increased risk of squamous cell invasive cervical cancer.”
Ehrlichia associated with myelodysplastic disease and leukaemia

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

Charles A. Kallick, Daniel A. Friedman, Mramba B.A. Nyindo

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...
Toxoplasma may increase the risk of brain cancer

“We predicted that T. gondii could increase the risk of brain cancer because it is a long-lived parasite that encysts in the brain, where it provokes inflammation and inhibits apoptosis. ... Infection with T. gondii was associated with a 1.8-fold increase in the risk of brain cancers across the range of T. gondii prevalence in our dataset (4-67%).”
Toxoplasmosis higher in patients with solid organ tumours

“Among cancer patients, prevalence of *T. gondii* was significantly higher (20% & 4% for IgG and IgM respectively) compared with controls (8% and 2%) (*p* = 0.003). *Toxoplasmosis was higher in patients having solid organ tumors (24%) than in patients with haematological malignancies (12%) (*p* = 0.06).”

*Toxoplasmosis: an overlooked infection in cancer patients*  
*Annals of Oncology*, Volume 27, Issue suppl_6, 1 October 2016, 1383P,  
https://doi.org/10.1093/annonc/mdw387.20  
Published: 11 October 2016

**Background:** Toxoplasmosis is a widespread disease caused by the Apicomplexan, coccidian protozoan *Toxoplasma gondii* (*T. gondii*). Human prevalence rates for toxoplasmosis vary greatly in different parts of the world ranging from 0% in North Alaska and Canada to 94% in Costa Rica and Guatemala. Once the host acquires the infection by ingestion, *T. gondii* crosses the intestinal epithelium, disseminates into the deep tissues and traverses biological barriers to reach sites where it causes severe pathology. Normally, the immune response efficiently prevents the dissemination of the parasite. In immunocompromised hosts, however, such reactivation may be more frequent, leading to a massive and potentially fatal recrudescence. Studies of prevalence of Toxoplasmosis in patients with neoplasms are scarce. This report represents the first prevalence study of Toxoplasmosis in cancer patients in Egypt.

**Methods:** Blood samples were collected from 150 immunocompromised patients having different types of malignancies as well as 50 immunocompetent individuals as a control group, to assess the seroprevalence of anti-*T. gondii* antibodies. The “CTK biotech Onsite Toxo IgG/IgM Rapid Test Cassettes” was used according to the manufacturer’s enclosed manual for the detection of infection.
### Which bacterial tests to consider, in which cancers?

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Bacterial tests to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Borrelia (Elispot/Seraspot), Babesia (Elispot), Ehrlichia/Anaplasma (Elispot/IgG, IgM)</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>Bartonella (Elispot)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Ehrlichia/Anaplasma (Elispot/ IgG, IgM) Coxiella (Q fever) (IgG, IgM)</td>
</tr>
<tr>
<td>Glioma/brain cancers</td>
<td>Borrelia (Elispot/Seraspot) Mycoplasma (Elispot/IgG, IgA) Toxoplasma (IgG, IgM)</td>
</tr>
<tr>
<td>Angiogenic tumours</td>
<td>Bartonella (Elispot)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Chlamydia pneumoniae (Elispot/IgG, IgA), Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Chlamydia pneumoniae (Elispot/IgG, IgA), Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Breast</td>
<td>Mycoplasma (Elispot/IgG, IgA) Bartonella (Elispot)</td>
</tr>
<tr>
<td>Metastases</td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Cervical cancer, downregulation of p53</td>
<td>Chlamydia trachomatis (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Solid tumours (if cat owner/contact with cats)</td>
<td>Toxoplasma</td>
</tr>
<tr>
<td>General</td>
<td>CD3/CD57+</td>
</tr>
</tbody>
</table>
Infectious Pathogens and Cancer: The Emerging Evidence

1. Stealth bacteria involvement

2. Viral involvement
   - Epstein Barr Virus
   - Cytomegalovirus
   - HHV6
   - Herpes Simplex Virus 1 & 2

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

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


Epstein–Barr virus (EBV) is a tumorigenic herpes virus, which is associated with several human hematologic neoplasias such as Burkitt lymphoma, Hodgkin disease, and posttransplantation lymphoproliferative disease (PTLD).

B-Cell Non-Hodgkin’s Lymphoma: EBV/CMV


History of the discovery of EBV points to its tumorigenic origin

“The fact that the geographical distribution of Burkitt’s lymphoma (BL) overlapped that of several mosquito-borne diseases suggested the possibility that the disease was transmittable. Burkitt gave several talks about his findings on a visit to London, and Anthony Epstein, a virologist interested in tumor viruses, was present. He had Burkitt send him samples of the tumors and was able to detect a herpes-like virus by electron microscopy.”

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis
EBV/CMV and tumours

"The role of EBV was then established in a number of tumors"
EBV: Latency antigens associated with various types of cancer

The pathogenesis of encephalitis (or meningitis or hepatitis or other focal visceral involvement) is not completely clear and there are several possibilities, which are not mutually exclusive. First, EBV may affect neurons (or other neural cells or endothelium) directly (Jones et al. 1995). There have been a few scattered reports of neurons and glial cells staining with EBV antigens, although there is not much detail (Biebl et al. 2000). In some patients with EBV encephalitis, as well as some with primary CNS lymphoma, lytic EBV mRNA was detected in the CSF, suggesting lytic replication of EBV in the brain in addition to latent replication (Weinberg et al. 2002a). Secondly, EBV-infected B cells are in an activated state and elaborate several proinflammatory cytokines, which can cause injury of the surrounding parenchyma (Foss et al. 1994). This injury is not necessarily irreversible. Third, EBV-infected B cells are actively attacked by EBV-specific cytotoxic T cells, and this can also injure the surrounding parenchyma. Finally, an acute disseminated encephalomyelitis can be triggered as in other viral infections.

Normally, EBV-infected B cells are suppressed (though not eliminated) by the immune system and lymphoproliferation can result during immunosuppression. In tissue culture in which T cells have been eliminated, B cells are immortalized and proliferate. In vivo, the B cell lymphoproliferation proceeds sequentially from polyclonal to oligoclonal to monoclonal, and evolves into a lymphoma. This can occur under circumstances of immunosuppression in transplant, chemotherapy, and AIDS patients as mentioned above. The lymphoproliferation can be accompanied by the elaboration of various cytokines, and a severe systemic illness resembling

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis

Different latencies associated with Burkitt’s lymphoma, nasopharyngeal carcinoma, Hodgkin’s disease, lymphoproliferative disease
Scientists reveal how a common virus triggers blood cancer

Scientists at the University of Sussex, trying to uncover how the common Epstein-Barr virus causes blood cancer in adults and children, have discovered how the virus takes control of two genes involved in cancer development so it can switch them on or off.

The research team, led by Professor Michelle West, set out to determine how the Epstein-Barr virus controls two genes; MYC, a gene known to drive cancer development when it is altered or switched on at high level and BCL2L11, a gene which normally triggers cell death to prevent cancer, but can be turned off by the virus.

With thanks to funding from the blood cancer charity Bloodwise, the scientists discovered that the virus controls the MYC and BCL2L11 genes by hijacking "enhancer" DNA regions which are situated far away from the genes. These enhancers act as ‘control centres’ and are able to contact and control genes from long distances by the looping out of the intervening stretches of DNA.

Professor West's team found that Epstein-Barr virus turns on the MYC gene by increasing contacts between a specific set of enhancers and the gene. The scientists believe this may explain how the virus causes the changes to the MYC gene that are found in Burkitt’s lymphoma.

The team also discovered new enhancers which control the BCL2L11 gene. In this case, they found that Epstein-Barr virus stops these control centres from contacting the gene. Encouragingly the team have discovered that this blocking effect can be reversed by using a specific drug - paving the way for new treatments.

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

“It is now important to carry out further studies to determine whether these findings will help us to develop new drugs that could target the virus.”

Dr Alasdair Rankin, Research Director at Bloodwise, said: “We are really excited about this research. We have been investigating Epstein-Barr virus for many years, but we were never sure of the exact mechanisms. These findings offer promise for the development of new drugs that could stop the virus from causing disease.

“By mapping out the complex genetic interactions that help lymphoma cells grow and survive, this research can guide the design of new treatments to target the disease. It may also help to identify those drugs currently used to treat other diseases that could be effective in treating these types of lymphoma.”

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


**Patients with Hodgkin's disease (HD) frequently show elevated serum titers against human herpesvirus-6 (HHV-6) and their tissues contain significantly increased numbers of cells with HHV-6 DNA.**
Herpes viruses and blood cancers: tests suggested

1. EBV EliSpot, Tickplex Basic
2. EBV IgG/IgM, anti-EBNA antibodies and early antigen
3. CMV EliSpot and possibly IgG/IgM
4. HHV6 EliSpot
5. CD3/CD57+ cells
Link between HSV1 and oral cancer well established; HSV2 and cervical cancer more equivocal

“The present study clearly indicates that quantitative estimation of IgG antibody against HSV-1 in cancer/precancer patients will give the clue in the etiology of cancer or precancer.”
Infectious Pathogens and Cancer: The Emerging Evidence

1. Bacterial involvement

2. Viral involvement

3. Indirect involvement:
   
   .... *these stealth pathogens indirectly cause a conducive environment to multiple diseases, including cancer* ...
Borrelia – and other intracellular bacterial/viral infections – cause mitochondrial dysfunction

“The results suggest that oxidative stress and interrupted intracellular communication may ultimately contribute to a condition of mitochondrial dysfunction in the immune cells of Lyme borreliosis patients.” ... 

... potentially contributing to cancer, as we have heard from other speakers today.
### Indirect links: unfortunately a perfect physiological storm

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Borrelia</strong></td>
<td>Oxidative stress causes damage to DNA, proteins and lipids&lt;br&gt;Utilises host purines (ATP)&lt;br&gt;Depletes cell and mitochondrial membranes&lt;br&gt;Upregulates mitochondrial superoxide levels&lt;br&gt;This together can cause huge inflammation</td>
</tr>
<tr>
<td><strong>Babesia</strong></td>
<td>Infects erythrocytes = can cause haemolysis and intravascular coagulation = hypoxia&lt;br&gt;thrombocytopenia = immunosuppression</td>
</tr>
<tr>
<td><strong>Bartonella</strong></td>
<td>Parasitised erythrocytes sequestered by the spleen = immunosuppression</td>
</tr>
<tr>
<td><strong>Mycoplasma</strong></td>
<td>Prefers low-oxygen environments, stimulates ROS, which causes&lt;br&gt;damage to cell membranes – membrane potential is lost</td>
</tr>
<tr>
<td><strong>Ehrlichia</strong></td>
<td>Infects leukocytes = immunosuppression</td>
</tr>
<tr>
<td><strong>Anaplasma</strong></td>
<td>Infects granulocytes = immunosuppression</td>
</tr>
<tr>
<td><strong>All these stealth pathogens ...</strong></td>
<td>... cause inflammation, as inflammation breaks down tissues and allows the bacteria to gain access to the host’s resources&lt;br&gt;Interfere with/disable the host’s immune system, upregulate cytokines, trigger ROS/RNS&lt;br&gt;... shift host’s immune response from Th1 (intracellular) towards Th2 (extracellular) to distract attention from their location – but Th2 is conducive to cancer</td>
</tr>
</tbody>
</table>

*Sources: All available on request*
Thank you very much for your attention!

For tests, please go to
www.aonm.org
https://aonm.org/arminlabs

or call the AONM helpline
on 0333 121 0305