Is there Evidence of Pathogen Involvement in Hypercoagulation and Histamine Upregulation/MCAS?

Holiday Inn Regents Park, 17th November 2019, London, UK

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Evidence of pathogen involvement?

- **Hypercoagulation**
  - Correlation with bacterial and viral pathogens

- Histamine upregulation/MCAS/MCAD
  - Correlation with stealth infections

The blood coagulation system is activated during infections

rpth research and practice in thrombosis and haemostasis™ Open Access

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PMCID: PMC6046589
PMID: 30046760

The coagulation system in host defense

Silvio Antoniak, PhD[1]

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Abstract Go to:

The blood coagulation system and immune system of higher organisms are thought to have a common ancestral origin. During infections, the blood coagulation system is activated and components of the hemostatic system are directly involved in the immune response and immune system modulations. The current view is that the activation of coagulation is beneficial for infections with bacteria and viruses. It limits pathogen dissemination and supports pathogen killing and tissue repair. On the other hand, over-activation can lead to thrombosis with subsequent depletion of hemostatic factors and secondary bleeding. This review will summarize the current knowledge on blood coagulation and pathogen infection with focus on most recent studies of the role of the different parts of the blood coagulation system in selected bacterial and viral infections.

Keywords: coagulation, hemostasis, infection, inflammation, peritonitis, pneumonia

"The current view is that the activation of coagulation is beneficial for infections with bacteria and viruses ... Activation of coagulation system limits pathogen dissemination and supports pathogen killing."

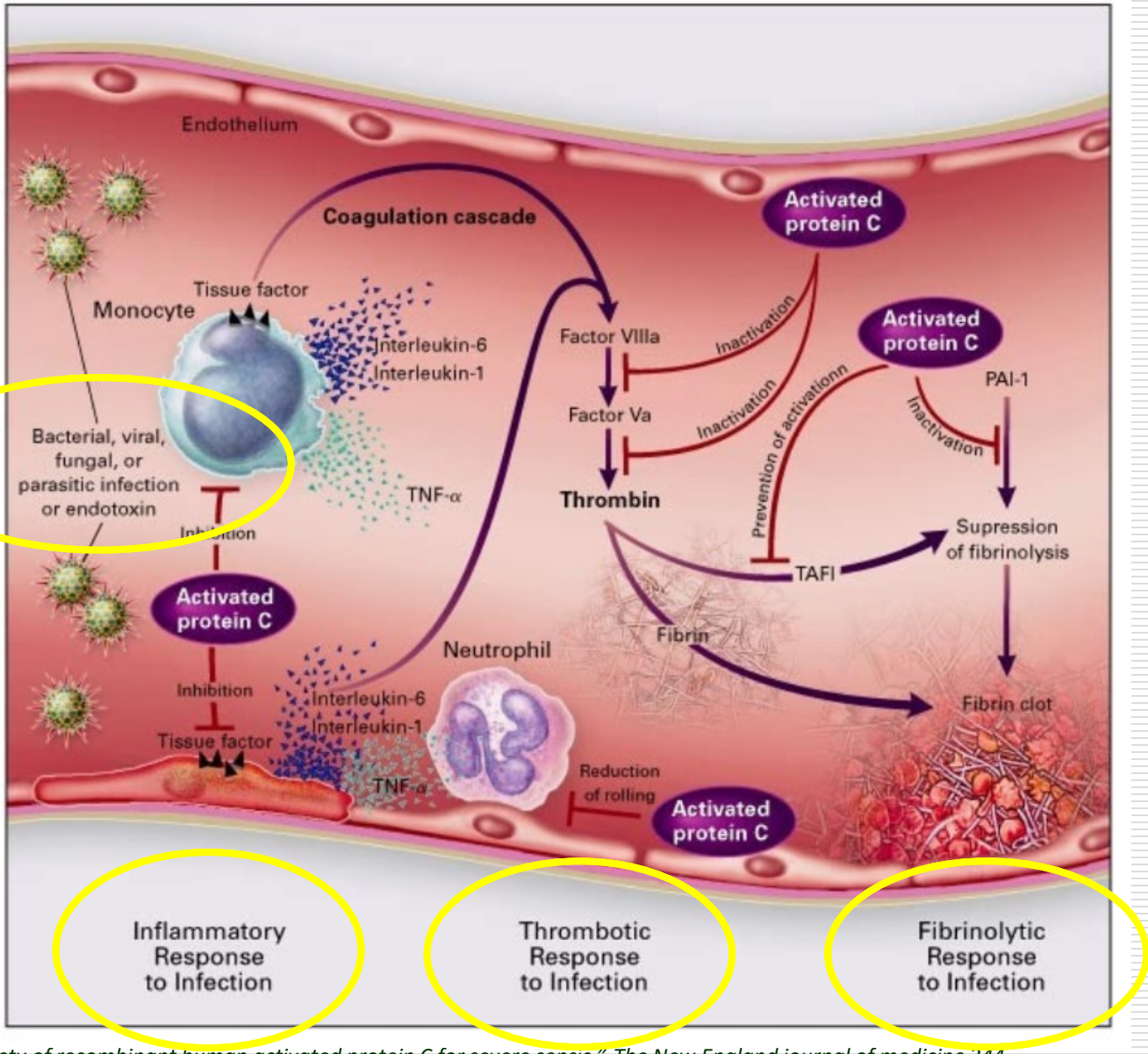
Source: Antoniak S. (2018). The coagulation system in host defense. Research and practice in thrombosis and haemostasis, 2(3), 549–557. doi:10.1002/rth2.12109

Infection =

Inflammation =

Thrombotic response =

Fibrin deposition



Source: Bernard, Gordon R. et al. "Efficacy and safety of recombinant human activated protein C for severe sepsis." The New England journal of medicine 344 10 (2001): 699-709 .

How infection triggers hypercoagulation

Infection triggers inflammation, which triggers a thrombotic response:

1. Cytokines from white blood cells are released into the blood to protect the body from foreign attack They induce expression of Tissue Factor (TF) on the endothelial cell (EC) surfaces, which **drives a coagulation cascade.**

2. Antibodies are also formed in response to the pathogens and contribute to the **local generation of thrombin**.

3. Thrombin triggers fibrin formation.

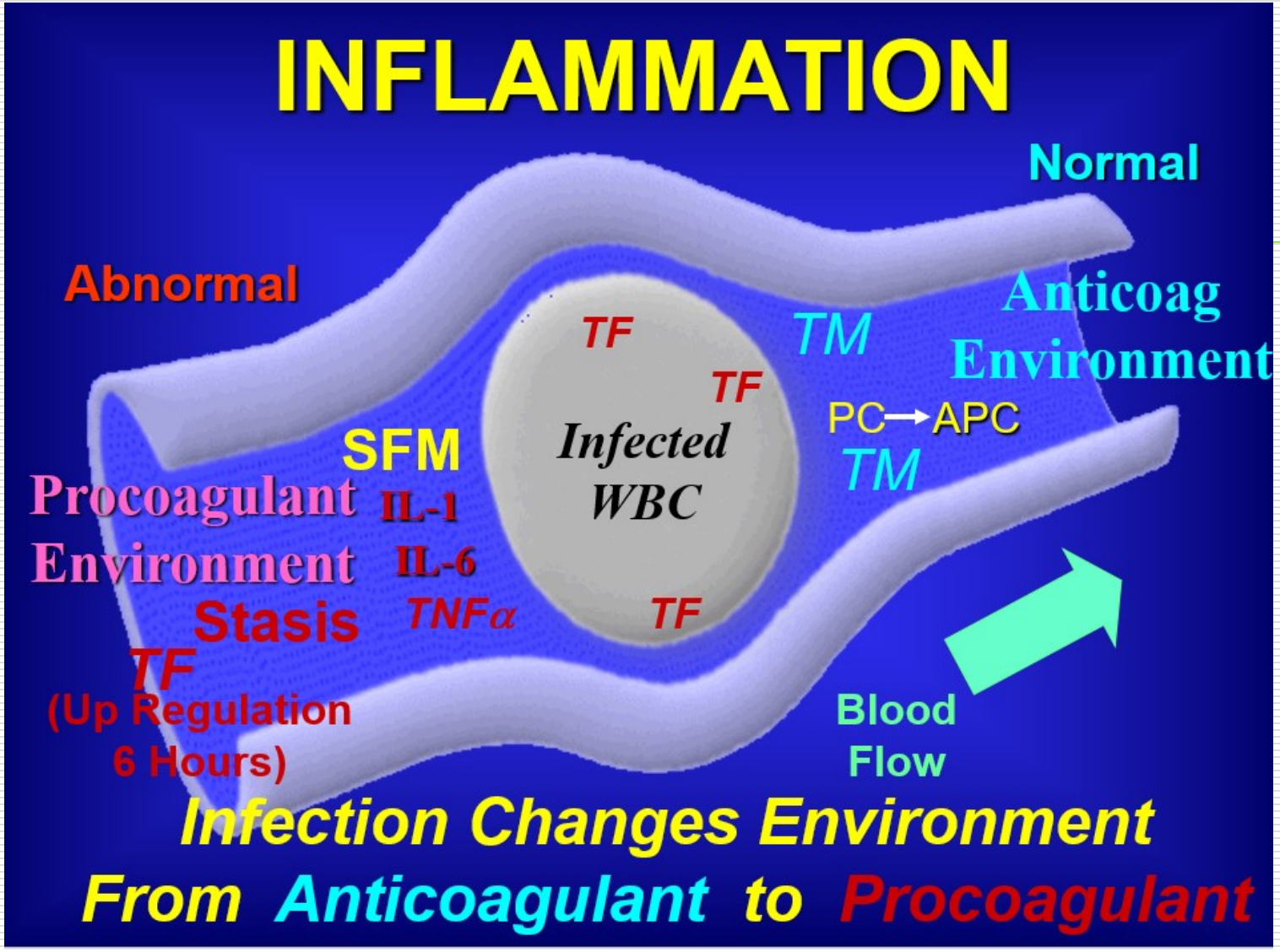
This fibrin deposition grows over time and

a. **Blocks the passage of oxygen and nutrients to the tissues around the capillaries, and**

b. **Diminishes capillary size.**

Source: Birlutiu, Victoria & Birlutiu, Rares. (2016). Lyme Borreliosis as a Trigger of Dermatomyositis and Cerebral Thrombosis. Clinical Presentations of This Unusual Manifestation of Lyme Disease.

RBCs are ~ 7 microns, while WBCs are 14 - 16 microns: Diminished capillary size + more WBCs = logjam



+

Hypoxia: 1 micron of fibrin = O2 diffusion time of 5.3 mins instead of 2 seconds

Source: David Berg Coagulation 202 Proteins and Coagulation Pathways, from The Role of Hypercoagulation and Biofilms in Chronic Illness Conference (2011)

Borrelia have been shown to induce platelet aggregation

INFECTION AND IMMUNITY, Mar. 1996, p. 1026–1029
0019-9567/96/$04.00+0

Vol. 64, No. 3

Platelet-Activating-Factor-Mediated Pathogenesis in Lyme Disease

EMIKO ISOGAI,[1]* KOICHI KIMURA,[2] NOBUHIRO FUJII,[2] TAKESHI NISHIKAWA,[2] NORIHISA ISHII,[3] DANIELE POSTIC,[4] GUY BARANTON,[4] AND HIROSHI ISOGAI[5]

Department of Preventive Dentistry, Health Sciences University of Hokkaido, Ishikari-Tobetsu 1757, Hokkaido 061-02,[1] Department of Microbiology[2] and Division of Animal Experimentation,[5] Sapporo Medical University, Sapporo 060, and Department of Dermatology, Yokohama City University Medical School, Fukuura, Yokohama 234,[3] Japan, and Unité de Bactériologie Moléculaire et Médicale, Institut Pasteur, Paris Cedex 15, France[4]

Received 7 August 1995/Returned for modification 22 September 1995/Accepted 12 December 1995

This study describes a role of platelet-activating factor (PAF) as a potential inducer of inflammation in infection with *Borrelia burgdorferi*. Two approaches were taken. The first involved the use of a PAF antagonist to show the lack of an inflammatory response in skin lesions. The second was to show that the PAF antagonist reduced platelet aggregation when the spirochetes were incubated w

"Borrelia-stimulated polymorphonuclear leukocytes induce platelet aggregation"

Lyme disease is a chronic, multisystemic infection caused by the tick-borne spirochetes *Borrelia burgdorferi*, *B. garinii*, and *B. afzelii* (2, 10, 26, 28). Localized skin infection was first recognized at the site of the tick bite. In untreated patients, *B. burgdorferi* is able to survive in the face of a specific immune response and has been recovered from some patients years after infection. It therefore seems likely that the spirochete

PCR with p… 548 and 67… described p… PAF anta… bomoyloxy… Lorei, Frankfurt, Germany] (32) was used for mice. This compound inhibited the aggregation of platelets induced by PAF,

Source: Isogai, Emiko & Kimura, K & Fujii, N & Nishikawa, T & Ishii, N & Postic, D & Baranton, G & Isogai, H. (1996). Platelet-activating-factor-mediated pathogenesis in Lyme disease. Infection and immunity. 64. 1026-9.

Clear correlation between concentration of B. afzelii and platelet aggregation

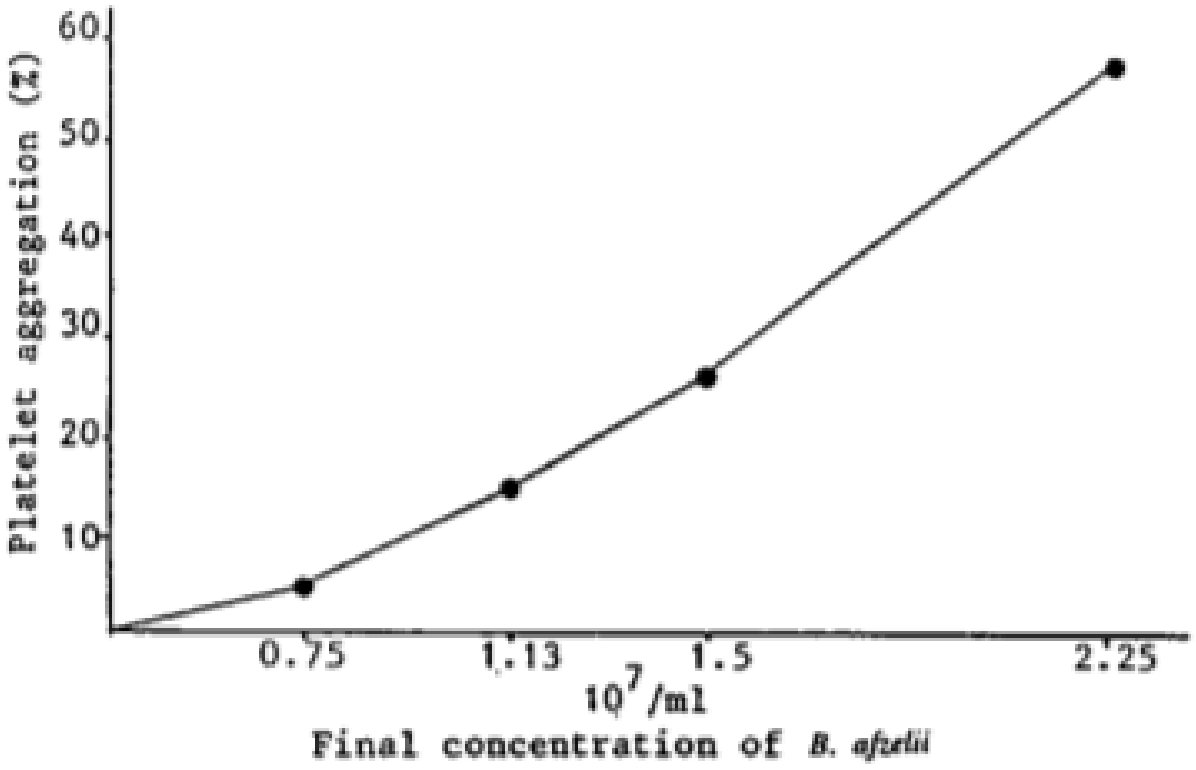
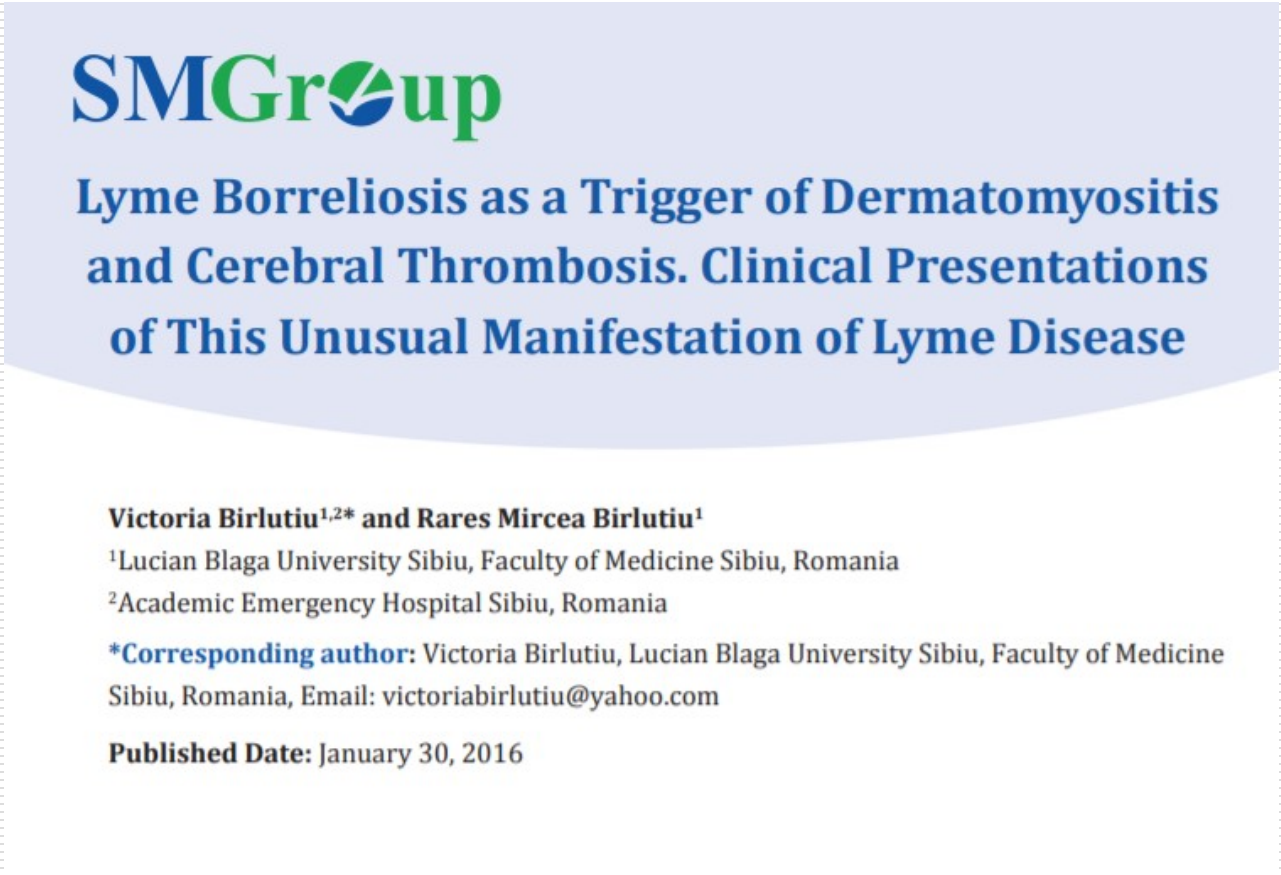


FIG. 2. Platelet aggregation induced by *B. afzelii* and relationship to bacterial concentration in the PMN-platelet mixture system.

Source: Isogai, Emiko & Kimura, K & Fujii, N & Nishikawa, T & Ishii, N & Postic, D & Baranton, G & Isogai, H. (1996). Platelet-activating-factor-mediated pathogenesis in Lyme disease. Infection and immunity. 64. 1026-9.

Even reports of Borreliosis causing cerebral thrombosis



SMGroup

Lyme Borreliosis as a Trigger of Dermatomyositis and Cerebral Thrombosis. Clinical Presentations of This Unusual Manifestation of Lyme Disease

Victoria Birlutiu[1,2]* and Rares Mircea Birlutiu[1]

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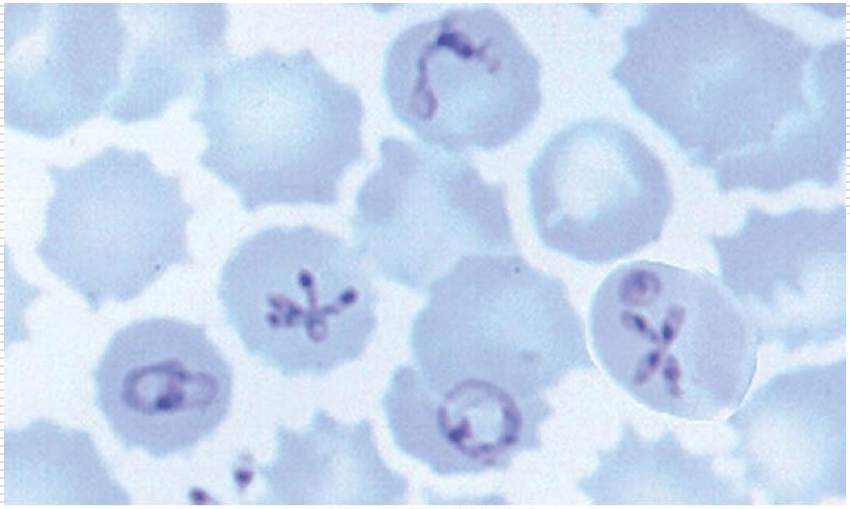
Published Date: January 30, 2016

Source: Birlutiu, Victoria & Birlutiu, Rares. (2016). Lyme Borreliosis as a Trigger of Dermatomyositis and Cerebral Thrombosis. Clinical Presentations of This Unusual Manifestation of Lyme Disease.

Babesia can also have a coagulant effect

Babesiosis, according to the CDC, can cause disseminated intravascular coagulation (DIC, or consumptive coagulopathy) https://www.cdc.gov/parasites/babesiosis/disease.html



(Courtesy of Lynne Garcia, LSG and Associates, Santa Monica, CA.)

"These findings indicate that the heparin covers the surfaces of babesial merozoites and inhibits their subsequent invasion of erythrocytes."

Source: Image:Lynne Garcia LSG and Associates;
http://www.klinghardtacademy.com/images/stories/powerpoints/2006%20e%20babesia%20and%20heparin.pdf

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Antimicrob Agents Chemother. 2004 Jan; 48(1): 236–241.
doi: 10.1128/AAC.48.1.236-241.2004

PMCID: PMC310193
PMID: 14693545

Growth-Inhibitory Effect of Heparin on *Babesia* Parasites

Sabine Bork,[1] Naoaki Yokoyama,[1] Yuzuru Ikehara,[2] Sanjay Kumar,[1] Chihiro Sugimoto,[1] and Ikuo Igarashi[1,*]

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ABSTRACT

Go to:

We examined the inhibitory effects of three heparins on the growth of *Babesia* parasites. The multiplication of *Babesia bovis*, *B. bigemina*, *B. equi*, and *B. caballi* in in vitro cultures and that of *B. microti* in vivo were significantly inhibited in the presence of heparins, as determined by light microscopy. Treatment with various concentrations of heparin showed complete clearance of the intracellular parasites. Interestingly, a higher percentage of abnormally multidividing *B. bovis* parasites was observed in the presence of low concentrations of heparin. Furthermore, fluorescein isothiocyanate-labeled heparin was preferably found on the surfaces of extracellular merozoites, as detected by confocal laser scanning microscopy. These findings indicate that the heparin covers the surfaces of babesial merozoites and inhibits their subsequent

Antimicrob Agents Chemother

”Different types of viruses can cause hypercoagulability”

Review: Infectious Diseases and Coagulation Disorders

E. C. M. van Gorp,[1] C. Suharti,[4] H. ten Cate,[1,2]
W. M. V. Dolmans,[3] J. W. M. van der Meer,[3]
J. W. ten Cate,[2] and D. P. M. Brandjes[1,2]

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Infection, both bacterial and nonbacterial, may be associ
resulting in disseminated intravascular coagulation and m
decades a series of in vivo and in vitro studies has provided n
mechanisms and the role of cytokines in these processes. B
this field, the complexity of the subject, and the fact that m
variety of infections, current data are reviewed on the associ
and the coagulation system. Novel therapeutic intervention
come available in the near future are mentioned, along w
infectious disorders for which only supportive care can be g

Systemic infections may be complicated by activation of the coagulation cascade, varying from subclinical activation, which is indicated by a rise in laboratory markers for thrombin and fibrin generation, to fulminant disseminated intravascular coagulation (DIC) with the formation of microvascular thrombi in various organs [1]. Bleeding, thrombosis, or both may be the presenting clinical features. DIC may contribute to multiorgan failure (MOF) and is associated with a high mortality in both bacterial and nonbacterial disease [2, 3].

Studies of gram-negative sepsis in humans and experimental animals have shown that cytokines play a pivotal role in the activation and regulation of the coagulation cascade, although the interactions are complicated, and the effects are time-dependent and transient [4]. Activation of the coagulation system has also been documented for nonbacterial pathogens (i.e., vi-

supportive
bleeding an
apeutic agents that intervene in the coagulation and cytokine cascades will become available in the near future and may have a positive clinical effect, especially for in
supportive care can be given.

Because of the growing interest in th
of the subject, and the fact that many
variety of infections, we will review cu
ciation between infectious diseases and

Clinical Aspects of Hemostasis in Bacterial and Viral Infections

Critical Care Medicine describes in detail the number of different types of viruses that can cause hypercoagulability:
“Endothelial cells can be directly infected by a number of viruses, e.g., **herpes simplex virus, adenovirus, parainfluenzavirus, poliovirus, echovirus, measles virus, mumps virus, cytomegalovirus, human T-cell lymphoma virus type I, and HIV**.”

“Viruses can downregulate physiological anticoagulant mechanisms and inhibit fibrinolysis”[2]

Source: 1. E. C. M. van Gorp, C. Suharti, H. ten Cate, W. M. V. Dolmans, J. W. M. van der Meer, J. W. ten Cate, D. P. M. Brandjes, Review: Infectious Diseases and Coagulation Disorders, The Journal of Infectious Diseases, Volume 180, Issue 1, July 1999, Pages 176–186; 2. Galli, L. et al. (2014). Thrombosis Associated with Viral Hepatitis. Journal of clinical and translational hepatology, 2(4), 234–239.

HHV-6 known to drive hypercoagulation …

Hypercoaguable State Associated with Active Human Herpesvirus6 (HHV-6) Viremia in Patients with Chronic Fatigue Syndrome

Article *in* Journal of Chronic Fatigue Syndrome 8(3):111-116 · September 2001 *with* 6 Reads
DOI: 10.1300/J092v08n03_10
Cite this publication

Objectives: A subset of patients with Chronic Fatigue Syndrome (CFS) hav
analyze the incidence of a hypercoaguable state and assess hereditary hyp
viremia. Methods: Thirty patients diagnosed with CFS that had at least one
studied. A hypercoaguable panel was obtained to assess activation of coag
of coagulation. Hereditary thrombosis risk panels were also performed whi
Results: Twenty-four of thirty (80%) patients had a hypercoaguable state, t
hereditary abnormality. Conclusions: CFS patients with active HHV-6 infect
Hereditary thrombosis risk factors are very prevalent in these patients. The
hypercoaguable state associated with active HHV-6 infection may be a sign

"Conclusions: CFS patients with active HHV-6 infection (viremia) have activation of coagulation and are hypercoaguable. ….The hypercoaguable state associated with active HHV-6 infection may be a significant contributing factor to the symptoms seen in CFS patients."

… as well as Epstein-Barr Virus

"One way that HHV-6 and Epstein-Barr virus cause illness is by thickening the blood ever so slightly, a state called "hypercoagulation." Hypercoagulation accomplishes two things for the virus. First, when the blood is thicker, it is more difficult for our immune system to suppress these viruses. **Viruses thrive in thicker blood**. **Second, thicker blood prevents maximum delivery of oxygen and nutrients** at the cellular level."[2]

Source: 1. Brewer, Joseph & Berg, David. (2001). Hypercoaguable State Associated with Active Human Herpesvirus6 (HHV-6) Viremia in Patients with Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome. 8. 111-116; 2. http://www.medicalinsider.com/viruses.html

Cytomegalovirus influences the coagulation system

Review Article

Effects of human cytomegalovirus infection on the coagulation system

Alessandro Squizzato, Victor E. A. Gerdes, Harry R. Büller
Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Summary
Pathophysiological mechanisms of acute vascular thrombosis are not fully understood. It has been suggested that different infectious pathogens are responsible agents of thrombotic disorders. The infection hypothesis is supported by an increasing number of reports on the interaction between acute infection and coagulation. Cytomegalovirus (CMV) is supposed to play an important role in apparently unprovoked thrombosis. We reviewed all human *in vitro* and *in vivo* studies on the influence of human CMV infection on the coagulation system, as well as all case reports of acute thrombosis during acute human CMV infection. In the published literature there is mounting evidence that human CMV may play a role in thrombotic disorders. Definitive conclusions, however, cannot be drawn, although the *in vitro* studies are convincing and offer insight in the pathogenesis.

Keywords
Infection / bacterial, viral, hypercoagulability, inflammatory mediators, endothelial cells

Thromb Haemost 2005; 93: 403

Introduction

Acute vascular thrombosis represents a major socioeconomic challenge for its heavy burden on mortality and morbidity. Acute vascular thrombosis also represents a scientific challenge since

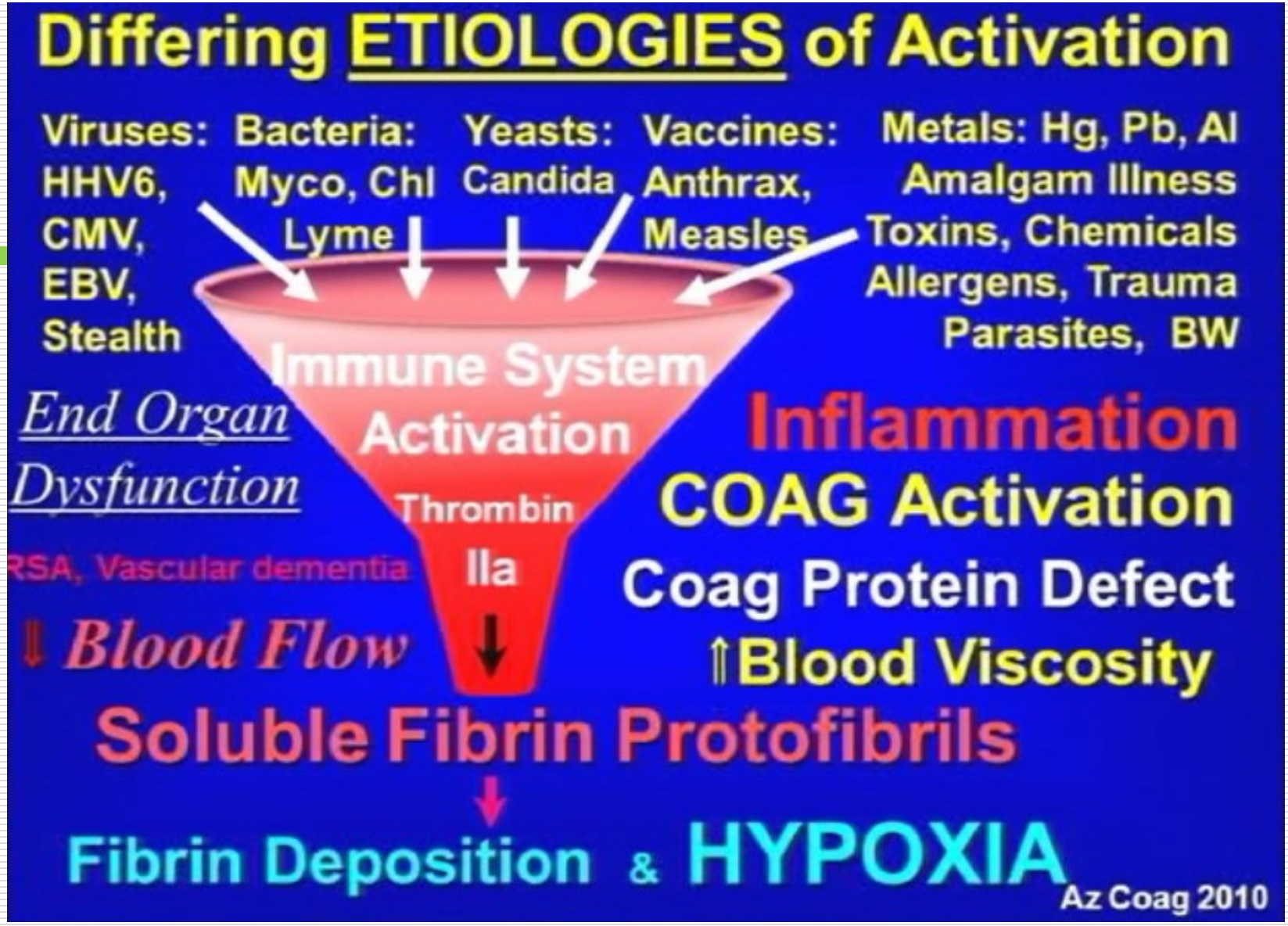
CMV: relevant biologi… features

CMV, or Human Herpes Virus 5, is a double-stranded enveloped

"Mounting evidence that CMV may play a causal role in thrombotic disorders"

Source: Squizzato A, Gerdes VEA, Büller HR. Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost. 2005;93:403–410;

Indebted to the outstanding work of Dr. David Berg on hypercoagulation



Source: David Berg Coagulation 202 Proteins and Coagulation Pathways, from The Role of Hypercoagulation and Biofilms in Chronic Illness Conference (2011)

The role of anti-cardiolipin antibodies in detecting hypercoagulation

Cardiolipin … is the common phospholipid used to detect **anti-phospholipid syndrome**.[1] Cardiolipin is an important component of the inner mitochondrial membrane, where it constitutes ~ 20% of the total lipid composition.

"Interaction of [these] antibodies with phospholipids of cell membranes leads to conformational and metabolic changes in membranes, disruption of cell function, **stasis of blood in capillaries and venules**."[3]

Anti-cardiolipin antibodies (ACA) are a form of antibody directed against cardiolipin. When the immune system recognizes cardiolipin as a foreign substance, ACA is produced and results in an autoimmune disorder. It is a kind of anti-mitochondrial antibody.[2]

Disease	Number of positive	Percentage of positive	Associated features in positive patients	Ref.
Antibodies against cardiolipin (anti-cardiolipin) IgM+ and/or IgG+				
CFS	38/40	95.0%	-	(1)
Behçet's disease	13/70	24.8%	Retinal vascular disease	(4)
Rheumatoid arthritis	55/173	32%	Rheumatoid nodules	(6)
Systemic Lupus	32/59	54.2%	-	(5)
HIV-1	16/44	36%	-	(7)
Infectious mononucleosis	13/35	37%	-	(9)
Leprosy	22/33	67%	-	(10)
Tubercolosis	16/30	53%	-	
HCV	28/75	37.3%	-	(11)
Q fever	17/26	65%	-	(12)
Neuroborreliosis	-	50%	Neurological abnormalities	(14)

4

Source: 1. Celli, C.M., & Gharavi, A.E.. (1998). Origin and pathogenesis of antiphospholipid antibodies. Brazilian Journal of Medical and Biological Research, 31(6), 723-732; 2. https://www.slideshare.net/MArun2rocket/anti-cardiolipin-antibody 3. https://www.uptodate.com/contents/pathogenesis-of-antiphospholipid-syndrome 4. https://paolomaccallini.com/2016/07/13/mecfs-lyme-disease-anti-cardiolipin-antibodies-and-mast-cells/

Testing protocol for pathogen-driven hypercoagulation

Important to do the **checklists** and find out which infection/s could be involved.

Testing with your GP/specialist for hypercoagulation if you appear to have the indications for it (fibrinogen? D-Dimer? thrombotic profile?)

"**Anti-cardiolipin antibodies**" are often a useful first-line test available from Arminlabs, and can be added on to other tests you are doing.

Also may be useful to check your/your patients' **ESR (US: "sedimentation rate")**: Dr. Berg: "The normal range for sed rates should start above 3 or 4. Values below this are correlated with high Soluble Fibrin Monomer values. As the SFM goes up in the plasma, these molecules form dimers (2 stuck together). This physically blocks the RBCs from settling out of the plasma, thus a low sed rate."

Evidence of pathogen involvement?

- Hypercoagulation
  - Correlation with bacterial and viral pathogens

- **Histamine upregulation/MCAS/MCAD**
  - Correlation with stealth infections

Viral and bacterial infections can trigger mast cell activation

Figure 1. Some *Potential* Mast Cell Triggers[2-5]

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Exercise
- Fatigue
- Food or beverages, including alcohol
- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)
- Infections (viral, bacterial or fungal)
- Mechanical irritation, friction, vibration
- Sun/sunlight

Borrelia induce Mast Cell Activation

Journal List › Infect Immun › v.67(3); 1999 Mar › PMC96436

Infection and Immunity

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Infect Immun. 1999 Mar; 67(3): 1107–1115. PMCID: PMC96436

Borrelia burgdorferi Spirochetes Induce Mast Cell Activation and Cytokine Release

Jeffrey Talkington and Steven P. Nickell*

Editor: J. R. McGhee

ABSTRACT

The Lyme disease spirochete, *Borrelia burgdorferi*, is introduced into human hosts via tick bites. Among the cell types present in the skin which may initially contact spirochetes are mast cells. Since spirochetes are known to activate a variety of cell types in vitro, we tested whether *B. burgdorferi* spirochetes could activate mast cells. We report here that freshly isolated rat peritoneal mast cells or mouse MC/9 mast cells cultured in vitro with live or freeze-thawed *B. burgdorferi* spirochetes undergo low but detectable degranulation, as measured by [5-^{3}H] hydroxytryptamine release, and they synthesize and secrete the proinflammatory cytokine tumor necrosis factor alpha (TNF-α). In contrast to findings in previous studies, where *B. burgdorferi*-associated activity was shown to be dependent upon protein lipidation, mast cell TNF-α release was not induced by either lipidated or unlipidated recombinant OspA. This activity was additionally shown to be protease sensitive and surface expressed. Finally, comparisons of TNF-α-inducing activity in known low-, intermediate-, and high-passage *B. burgdorferi* B31 isolates demonstrated passage-dependent loss of activity, indicating that the activity is probably plasmid encoded. These findings

"We report the partial characterization of a *B. burgdorferi* **spirochete-associated activity which induces mast cells** to undergo low-level degranulation and secretion of the proinflammatory cytokine TNF-α … Mast cells activated by spirochetes in vivo probably participate in subsequent immune and/or inflammatory events. … early TNF-α production by spirochete-activated dermal mast cells **would help initiate local inflammation**, attracting inflammatory cells into sites of spirochete replication in the skin. Such early inflammatory responses **would lead eventually to the generation of T- and B-cell-dependent acquired immune responses, which control spirochete replication**."

Borrelia and Mast Cell Activation Syndrome/Disease (MCAS/MCAD)

Format: Abstract Send to

Parasit Vectors. 2017 Jun 27;10(1):313. doi: 10.1186/s13071-017-2243-0.

Interaction of primary mast cells with Borrelia burgdorferi (sensu stricto): role in transmission and dissemination in C57BL/6 mice.

Bernard Q[1,2], Wang Z[3], Di Nardo A[3], Boulanger N[4,5].

Author information

Abstract

BACKGROUND: Borrelia burgdorferi (sensu lato), the causative agent of Lyme borreliosis is a bacterium transmitted by hard ticks, Ixodes spp. Bacteria are injected into the host skin during the tick blood meal with tick saliva. There, Borrelia and saliva interact together with skin cells such as keratinocytes, fibroblasts, mast cells and other specific immune cells before disseminating to target organs.

METHODS: To study the role of mast cells in the transmission of Lyme borreliosis, we isolated mouse primary mast cells from bone marrow and incubated them in the presence of Borrelia burgdorferi (sensu stricto) and tick salivary gland extract. We further analyzed their potential role in vivo, in a mouse model of deficient in mast cells (Kit $^{wsh-/-}$ mice).

RESULTS: To our knowledge, we report here for the first time the bacteria ability to induce the inflammatory response of mouse primary mast cells. We show that OspC, a major surface lipoprotein involved in the early transmission of Borrelia, induces the degranulation of primary mast cells but has a limited effect on the overall inflammatory response of these cells. In contrast, whole bacteria have an opposite effect. We also show that mast cell activation is significantly inhibited by tick salivary gland extract. Finally, we demonstrate that mast cells are likely not the only host cells involved in the early transmission and dissemination of Borrelia since the use of mast cell deficient Kit $^{wsh-/-}$ mice shows a limited impact on these two processes in the context of this mouse genetic background.

CONCLUSIONS: The absence of mast cells did not change the replication rate of Borrelia in the skin. However, in the absence of mast cells, Borrelia dissemination to the joints was faster. Mast cells do not control skin bacterial proliferation during primary infection and the establishment of the primary infection, as shown in the C57BL/6 mouse model studied. Nevertheless, the Borrelia induced cytotokine modulation on mast cells might be involved in long term and/or repeated infections and protect from Lyme borreliosis due to the development of a hypersensitivity to tick saliva.

KEYWORDS: Borrelia; Ixodes tick; Kit wsh−/− mouse; Mast cells; Pathogen transmission; Tick saliva

PMID: 28655322 PMCID: PMC5488306 DOI: 10.1186/s13071-017-2243-0

"We report here for the first time the bacteria ability to induce the inflammatory response of mouse primary mast cells. We show that OspC, a major surface lipoprotein involved in the early transmission of Borrelia, induces the degranulation of primary mast cells …"

Bartonella also attracts mast cells and triggers histamine release

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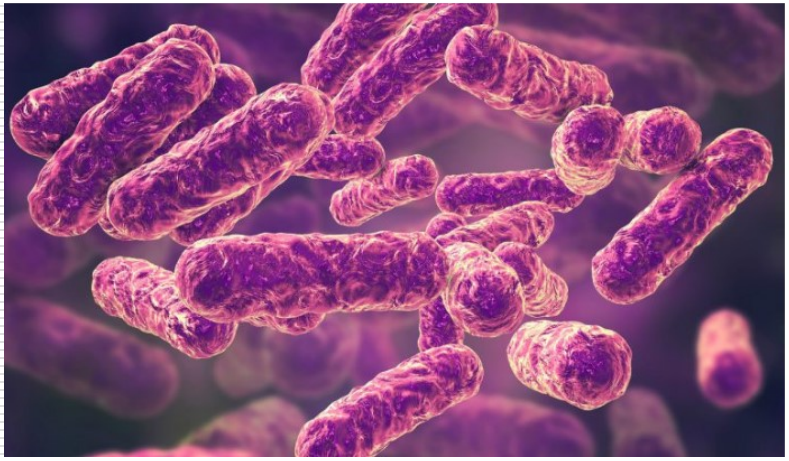
Home › Knowledge › Co-infections › Bartonella henselaequintana and others – absolutely everything about this gram negative bacteria

Knowledge Co-infections

Bartonella henselaequintana and others – absolutely everything about this gram negative bacteria

By **Lyme Academy** - 18 September 2018 1517 0



MOST

Borrel… Autor -

Bladd… Autor -

The w… endoc… Autor - 27 June 2019

CBA test Autor - 27 June 2019

Don't lie, you look healthy Autor - 27 May 2019

Bartonella henselae **overactivates the MCP-1 gene** …. The functions of this gene are as follows: **luring** monocytes and T-lymphocytes, eosinophils, **mast cells** and basophils, and additionally stimulating cytotoxic destruction of cells by CD8 + lymphocytes and NK lymphocytes. … In addition, **it affects the release of histamine and synthesis of leukotrienes by mast cells** and basophils.

Source: https://lymedisease.uk/2018/09/18/bartonella-henselaequintana-and-others-absolutely-everything-about-this-gram-negative-bacteria/

Mast Cells and Mycoplasma

Clinical Therapeutics
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< Previous Article May 1, 2015 Volume 37, Issue 5, Pages 941–953 Next Article >

Mast Cell Activation Disease and Microbiotic Interactions

Lawrence B. Afrin, MD, Alexander Khoruts

PlumX Metrics

DOI: https://doi.org/10.1016/j.clinthera.2015.02.008

Article Info

Abstract Full Text Images References

Article Outline

I. Introduction
II. Materials and Methods
III. Results
A. Mast Cell Activation Disease
1. Epidemiology, Natural History, Prognosis, and Familial Considerations
2. Clinical Presentation
B. Interactions between Human Microbiota and Mast Cells
IV. Conclusions
V. Conflicts of Interest
VI. References

Mycoplasma pneumoniae induces mast cell activation and degranulation

Mechanisms of allergy

Mycoplasma pneumoniae–induced activation and cytokine production in rodent mast cells

Kristen L. Hoek, BS, Gail H. Cassell, PhD, Lynn B. Duffy, MT, and T. Prescott Atkinson, MD, PhD *Birmingham, Ala*

Background: ***Mycoplasma pneumoniae*** **is a respiratory tract pathogen that has been associated with severe exacerbations in patients with chronic asthma. Murine models of infection have recently been established, with disease manifestations similar to those observed in human subjects. Previous studies have suggested that this organism is capable of producing activation of a wide range of immunologic cell types.**
Objective: We sought to determine whether *M pneumoniae* can induce mast cell activation in the rodent mast cell line RBL-2H3.
Results: After 4 hours of coculture, morphologic changes indicative of activation were observed by means of electron microscopy, and *M pneumoniae* was identified, by means of immunoelectron microscopy, adhering to mast cell membranes. Coculture of rat basophilic leukemia cells with viable *M pneumoniae* for 4 hours resulted in net release of β-hexosaminidase and serotonin into the supernatant. Live, but not heat-killed, organisms induced the release of IL-4 protein into the culture supernatant, with a peak at 4 hours. During coculture with *M pneumoniae*, production of mRNA for IL-4, IL-6, and TNF-α was upregulated after 2 hours and had returned to near baseline by 24 hours after infection.
Conclusions: We conclude that viable *M pneumoniae* induces activation of mast cells with release of granule contents, as well as cytokine production. (J Allergy Clin Immunol 2002;109:470-6.)

Key words: Mycoplasma pneumoniae, *asthma, mast cells, cytokines*

Mycoplasma pneumoniae is a human pathogen that typically infects ciliated epithelial cells in the respiratory tract, producing upper and lower respiratory tract infec-

Abbreviations used
AHR: Airway hyperresponsiveness
β-hex: β-D-hexosaminidase
RBL: Rat basophilic leukemia

been associated with asthma exacerbations.[6-11] Two recent studies have revealed the presence of *M pneumoniae* DNA in the lower respiratory tracts of about 50% of patients with chronic asthma, suggesting a role for this organism in a subset of patients.[7,8]

Recently, several groups have established murine models of *M pneumoniae* infection that lead to clinical manifestations of pneumonia similar to those observed in human subjects: pulmonary inflammation, as evidenced by histology; airway hyperresponsiveness (AHR), as measured by means of whole-body unrestrained plethysmography; proinflammatory cytokine mRNA upregulation and protein release into bronchoalveolar lavage; and production of antibodies to *M pneumoniae*.[12-16] In these studies *M pneumoniae* was detected by means of culture, PCR, or both throughout the entire study, suggesting that long-term pulmonary colonization occurred after nasal installation; the organism could be detected even after symptoms abated. This observation is similar to that seen in human infections with this pathogen, in which *M pneumoniae* can be detected months after the clinical pneumonia has resolved.[14]

Evident role of histamine in the pathomechanism of Chlamydia pneumoniae infections

Immunol Lett. 2003 Oct 31;89(2-3):229-36.

Chlamydophila (Chlamydia) pneumoniae induces histidine decarboxylase production in the mouse lung.

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Abstract

Chlamydophila (Chlamydia) pneumoniae (C. pneumoniae) is the third most common cause of community-acquired pneumonia and is probably involved in the development of certain chronic inflammatory diseases, including atherosclerosis and adult-onset asthma. Histamine, synthesized by histidine decarboxylase (HDC) from L-histidine, plays an essential role in allergic and inflammatory processes and in cell differentiation. The effect of C. pneumoniae infection on the expression of HDC has not been examined. In the present study, normal Balb/c mice and HDC knockouts, and control mice with a CD1 background were infected intranasally with C. pneumoniae. On days 1, 3, 7, 16 and 31 after infection, the normal Balb/c mice were sacrificed and divided into three groups. In the homogenized lungs of the first group, C. pneumoniae titres were determined and demonstrated peak levels on day 7. HDC production was revealed by a Western blot assay throughout the observation period of 1-16 days, and cytokine concentrations were determined by ELISA. The interleukin-3 (IL-3) and interleukin-6 (IL-6) levels were highest on day 1 and on days 1-3, respectively; the interferon-gamma (IFN-gamma) and interleukin-4 (IL-4) levels reached the maximum on day 7, but the quantity of IL-4 was still three times higher than that in the control group 16 days after infection. The lungs of the mice in the second group were processed for the in situ demonstration of HDC activity, while the lungs in the third group were stained for C. pneumoniae antigen. The HDC activity was increased predominantly in the bronchial epithelial cells, while C. pneumoniae antigens were expressed especially in the interstitial macrophages. The HDC knockout mice exhibited a higher survival rate after C. pneumoniae infection than did the control mice. These results point to a strong association between local histamine production and other inflammatory mediators and are novel in demonstrating the role of histamine in the pathomechanism of C. pneumoniae infections.

Source: https://www.ncbi.nlm.nih.gov/pubmed/14556983

Yersinia enterocolitica and histamine signalling

Activation of H_2 has been shown to have a variety of effects including altering the production of inflammatory cytokines and disrupting the Th1–Th2 balance during the immune response (**34**). The Th1–Th2 balance is known to be important for controlling *Y. enterocolitica* infection (**13**). However, the very early manifestations of the phenotypes described in this article suggest that the key effect of signaling of histamine through H_2 likely involves effects on early innate immune responses.

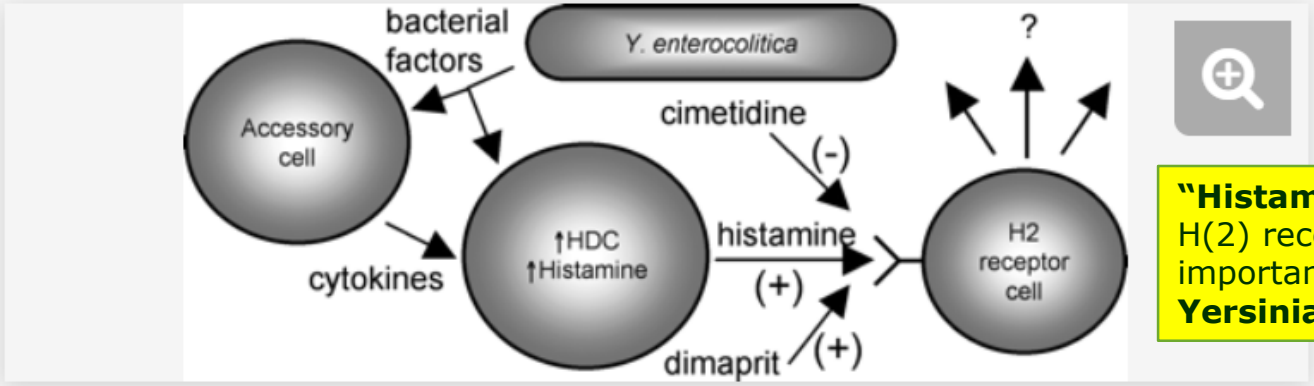

Fig. 3.

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Model of the histamine H_2-mediated response to *Y. enterocolitica* infection. See *Discussion* for a detailed explanation.

"Histamine signaling through the H(2) receptor in the Peyer's patch is important for controlling **Yersinia** enterocolitica infection."

Source: https://www.ncbi.nlm.nih.gov/pubmed/16717182, Handley, Scott A et al. "Histamine signaling through the H(2) receptor in the Peyer's patch is important for controlling Yersinia enterocolitica infection." Proceedings of the National Academy of Sciences of the United States of America vol. 103,24 (2006): 9268-73. doi:10.1073/pnas.0510414103

"Mast cells recognize and respond to viruses through several different receptors"

frontiers in Immunology

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Published online 2015 May 18. doi: 10.3389/fimmu.2015.00238
PMCID: PMC4435071
PMID: 26042121

Mast Cells and Influenza A Virus: Association with Allergic Responses and Beyond

"…. These receptors include TLR signaling, such as TLR3 detection of dsRNA, sphingosin-1-phosphate (S1P) binding to its receptor S1PR, and RIG-I recognition of uncapped vRNA. **Engagement of these receptors results in mast cell activation leading to immediate degranulation**, the *de novo* synthesis of eicosanoids within minutes of activation, and the *de novo* synthesis of numerous cytokines, chemokines, and growth factors within hours of activation."

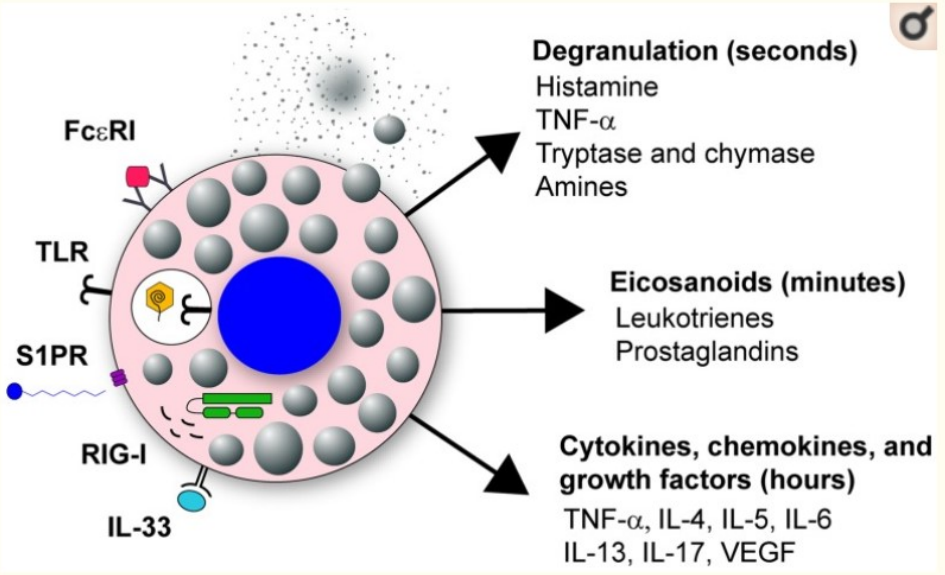

Figure 1

Mast cell activation in response to viral infection. Mast cells are classically known for their response to polyvalent cross-linking of IgE in the FcεR1 receptor, which is important in protective immunity to helminth worm infection and pathologically associated with allergic disease. However, mast cells also are important tissue sentinel cells for initiating inflammatory response to pathogens. Mast cells can recognize and respond to viruses through several different receptors. These receptors include TLR signaling, such as TLR3 detection of dsRNA, sphingosin-1-phosphate (S1P) binding to its receptor S1PR, and RIG-I recognition of uncapped vRNA. Engagement of these receptors results in mast cell activation leading to immediate degranulation, the *de novo* synthesis of eicosanoids within minutes of activation, and the *de novo* synthesis of numerous cytokines, chemokines, and growth factors within hours of activation.

Source: Graham, A. C., Temple, R. M., & Obar, J. J. (2015). Mast cells and influenza A virus: association with allergic responses and beyond. Frontiers in immunology, 6, 238

"Mast cell activation can participate in limiting viral replication in the local tissue and viral dissemination"

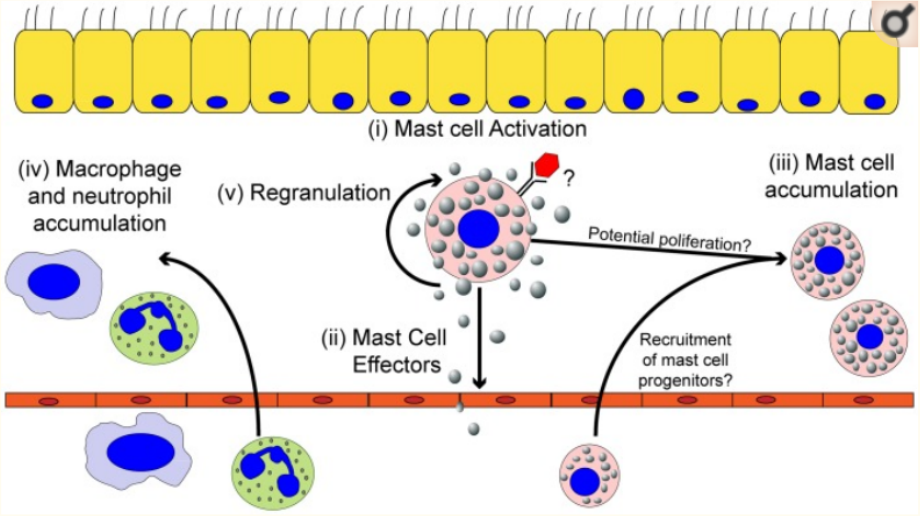

Figure 2

The effects of mast cell activation on the inflammatory environment induced by viruses. Within the tissues, mast cells can be activated by viruses (i) resulting in the secretion of effector molecules (ii). Mast cell-derived effector molecules act within the local tissue environment or at distal site to mediate the accumulation of mast cell progenitors (iii) and leukocytes (iv) to the site of infection. Mast cell accumulation in the infected tissues could be due to either the recruitment and differentiation of mast cell progenitors to the infected tissue and/or proliferation of the tissue-resident mast cell population. Mast cell activation can participate in limiting viral replication in the local tissue and viral dissemination, but if left unchecked can cause significant tissue damage, vascular leakage, and tissue edema. Finally, activated mast cells can survive the pathogenic insult and replenish mast cell granules to return the mast cell to a basal state to survey the tissue for future pathogenic insults (v).

Within the tissues, mast cells can be activated by viruses, resulting in a cascade of actions intended to curb and overcome the pathogenic insult

Source: Graham, A. C., Temple, R. M., & Obar, J. J. (2015). Mast cells and influenza A virus: association with allergic responses and beyond. Frontiers in immunology, 6, 238

Coxsackie, an RNA virus, also upregulates mast cells …

Review Article

Viruses as adjuvants for autoimmunity: evidence from Coxsackievirus-induced myocarditis

DeLisa Fairweather, Sylvia Frisancho-Kiss, Dr Noel R. Rose

First published: 16 December 2004 | https://doi.org/10.1002/rmv.445 | Cited by: 84

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Abstract

Adjuvants historically are considered to stimulate immune responses 'non-specifically'. Recently, a renewed understanding of the critical role of innate immunity in influencing the development of an adaptive immune response has led researchers to a better understanding of 'the adjuvant effect'. Although innate immune cells do not respond to specific antigenic epitopes on pathogens, they do produce restricted responses to particular classes of pathogens via pattern recognition receptors such as Toll-like receptors (TLR). Coxsackievirus infection was found to upregulate TLR4 on mast cells and macrophages immediately following infection. Although both susceptible and resistant mice produce a mixture of Th1 and Th2 cytokines, susceptible mice have increased levels of key proinflammatory cytokines, increased numbers of mast cells, and go on to develop chronic autoimmune heart disease. TLR4 signalling also increases acute myocarditis and proinflammatory cytokines in the heart. Many similarities are described in the pathogenesis of Coxsackievirus and the adjuvant-induced model of myocarditis including upregulation of particular TLRs and cytokines soon after inoculation. Recent findings suggest that mast cell activation by viruses or adjuvants may be important in initiating autoimmune disease.

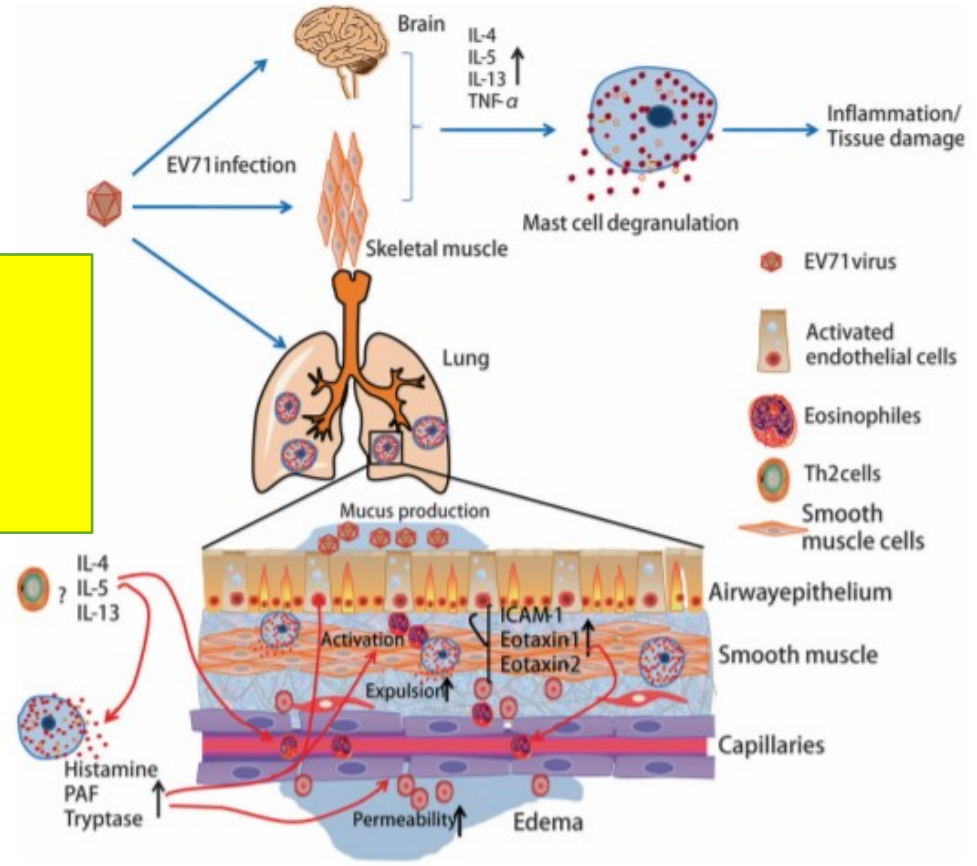
"Coxsackievirus infection was found to upregulate TLR4 on mast cells and macrophages immediately following infection"

"Mast cell activation by viruses … may be important in initiating autoimmune disease."

Source: https://www.ncbi.nlm.nih.gov/pubmed/15386590

… as do various other enteroviruses

Fig. 6 Proposed mechanism of action for mast cell in the the pathogenesis of EV71 infection



"Enterovirus 71 infection activated mast cells and induced allergic inflammation in target organs or tissues"

Source: Jin, Yuefei & Zhang, Chao & Wang, Hui & Zhou, Guangyuan & Wang, Xiangpeng & Zhang, Rongguang & Chen, Shuaiyin & Ren, Jingchao & Chen, Lu & Dang, Dejian & Zhang, Peng & Xi, Yuanlin & Zhang, Weiguo & Duan, Guangcai. (2018). Mast cells contribute to Enterovirus 71 infection-induced pulmonary edema in neonatal mice. Laboratory Investigation. 98. 1. 10.1038/s41374-018-0075-y.

Testing for infections in histamine upregulation/MCAS: Considerations

1. Borrelia (Elispot/Tickplex)
2. Chlamydia pneumoniae?
3. Mycoplasma?
4. Bartonella?
5. Yersinia enterocolitica?
6. Any of the viruses, e.g., Enteroviruses/Coxsackie?

Best again to do the checklists, and look at the patient's situation overall, with any comorbidities …

… and factor in the expertise of Dr. Afrin from this afternoon!

Thank you very much for your attention!

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