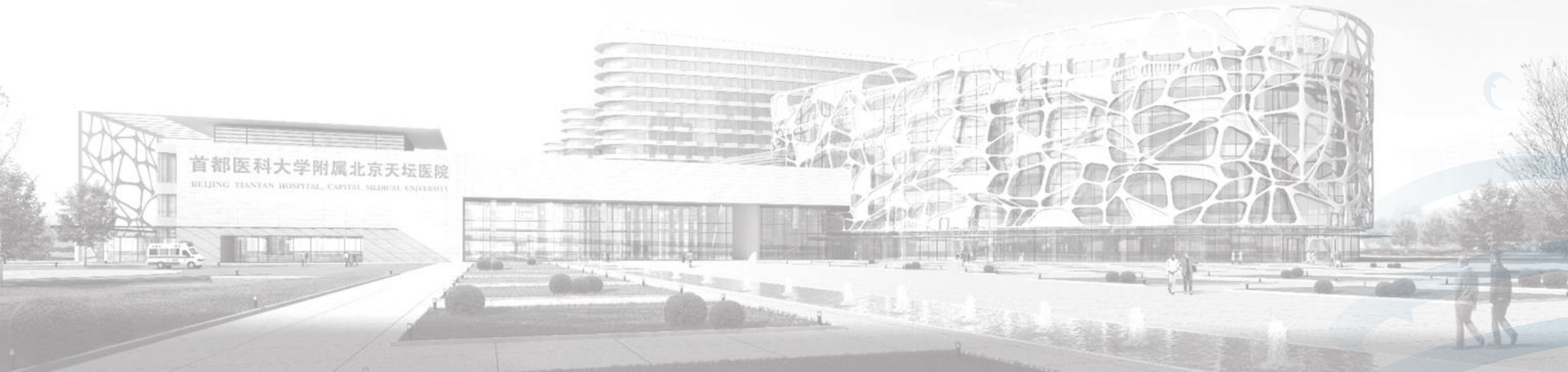
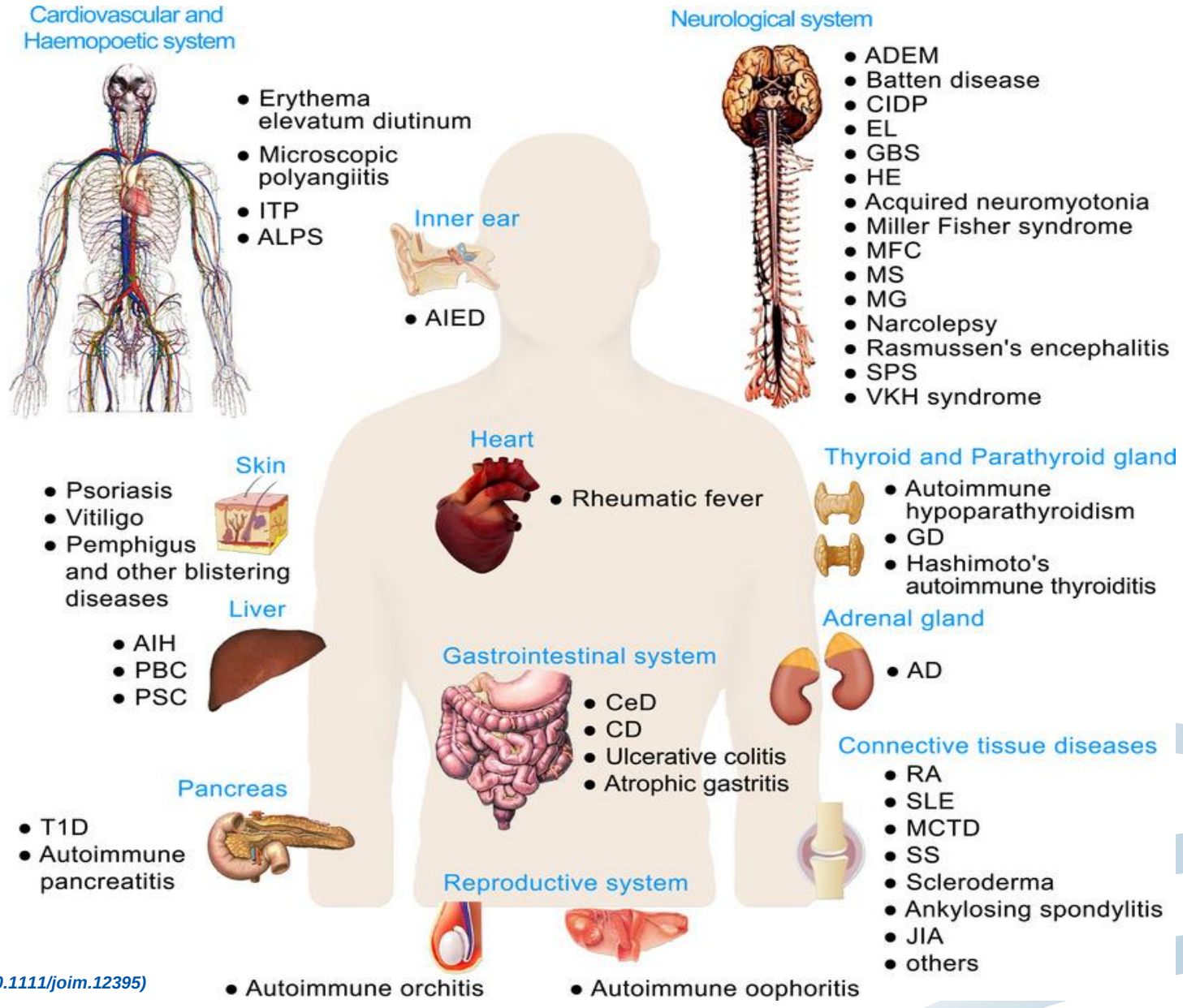
自身免疫认知简史及研究鉴赏



背景-自身免疫疾病

- 至今，已确认80-100多种自身免疫性疾病
- 自身免疫疾病影响大约8%-10%的世界人口
- 工业化国家发病率仍在上升
- 共同的机制：免疫介导的对自身器官的攻击
- 发病机制复杂难懂：病因无迹 自身免疫



Journal of Internal Medicine, Volume: 278, Issue: 4, Pages: 369-395, First published: 25 July 2015, DOI: (10.1111/joim.12395)

自身免疫疾病研究代表性科学家

- 保罗•埃利希 1904
- 欧内斯特•维特斯基 甲状腺自身抗体
- 诺埃尔•罗斯 维特斯基法则
- 彼得•梅达瓦 自身耐受
- 麦克法兰•伯内特 克隆选择

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PERSPECTIVES | HISTORICAL KEYWORDS | VOLUME 367, ISSUE 9508, P389, FEBRUARY 04, 2006

Autoimmune disease

Ohad Parnes

Published: February 04, 2006 • DOI: https://doi.org/10.1016/S0140-6736(06)68125-7

Article Info

Despite its emergence only in the 1950s, autoimmune aetiology now applies to, or is suspected in, a long list of chronic diseases—multiple sclerosis, type I diabetes, and Crohn's disease being prominent examples.

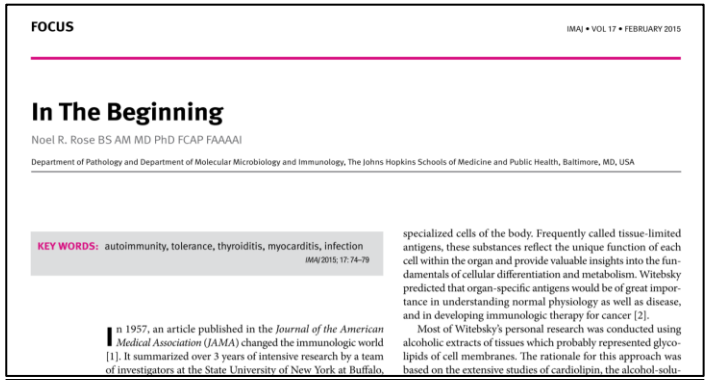
The idea of disease as a self-destructive process has been a part of disease theory since the beginning of the 20th century. Possibly the first definition of autoimmune disease was provided by Paul Ehrlich in 1904 when he coined the term “horror autotoxicus”. However, for many decades, Ehrlich's dictum was wrongly understood to mean that autoantibodies could not exist. It was only in the 1940s, and notably in the 1950s, that evidence accumulated on the existence of specific antibodies against specific bodily tissues. Germinal was the work of Ernst Witebsky and Noel Rose, which revealed the existence of antithyroid antibodies in rabbits. Shortly afterwards, in 1956, British scientists showed that these antibodies were indeed manifest in people with chronic thyroiditis. Within a few years, a whole series of diseases was shown to have similar autoimmunological components, thus giving birth to this new nosological category.

Also in the early 1950s, Peter Medawar, in London, UK, introduced the idea of self-tolerance—ie, a mechanism preventing the immune system from attacking its host tissues. He further argued that self-tolerance was not the result of inherently inborn genetic differences, but was an adaptive process taking place during embryonic development. In 1957, this idea was elaborated by the Australian immunologist, Macfarlane Burnet. His “clonal selection theory” contended that the immune system was made of numerous “immunologically competent” clones of cells (lymphocytes) circulating around the body in a constant surveillance for harmful invaders. Autoimmune disease must then be the result of the appearance of a “forbidden clone”. Burnet's theoretical framework served until the 1990s, when it was supplanted by an understanding that autoimmune processes were part of the normal physiology of an individual, and autoimmune components (antibodies, T cells) were permanent parts of the immune repertoire, even in the absence of a pathological condition. Answers now focus less on the autospecificity of immune components, than on the regulation mechanisms that seem able to control the pathogenicity of these components.

Parnes O. Autoimmune disease. The Lancet (2006) 367(9508). doi: 10.1016/s0140-6736(06)68125-7

自身免疫认知简史

- 既往及1950年代的十年：创世纪，1957，JAMA
- 1960年代：机制，自身抗体，T细胞，动物实验模拟
- 1970年代：遗传学，MHC，甲状腺炎
- 1980年代：环境，触发器，感染与免疫
- 1990年代：流行病学，24种自身免疫病流调人口负担
- 2000年代：政策/问题
- 60 年 自身免疫史 研究史 认知史
- 2015年 88岁



FOCUS

IMAJ • VOL 17 • FEBRUARY 2015

In The Beginning

Noel R. Rose BS AM MD PhD FCAP FAAAAI

Department of Pathology and Department of Molecular Microbiology and Immunology, The Johns Hopkins Schools of Medicine and Public Health, Baltimore, MD, USA

KEY WORDS: autoimmunity, tolerance, thyroiditis, myocarditis, infection

IMAJ 2015; 17: 74–79

In 1957, an article published in the *Journal of the American Medical Association* (*JAMA*) changed the immunologic world [1]. It summarized over 3 years of intensive research by a team of investigators at the State University of New York at Buffalo,

specialized cells of the body. Frequently called tissue-limited antigens, these substances reflect the unique function of each cell within the organ and provide valuable insights into the fundamentals of cellular differentiation and metabolism. Witebsky predicted that organ-specific antigens would be of great importance in understanding normal physiology as well as disease, and in developing immunologic therapy for cancer [2].

Most of Witebsky's personal research was conducted using alcoholic extracts of tissues which probably represented glycolipids of cell membranes. The rationale for this approach was based on the extensive studies of cardiolipin, the alcohol-solu-

Figure 1. Dr. Rose examining a gel in his laboratory at Johns Hopkins, 1982

Rose NR. In The Beginning. Isr Med Assoc J. 2015 Feb;17(2):74-9. PMID: 26223081.

自身免疫的领路人

- 2020.07.30 死于中风, 享年92岁
- 伟大的科学家，自身免疫之父
- 领导国家层面自身免疫研究政策

著名职位和奖项

- 约翰·霍普金斯大学名誉教授
- 布莱根妇女医院病理学兼职高级讲师
- 美国科学促进协会金鹅奖(2019年)
- 约翰·霍普金斯自身免疫性疾病研究中心创始人兼主任(1999年至2015年)
- 美国国立卫生研究院自体免疫疾病协调委员会主席(2003-05年)
- 波兰科学院尼古拉·哥白尼奖章(2009年)
- 基石终身成就奖(2006年)
- 美国科学促进协会当选成员(1999年)

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Obituary | Published: 07 September 2020

Noel R. Rose 1927–2020

David W. Scott, Rachel R. Caspi & Kamal D. Moudgil

Nature Immunology **21**, 1306 (2020) | Cite this article

2250 Accesses | **1** Citations | **3** Altmetric | Metrics

We are profoundly saddened by the passing of Noel Rose, a pioneer in the study of autoimmune diseases, on 30 July 2020, in Boston. Noel spent most of his career at Johns Hopkins Medical School but initiated his seminal studies at the University of Buffalo. Graduating from Yale in 1948 in three years, he went on to the University of Pennsylvania to earn his PhD in 1951. He subsequently moved to the State University of New York at Buffalo as an instructor, where he began his studies under the aegis of Dr. Ernest Witebsky. He taught at Buffalo and went on to earn an MD degree there! He served on the faculty of Wayne State University in Detroit, then moved to Johns Hopkins Medical School in 1982, first as chair of the Department of Immunology and Infectious Diseases and later as chair of the Pathology Department. Noel directed the Bloomberg School of Public Health there for two decades. He played a major role as a mentor to generations of scientists, not only as chair at Hopkins but also as a principal advisor to the NIH on autoimmunity and autoimmune disease research.

Credit: Pathology Department, Johns Hopkins University

Noel was a pioneer in immunology and is deservedly called the 'father' of autoimmunity research. Using thyroglobulin (Tg) as a model antigen, Noel immunized rabbits with Tg from diverse species. Despite being relatively conserved in structure, all rabbits responded to these 'foreign' Tg antigens. Undeterred, he isolated rabbit Tg and immunized rabbits with this isologous, and even autologous, protein. These rabbits responded with antibody production, thus overturning the widely held concept of 'horror autotoxicus,' loosely translated as "fear of poisoning oneself", which caused a paradigm shift in immunology. As you can imagine, he had difficulty in getting his results published. Nonetheless, his studies launched further research on autoimmune diseases, and he remained a pioneer of the field for the duration of his career. Not surprisingly, he possessed a uniquely broad perspective and depth of knowledge in autoimmune diseases. Noel's later work at Johns Hopkins revealed some of the key immune mechanisms by which iodine can contribute to the autoimmune processes in thyroiditis.

自身免疫领域的年轻人

年轻人是拥有年轻思想的人 变化 发展 生命力

Autoimmunity Reviews 19 (2020) 102638

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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Comorbidity of autoimmune diseases: A visual presentation

Dear Editor,

It is well known that the autoimmune diseases share extensive comorbidities [1–7]. But the pattern of comorbidity is not well understood, leading to terms such as the "kaleidoscope of autoimmunity" [8], "polyautoimmunity" [9] and "the autoimmune tautology" [10]. Although many shared etiologic pathways are presumed to exist [11], individual autoimmune diseases are relatively rare, making it difficult to study patterns of comorbidity. Also, research tends to be conducted on subgroups connected to medical specialties, as opposed to analysis of a broad spectrum of diseases.

The most complete study of the pattern of comorbidities of autoimmune diseases used data from the National Patient Register of Denmark, focusing on the prevalence of 31 diseases and odds ratios for the 465 pairwise comorbidities [12]. The current paper uses the same data but focuses on the female subpopulation of 2,764,219 females in Denmark on December 31, 2001, where prevalence is higher, and examines a subset of 22 most frequent diseases for which there are mostly

(which is a projection of the leaves of the tree onto a line, or intuitively, a view of all the leaves from a best angle) that could be used to order the variables in the correlation matrix heat map. The clustering algorithm requires a full correlation matrix, so to deal with the two missing correlations, we ran four clustering exercises, each leaving out two diseases, one from each missing correlation. Results are synthesized in one single list of groupings of all the 22 diseases.

Fig. 1 is the correlation heat map with the ordering from the synthesis. Here high correlations are shown in dark red, with lighter colors on the red-orange-yellow spectrum indicating less strong correlations, and light blue indicating slight negative correlations. The suggested disease groups are marked in gray boxes. A note on reading the plot: the primary information in the plot is about which diseases are grouped together, while the ordering of the groups is much less meaningful. This is because, as noted above, the ordering is a projection of the clustering tree on to one dimension, so intuitively, if we look at a tree from just a slightly different angle, the order of the branches shifts, but we still have the same leaves on each big branch

REVIEW article

Front. Immunol., 06 August 2019 | https://doi.org/10.3389/fimmu.2019.01827

Fatigue, Sleep, and Autoimmune and Related Disorders

Mark R. Zielinski[1,2*], David M. Systrom[3,4] and Noel R. Rose[5]

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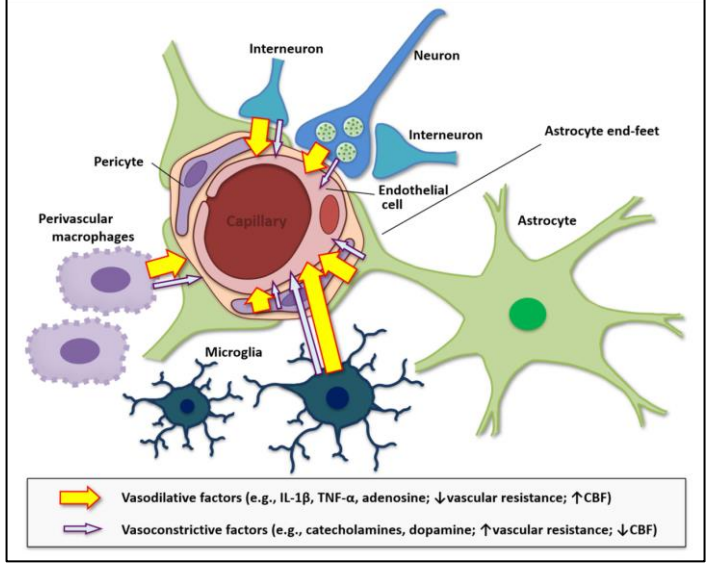
[2]Department of Psychiatry, Harvard Medical School, Boston, MA, United States
[3]Department of Medicine, Harvard Medical School, Boston, MA, United States
[4]Department of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, United States
[5]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States



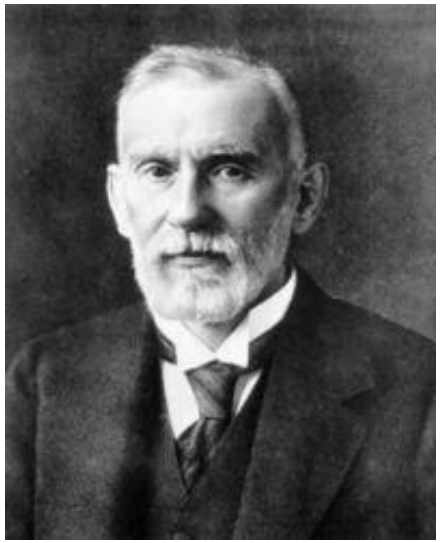
- 血管血流动力学的神经血管单元
- 2/3自身免疫病人主诉疲劳 虚弱
- 中枢神经系统是关键因素
- 炎症与中枢神经系统
- CNS调节 睡眠 压力 神经递质
- 迷走神经和中枢神经系统炎症

在生命的最后一段时间，Rose热衷于使用大数据研究自身免疫性疾病，他相信：为患者建立数据库在揭示患者病因和开发阻断方法方面具有巨大潜力

Eaton WW, Nguyen TQ, Pedersen MG, Mortensen PB, Rose NR. Comorbidity of autoimmune diseases: A visual presentation. Autoimmun Rev. 2020 Oct;19(10):102638. doi: 10.1016/j.autrev.2020.102638. Epub 2020 Aug 13.
Zielinski MR, Systrom DM, Rose NR. Fatigue, Sleep, and Autoimmune and Related Disorders. Front Immunol. 2019 Aug 6;10:1827. doi: 10.3389/fimmu.2019.01827.

自身免疫认知简史-起点

- 公元前，希波克拉底&盖伦 医学奠基 体液学说 外源物入侵致病
- 14世纪中国，整个欧洲的腺鼠疫和肺鼠疫大流行 经验医学 感染后获得免疫
- 16世纪中国，人痘 鼻苗法 痘痂干粉
- 18世纪 爱德华•詹纳，牛痘疫苗，影响 路易•巴斯德毒性抗体（细胞毒素）
- 1901保罗•埃利希“恐怖的自体毒性（Horror autotoxicus）”



- 自身毒性恐惧 羊红细胞免疫 没有产生自身抗体
- 生物染料
- 体液免疫的“侧链学说”
- 606 (抗梅毒药)
- 化学疗法的先驱
- 1908年诺贝尔生理学或医学奖

自身免疫认知简史-线索与困境

两次世界大战

- 1885年，巴斯德 减毒的狂犬病疫苗
- 感染有狂犬病毒的兔子脊髓 全干 半干 多次免疫
- 部分接种者出现脑脊髓炎的症状 瘫痪 死亡
- 认为是“狂犬病毒的副作用”
- 托马斯•瑞瓦斯 健康兔子组织反复去免疫猴子，部分猴子也出现了脑脊髓炎的症状
- 1942年弗氏佐剂　高效的免疫刺激剂
- 1947年，卡巴特 兔脑免疫猴子+弗氏佐剂，猴子出现了脑脊髓炎的症状。猴脑作为抗原去免疫，同样也会让猴子出现症状
- 奥里斯基 小鼠：实验性自身免疫脑脊髓炎模型

- 1904年，卡尔•兰德施泰纳 溶血 自身红细胞裂解因子
- 自身红细胞裂解因子=红细胞的自身抗体
- 1930年，卡尔•兰德施泰纳 发现ABO血型 诺奖
- 1906年，奥古斯特•保罗•冯•瓦瑟曼 检测梅毒抗体时发现针对正常肝细胞的自身抗体
- 类风湿因子 Erik waaler在1940年首次报道，1948年Rose再次描述，“ Waaler Rose test”
- 1948年，哈格雷维斯 红斑狼疮细胞效应

自身免疫认知简史-创世纪

J.A.M.A., July 27, 1957

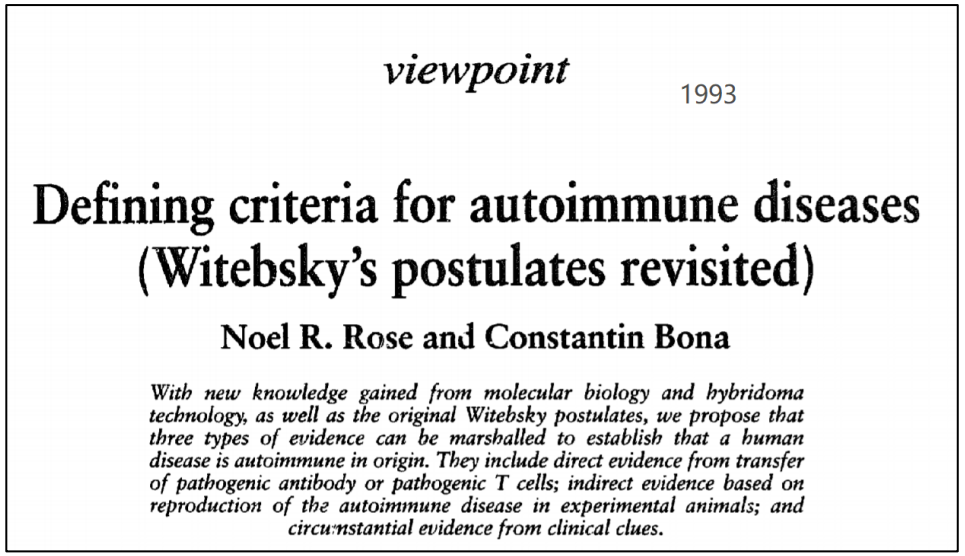
CHRONIC THYROIDITIS AND AUTOIMMUNIZATION

Ernest Witebsky, M.D., Noel R. Rose, Ph.D.
Kornel Terplan, M.D., John R. Paine, M.D., Ph.D.
and
Richard W. Egan, M.D., Buffalo

Noel Rose (left) and Ernest Witebsky (right)

- 1957年，JAMA
- 划时代，无可辩驳的证据证明了自身免疫病
- 鉴定自身免疫病的几条标准：
- 1. 直接显示血液中有**自身抗体存在**；
- 2. 自身抗体可以识别**特定的自身抗原**；
- 3. 能在动物模型里诱导这种自身抗体的产生；
- 4. 动物模型能够模拟病人的症状。
- **维特斯基法则**

自身免疫认知简史-创世纪



viewpoint 1993

Defining criteria for autoimmune diseases (Witebsky's postulates revisited)

Noel R. Rose and Constantin Bona

With new knowledge gained from molecular biology and hybridoma technology, as well as the original Witebsky postulates, we propose that three types of evidence can be marshalled to establish that a human disease is autoimmune in origin. They include direct evidence from transfer of pathogenic antibody or pathogenic T cells; indirect evidence based on reproduction of the autoimmune disease in experimental animals; and circumstantial evidence from clinical clues.

- 1993年，更新
- 罗斯对自身免疫病的鉴定标准进行了修正
- 1. 致病抗体/致病T细胞转移；
- 2.实验动物自身免疫性疾病复制的间接证据；
- 3.临床线索中的间接证据。
- 名字依然叫 “维特斯基法则”

自身免疫认知简史-创世纪时代背景

Noel Rose (left) and Ernest Witebsky (right)

- 1936年，欧内斯特·维特斯基流亡美国 保罗·埃尔利希学生 已成名
- 诺埃尔·罗斯 耶鲁本科 24岁 宾夕法尼亚大学 博士毕业
- 1951年，加入维特斯基实验室研究甲状腺的器官特异性抗原甲状腺球蛋白，当时被认为是具有明确器官特异性的稀有蛋白质之一
- 维特斯认为器官特异性抗原对于了解正常生理和疾病以及开发癌症免疫疗法非常重要
- 生化背景 制备高纯度甲状腺球蛋白（90%） 免疫兔子
- 保罗·埃利希的训诫与格言 同一物种天然蛋白质不会诱导抗体产生
- 继续提纯 同一只兔子的甲状腺球蛋白注射回兔子体内 出现抗体
- 病理上类似甲状腺炎表现 维特斯基认为蛋白质变性

自身免疫认知简史-创世纪时代背景

Noel Rose (left) and Ernest Witebsky (right)

- 当时可诱导自身免疫反应的自身抗原：脑，眼睛晶状体，精子
- 特权位点，隔离抗原；甲状腺，血管丰富组织，不会出现自身免疫反应抗原
- 豚鼠，狗同样的自身免疫反应
- 求助外科主任摘甲状腺小叶提甲状腺蛋白进行免疫
- 并收集了十几例甲状腺炎患者血清，鉴定出四例甲状腺球蛋白抗体，更严重
- 三年紧张工作 完成证据链 证明甲状腺炎是自身免疫介导的疾病
- 维特斯基改变了自己观点，成为了自身免疫病研究领域的支持者和领航人
- 被拒稿　再次选期刊　JAMA　新任主编是Buffalo医学院前教授
- 罗斯认为是大众没有彻底领悟保罗•埃利希研究的精髓，避免观点冲突

自身免疫认知简史-克隆选择

- 1957年,伯内特提出了“获得性免疫的克隆选择学说”
- 正常个体有**一整套能与所有抗原决定簇起反应的淋巴细胞系**,在胚胎期，凡是能与自身抗原起反应的细胞系，因接触自身抗原而被抑制；出生后，未被抑制的细胞系与相应抗原接触可以增殖并分化成抗体生成细胞；而在胚胎期被抑制的细胞,经再次刺激后会激活，导致自身免疫病（如移植排斥）的发生。解释了临床上移植排异反应的原因，而且使免疫学冲出了抗感染的狭小范围，进入了机体识别“自我”与“非我”的**现代免疫阶段**。
- 克隆选择学说指引了免疫学的研究，也为解释自身免疫现象提供了理论基础
- 1960年，诺贝尔生理学或医学奖
- 还提出了**抗体生成的理论**，即抗体在有效抗原从体内消失后很长时间内仍然继续产生

自身免疫认知简史-克隆选择

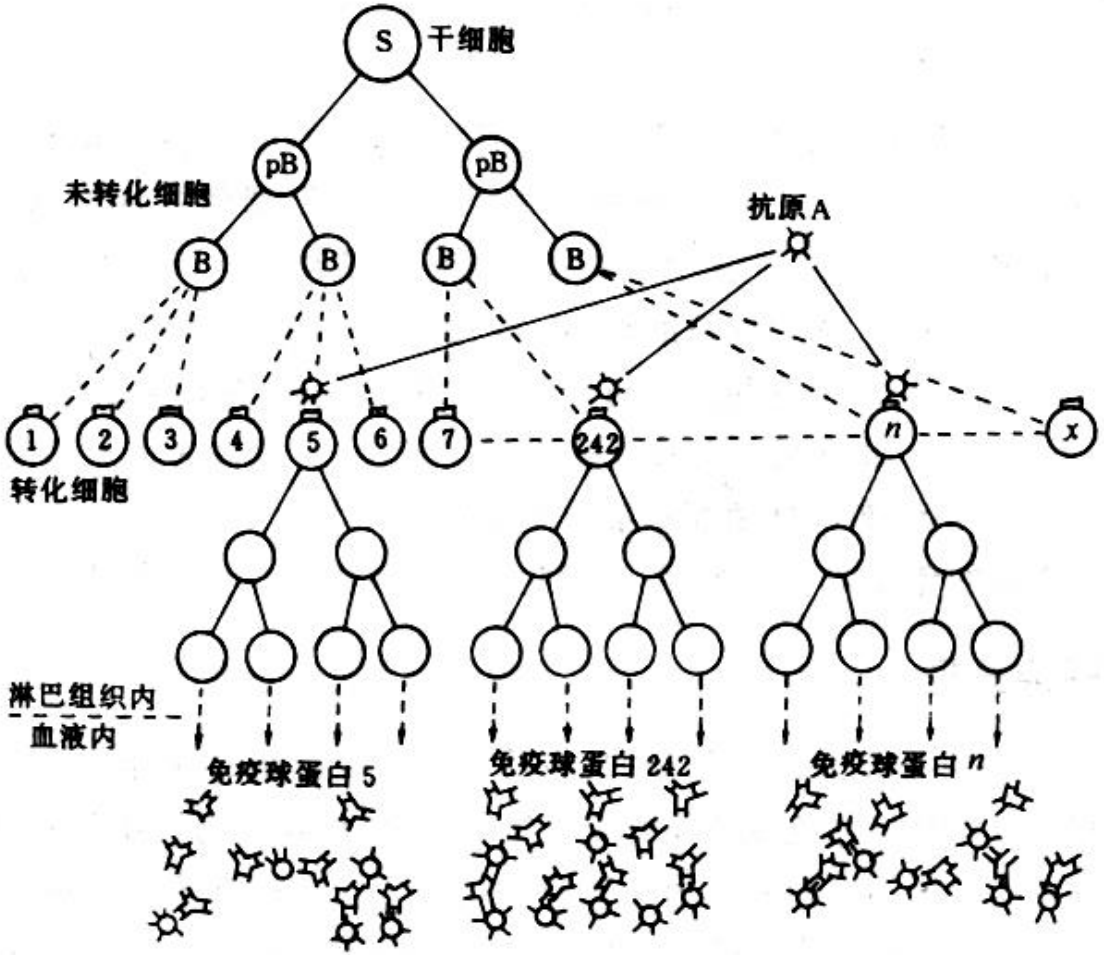


图 14－9　克隆选择学说图解

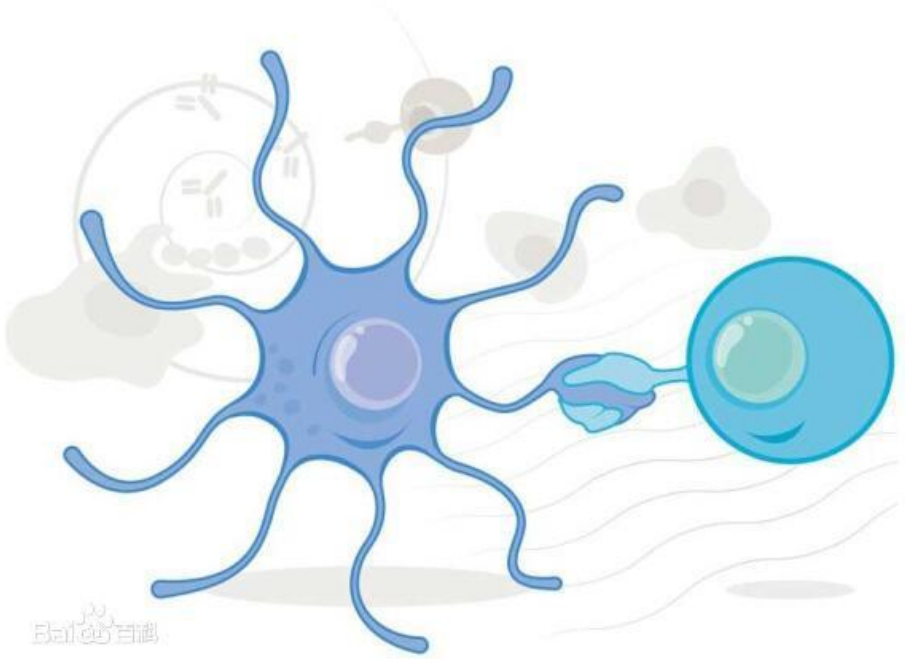
体内存在着许多免疫活性细胞克隆，不同克隆的细胞具有不同的表面受体，能与相对应的抗原决定簇发生互补结合。一旦某种抗原进入体内与相应克隆的受体发生结合后便选择性地激活了这一克隆，使它扩增并产生大量抗体（即免疫球蛋白），抗体分子的特异性与被选择的细胞的表面受体相同

自身免疫认知简史-现代免疫

- 1955年，《抗体产生的自然选择理论》
- 依照他的理论，我们的免疫系统本身就有产生针对各种抗原的抗体的能力，而外来的抗原只是作为一种选择力量让这种特异的抗体选择性地被生产力出来
- 特异抗体产生的能力是一种免疫系统内在已有的；把达尔文的自然选择理论引了进来
- 伯内特从这个理论里得到了启发，提出来一个关于**免疫耐受的理论**
- 抗体多样性发生学说和免疫系统的网络学说
- 1984年，诺贝尔生理学或医学奖

自身免疫认知简史-免疫耐受

- 免疫耐受：机体对抗原刺激的特异性无反应状态
- 天然耐受和获得性耐受
- 免疫系统在胚胎发育期接触抗原，成熟后不应答，机体对胚胎期接触过的自身抗原所呈现的天然耐受称为自身耐受自身免疫：指机体因丧失自身耐受性而导致机体对自身抗原的免疫反应
- 胚胎时期或新生儿，引入外源抗原，很容易诱导个体发生对该抗原的耐受



自身免疫认知简史-现代免疫

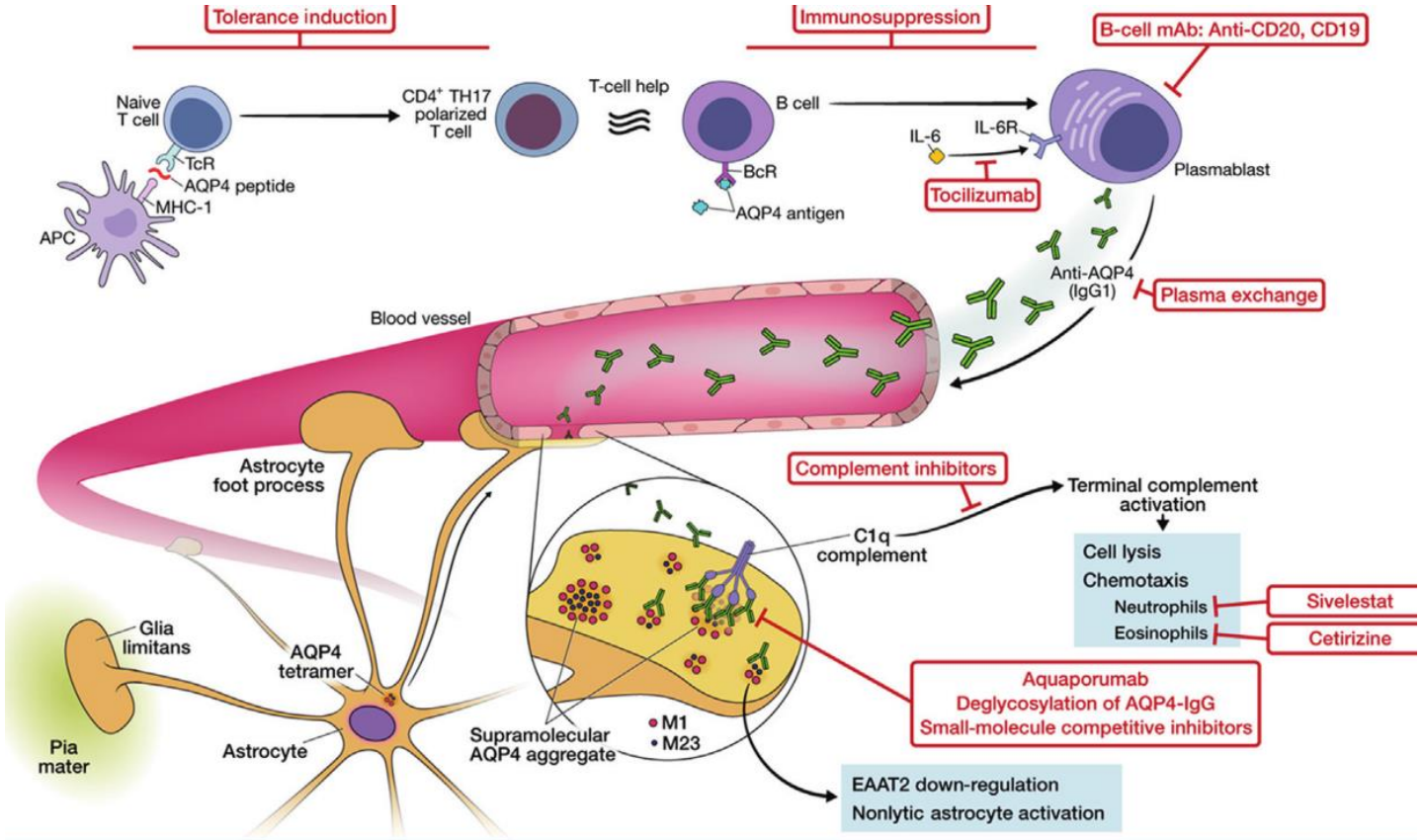
- 1964年，第一届国际自身免疫会议召开，研究领域进入了一个全新的时代。
- 疾病的发病机制上，科学界不仅阐明了免疫系统如何防止自身免疫发生的主要原理：在**中枢免疫系统**和外周免疫系统里建立多种免疫耐受机制，而且对由自身抗体和自身反应性T细胞介导的疾病原理有了更多的理解

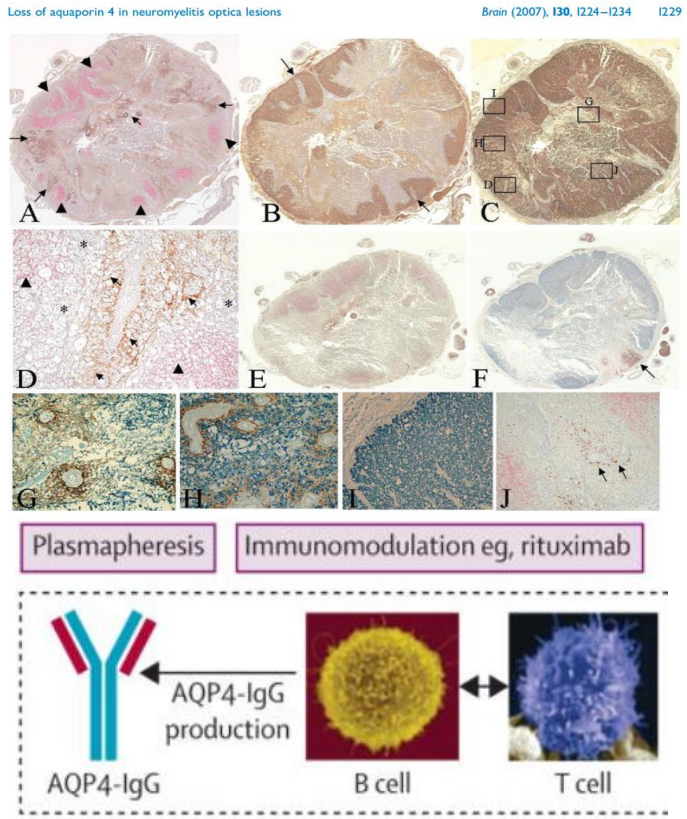
自身免疫认知简史-中国篇

- 《神经简史：中国神经免疫学的过去、现在和将来》-许贤豪
- 《我国神经免疫发展概要》- 胡学强
- 中国神经免疫学和神经病学杂志

https://zsmb.cbpt.cnki.net/WKD3/WebPublication/wkTextContent.aspx?contentID=71d4ccba-0d08-43cd-8765-94a748730f0e&mid=zsmb
https://mp.weixin.qq.com/s/SRDpS580m3wspJmtfMbItQ

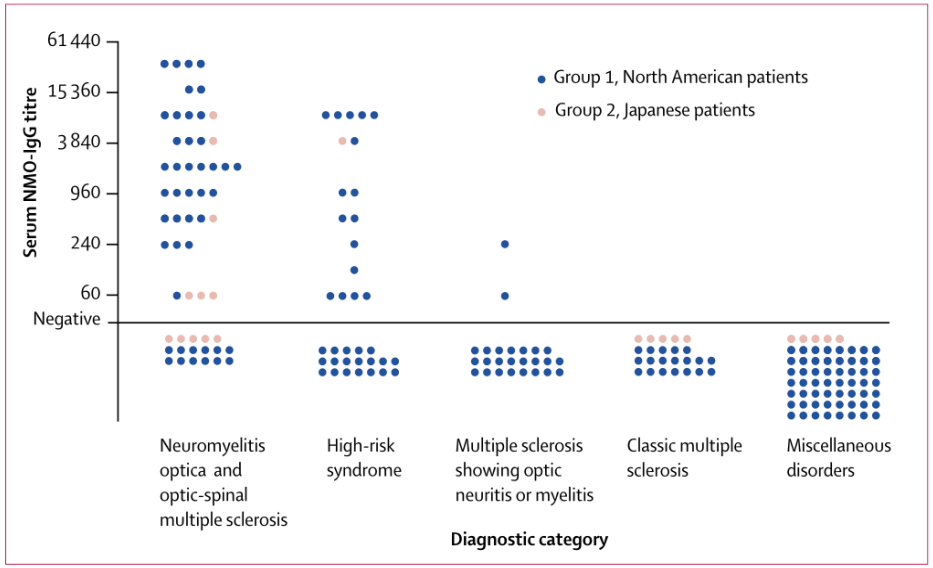
自身免疫疾病-神经免疫

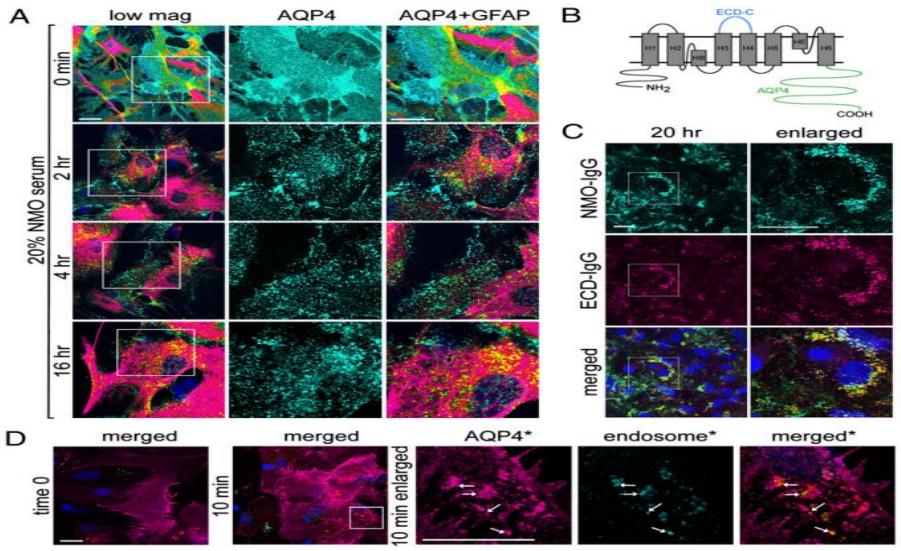




- 神经免疫疾病是累及神经系统的自身免疫疾病
- 自身免疫反应的靶点是神经系统的自身抗原
- 组织损害和功能障碍由相应自身抗体或特异性自身反应性T细胞介导

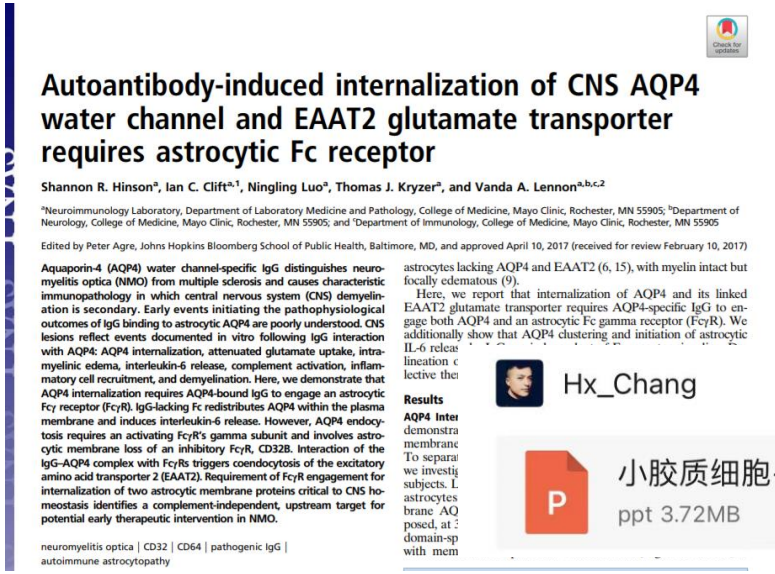
神经免疫研究鉴赏-NMO为例





- 既往研究，NMO存在一种能与32kda蛋白结合的自身抗体
- 视神经型MS不同于MS的一些免疫表现，治疗反应等临床线索
- 2004年发现NMO-Ig Lancet 既往研究+样本 +平台
- NMO-IgG binding to aquaporin-4 in astrocytes 2012 PNAS
- 免疫淘洗 AQPAb 单独激活损伤星胶 2017 PNAS

神经免疫研究鉴赏-NMO为例



Autoantibody-induced internalization of CNS AQP4 water channel and EAAT2 glutamate transporter requires astrocytic Fc receptor

Shannon R. Hinson[a], Ian C. Clift[a,1], Ningling Luo[a], Thomas J. Kryzer[a], and Vanda A. Lennon[a,b,c,2]

[a]Neuroimmunology Laboratory, Department of Laboratory Medicine and Pathology, College of Medicine, Mayo Clinic, Rochester, MN 55905; [b]Department of Neurology, College of Medicine, Mayo Clinic, Rochester, MN 55905; and [c]Department of Immunology, College of Medicine, Mayo Clinic, Rochester, MN 55905

Edited by Peter Agre, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, and approved April 10, 2017 (received for review February 10, 2017)

Aquaporin-4 (AQP4) water channel-specific IgG distinguishes neuromyelitis optica (NMO) from multiple sclerosis and causes characteristic immunopathology in which central nervous system (CNS) demyelination is secondary. Early events initiating the pathophysiological outcomes of IgG binding to astrocytic AQP4 are poorly understood. CNS lesions reflect events documented in vitro following IgG interaction with AQP4: AQP4 internalization, attenuated glutamate uptake, intramyelinic edema, interleukin-6 release, complement activation, inflammatory cell recruitment, and demyelination. Here, we demonstrate that AQP4 internalization requires AQP4-bound IgG to engage an astrocytic Fcγ receptor (FcγR). IgG-lacking Fc redistributes AQP4 within the plasma membrane and induces interleukin-6 release. However, AQP4 endocytosis requires an activating FcγR's gamma subunit and involves astrocytic membrane loss of an inhibitory FcγR, CD32B. Interaction of the IgG–AQP4 complex with FcγRs triggers coendocytosis of the excitatory amino acid transporter 2 (EAAT2). Requirement of FcγR engagement for internalization of two astrocytic membrane proteins critical to CNS homeostasis identifies a complement-independent, upstream target for potential early therapeutic intervention in NMO.

neuromyelitis optica | CD32 | CD64 | pathogenic IgG | autoimmune astrocytopathy

astrocytes lacking AQP4 and EAAT2 (6, 15), with myelin intact but focally edematous (9).

Here, we report that internalization of AQP4 and its linked EAAT2 glutamate transporter requires AQP4-specific IgG to engage both AQP4 and an astrocytic Fc gamma receptor (FcγR). We additionally show that AQP4 clustering and initiation of astrocytic IL-6 releas… lineation … lective the…

Results

AQP4 Inter… demonstra… membrane… To separa… we investig… subjects. I… astrocytes… brane AQ… posed, at … domain-sp… with mem…

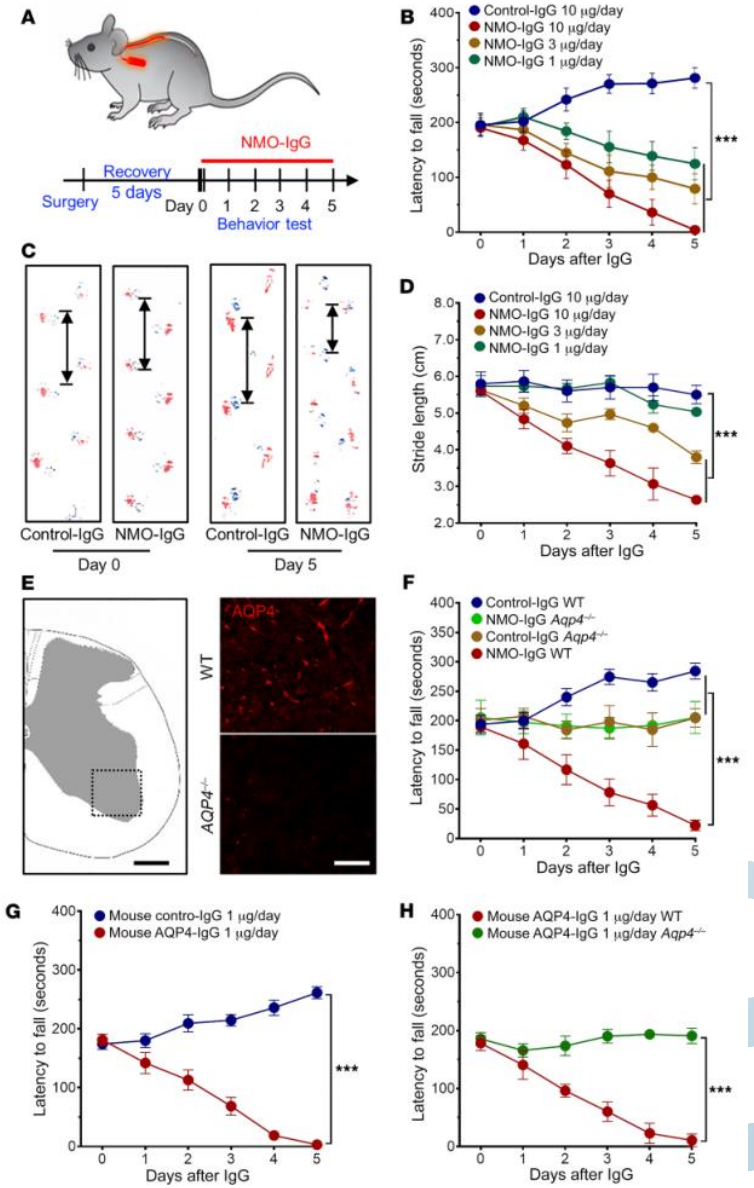
The Journal of Clinical Investigation RESEARCH ARTICLE

Astrocyte-microglia interaction drives evolving neuromyelitis optica lesion

Tingjun Chen,[1] Vanda A. Lennon,[1,2,3] Yong U. Liu,[1] Dale B. Bosco,[1] Yujiao Li,[1] Min-Hee Yi,[1] Jia Zhu,[1] Shihui Wei,[4] and Long-Jun Wu[1,2,5]

[1]Department of Neurology, [2]Department of Immunology, and [3]Department of Laboratory Medicine/Pathology, Mayo Clinic, Rochester, Minnesota, USA. [4]Department of Ophthalmology, Chinese PLA General Hospital, Beijing, China. [5]Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA.

Neuromyelitis optica (NMO) is a severe inflammatory autoimmune CNS disorder triggered by binding of an IgG autoantibody to the aquaporin 4 (AQP4) water channel on astrocytes. Activation of cytolytic complement has been implicated as the … secondarily involves myelin. We investigated early precytolytic events in the … by continuously infusing IgG (NMO patient serum–derived or AQP4-specific … complement, into the spinal subarachnoid space. Motor impairment and sublytic … IgG dose dependent, AQP4 dependent, and, unexpectedly, microglia dependent. … cing physical interaction between microglia and astrocytes that required signaling … eir upregulated complement C3 protein. Astrocytes remained viable but lost AQP4. … en astrocytes and microglia involving early-activated CNS-intrinsic complement … ignaling appears to be a critical driver of the precytolytic phase in the evolving NMO … Our results indicate that microglia merit consideration as a potential target for



- 免疫淘洗 AQPAb 单独激活损伤星胶 2017 PNAS
- Nature 2017 年度十大文章 反应性星胶依赖小胶激活
- 2018.10 小胶质细胞肯定参与NMO疾病进程 IF≈5
- 2020.08 NMO抗体损伤 IgG剂量依赖 **出人意料的小胶质依赖性**
- 结果可预期 对NMO发病机制没有什么推动 **缺乏美感**

Chen T, et al. Astrocyte-microglia interaction drives evolving neuromyelitis optica lesion. J Clin Invest 130, 4025-4038 (2020)

自身免疫研究鉴赏评级

- 简单的临床表型 入门级 中文/ IF 1~2 D
- 稍有意义的临床表型 入门级 IF 3~4.5 C
- 抗体/T细胞损伤靶器官 IF 4.6~14 B -A
- T 细胞 B细胞 IL-6 IF 10+ B+-A+
- T 细胞 B细胞 S
- 自身免疫病引入 普适性生命过程规律 SS

- CD8+ T BBB
- AQP4 B细胞检查点
- Naïve B 早熟 易被刺激反应
- Long-lived B& 浆细胞

自身免疫研究鉴赏评级-S

中华人民共和国科学技术部
Ministry of Science and Technology of the People's Republic of China

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科学家发现线粒体天冬氨酸调节肿瘤坏死因子的生物合成和自身免疫组织炎症的机制

日期： 2021年12月06日 15:48 来源：科技部生物中心 【字号：大 中 小】

错误的免疫反应会引起类风湿性关节炎等自身免疫组织炎症，肿瘤坏死因子（TNF）的过量产生是致病的关键因素。美国梅奥诊所医学与科学学院的研究团队发现，线粒体天冬氨酸能够调节TNF的生物合成和自身免疫组织炎症。该研究结果于近日发表在《Nature Immunology》上，题为：Mitochondrial aspartate regulates TNF biogenesis and autoimmune tissue inflammation。

研究人员发现，在类风湿性关节炎患者的T细胞中线粒体天冬氨酸的合成不足。线粒体天冬氨酸的缺乏破坏了烟酰胺腺嘌呤二核苷酸（NAD）的再生，引起内质网膜扩张，促进共翻译易位并增强跨膜TNF的生物合成。T细胞富含内质网，主要合成类风湿性关节炎关节中的TNF。若将完整的线粒体转录到相关T细胞，或者补充外源性天冬氨酸，都能够抑制线粒体驱动的内质网膜扩张，从而阻断TNF的合成释放以及类风湿性组织炎症的发生。

总之，该研究揭示了线粒体天冬氨酸合成的缺陷是自身免疫性T细胞异常的重要原因，线粒体和天冬氨酸的补充能够调节肿瘤坏死因子的生物合成和自身免疫组织炎症。

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-021-01065-2

Check for updates

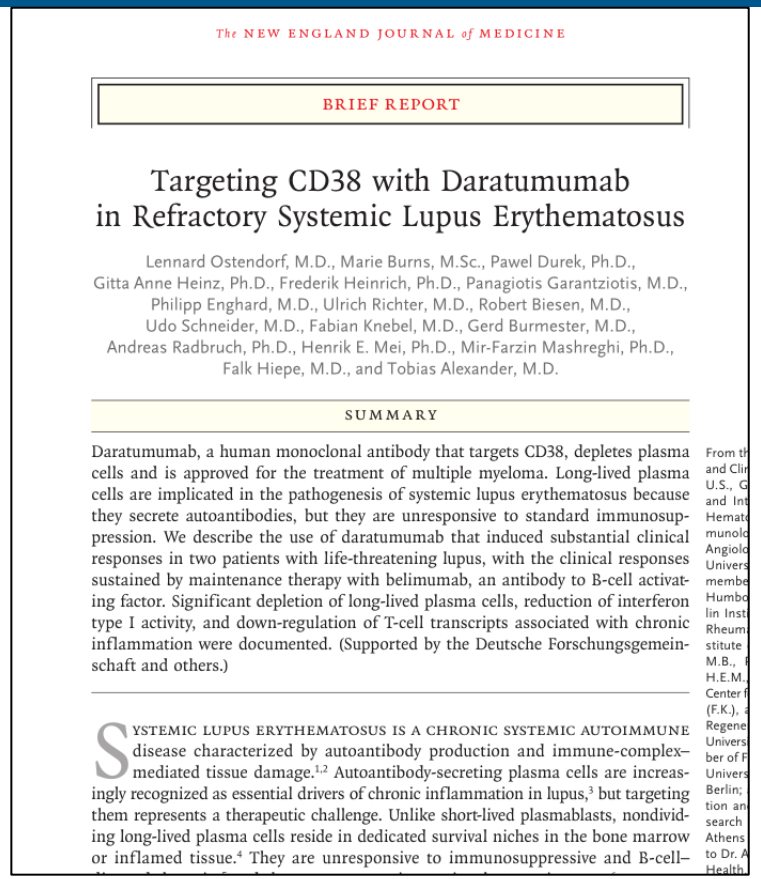
Mitochondrial aspartate regulates TNF biogenesis and autoimmune tissue inflammation

Bowen Wu[1], Tuantuan V. Zhao[1], Ke Jin[1], Zhaolan Hu[1], Matthew P. Abdel[2], Ken J. Warrington[1], Jörg J. Goronzy[1,3] and Cornelia M. Weyand[1,3]✉

Misdirected immunity gives rise to the autoimmune tissue inflammation of rheumatoid arthritis, in which excess production of the cytokine tumor necrosis factor (TNF) is a central pathogenic event. Mechanisms underlying the breakdown of self-tolerance are unclear, but T cells in the arthritic joint have a distinctive metabolic signature of ATP^{lo} acetyl-CoA^{hi} proinflammatory effector cells. Here we show that a deficiency in the production of mitochondrial aspartate is an important abnormality in these autoimmune T cells. Shortage of mitochondrial aspartate disrupted the regeneration of the metabolic cofactor nicotinamide adenine dinucleotide, causing ADP deribosylation of the endoplasmic reticulum (ER) sensor GRP78/BiP. As a result, ribosome-rich ER membranes expanded, promoting co-translational translocation and enhanced biogenesis of transmembrane TNF. ER^{rich} T cells were the predominant TNF producers in the arthritic joint. Transfer of intact mitochondria into T cells, as well as supplementation of exogenous aspartate, rescued the mitochondria-instructed expansion of ER membranes and suppressed TNF release and rheumatoid tissue inflammation.

- **类风湿关节炎**
- **T细胞内线粒体功能衰竭导致组织炎症和自身耐受崩溃**

自身免疫研究鉴赏评级-S



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Targeting CD38 with Daratumumab in Refractory Systemic Lupus Erythematosus

Lennard Ostendorf, M.D., Marie Burns, M.Sc., Pawel Durek, Ph.D., Gitta Anne Heinz, Ph.D., Frederik Heinrich, Ph.D., Panagiotis Garantziotis, M.D., Philipp Enghard, M.D., Ulrich Richter, M.D., Robert Biesen, M.D., Udo Schneider, M.D., Fabian Knebel, M.D., Gerd Burmester, M.D., Andreas Radbruch, Ph.D., Henrik E. Mei, Ph.D., Mir-Farzin Mashreghi, Ph.D., Falk Hiepe, M.D., and Tobias Alexander, M.D.

SUMMARY

Daratumumab, a human monoclonal antibody that targets CD38, depletes plasma cells and is approved for the treatment of multiple myeloma. Long-lived plasma cells are implicated in the pathogenesis of systemic lupus erythematosus because they secrete autoantibodies, but they are unresponsive to standard immunosuppression. We describe the use of daratumumab that induced substantial clinical responses in two patients with life-threatening lupus, with the clinical responses sustained by maintenance therapy with belimumab, an antibody to B-cell activating factor. Significant depletion of long-lived plasma cells, reduction of interferon type I activity, and down-regulation of T-cell transcripts associated with chronic inflammation were documented. (Supported by the Deutsche Forschungsgemeinschaft and others.)

SYSTEMIC LUPUS ERYTHEMATOSUS IS A CHRONIC SYSTEMIC AUTOIMMUNE disease characterized by autoantibody production and immune-complex–mediated tissue damage.[1,2] Autoantibody-secreting plasma cells are increasingly recognized as essential drivers of chronic inflammation in lupus,[3] but targeting them represents a therapeutic challenge. Unlike short-lived plasmablasts, nondividing long-lived plasma cells reside in dedicated survival niches in the bone marrow or inflamed tissue.[4] They are unresponsive to immunosuppressive and B-cell–

THE LANCET Neurology

COMMENT | VOLUME 21, ISSUE 4, P300-301, APRIL 01, 2022

Epstein-Barr virus and multiple sclerosis: supporting causality

Francesca Aloisi · Marco Salvetti

Published: April, 2022 · DOI: https://doi.org/10.1016/S1474-4422(22)00086-2

References

Article Info

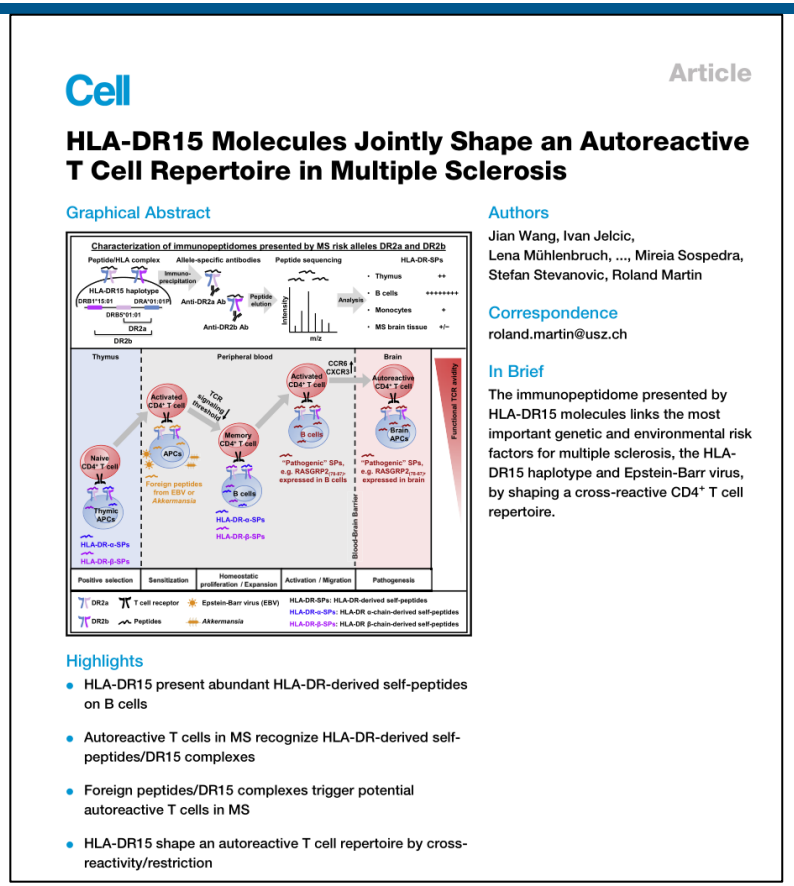
Epstein-Barr virus (EBV) is a γ-herpes virus that infects around 95% of individuals worldwide. Although the infection is generally asymptomatic when acquired in childhood, EBV can cause infectious mononucleosis in adolescents and several tumours, like lymphomas and nasopharyngeal carcinoma, in adults. EBV has also been associated with multiple sclerosis, the most common chronic inflammatory disease of the CNS. Robust evidence indicates that the risk of multiple sclerosis is nearly absent in EBV-seronegative individuals, increases considerably after EBV infection, and increases even more after infectious mononucleosis.[1] Furthermore, people with multiple sclerosis have an increased antibody response to EBV that becomes detectable years before disease onset.[2,3] These findings suggest that multiple sclerosis might develop in susceptible individuals due to an alteration of the EBV-host homoeostasis that ordinarily ensures a life-long, pacific coexistence under continuous immune surveillance in healthy EBV carriers.[4] To date, however, most of the available evidence has been correlative in nature and it has been difficult to prove that EBV causes multiple sclerosis.[5]

Science

BACK TO FIRST RELEASE

REPORT

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis



Cell

Article

HLA-DR15 Molecules Jointly Shape an Autoreactive T Cell Repertoire in Multiple Sclerosis

Graphical Abstract

Authors

Jian Wang, Ivan Jelcic, Lena Mühlenbruch, ..., Mireia Sospedra, Stefan Stevanovic, Roland Martin

Correspondence

roland.martin@usz.ch

In Brief

The immunopeptidome presented by HLA-DR15 molecules links the most important genetic and environmental risk factors for multiple sclerosis, the HLA-DR15 haplotype and Epstein-Barr virus, by shaping a cross-reactive CD4+ T cell repertoire.

Highlights

- HLA-DR15 present abundant HLA-DR-derived self-peptides on B cells
- Autoreactive T cells in MS recognize HLA-DR-derived self-peptides/DR15 complexes
- Foreign peptides/DR15 complexes trigger potential autoreactive T cells in MS
- HLA-DR15 shape an autoreactive T cell repertoire by cross-reactivity/restriction

- 靶向作用浆细胞的单克隆抗体—达雷木单抗
- 成熟的记忆浆细胞 骨髓 长时间产生大量抗体
- 狼疮 长寿命浆细胞 单抗应用多发骨髓瘤 骨髓中恶性浆细胞
- 对于抗体介导的自身免疫病也许都有很好效果？ 长效？

- EB与MS发病，因果支持

- 50%MS携带HLA-DR15基因突变 VS HC 20%
- 携带HLA-DR15基因突变且感染EB MS患病风险增加15倍
- 其他自身免疫病的携带率
- 对于EB病毒诱发参与的其他自身免疫疾病同样易感？

自身免疫研究鉴赏评级-SS

招募|视神经脊髓炎谱系疾病临床研究招募

首都医科大学宣武医院神经内科 2022-04-26 13:23

招募

尊敬的视神经脊髓炎谱系疾病患者：

首都医科大学宣武医院神经内科正在开展一项临床研究，评价一种布鲁顿
氨酸激酶（BTK）抑制剂用于视神经脊髓炎谱系疾病（NMOSD）患者的有效
和安全性。本研究已获得医院伦理委员会批准，批件号为：临研审[2021]18
号。

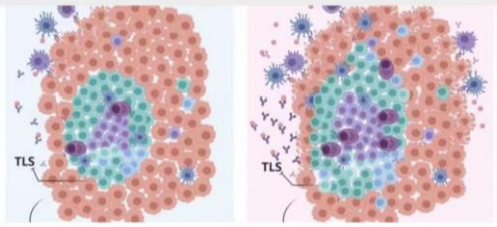
BTK信号通路异常激活可能参与了NMOSD的发生。在国外的临床研究中，
BTK抑制剂可有效降低中枢神经系统炎性脱髓鞘疾病患者的疾病活动且安全

泽布替尼这类的BTK 抑制剂可能是有希望接棒的。 不知道会是谁来做了。

New therapies for neuromyelitis optica spectrum disorder

2020年11月18日 13:17 删除

3月16日 08:56



清华大学刘万里/北京大学申占龙合作发现IgG1记忆性B细胞抗原受体变异...

清华大学刘万里/北京大学申占龙合作发现IgG1记忆性B细胞抗原受体变异体对肿瘤的抵御作用

- 研究兴趣、领域：

应用高速高分辨率的活细胞单分子荧光成像技术，并结合传统的免疫学、分子细胞、生物化学和生物物理研究手段，致力于B淋巴细胞机制和功能研究：（1）B淋巴细胞免疫识别和免疫活化的分子机制及调控机制的研究；（2）B淋巴细胞异常活化导致的自身免疫疾病及淋巴癌和白血病的研究；（3）B淋巴细胞生成-储存-读取长效型抗体记忆的研究；（4）B淋巴细胞依赖机械力感知调控免疫活化和功能的研究；（5）病原微生物作用于B淋巴细胞早期活化途径的免疫逃逸的研究；（6）整合攻关基于上述研究结果的新型疫苗和新型药物。

Science

An autoimmune disease variant of activation and differentiation

Xiangjun Chen[1], Sun Xiao-Lin[2]*, Wei Yang[3]*, Bing Yang[1]*, Xiaozhen Zhao[2], Shutin
Zai Chang[3], Jianping Guo[2], Jing He[2], Fuping Zhang[2], Fang Zheng[4], Zhibin Hu[7], Zhi
Chenqi Xu[11], Hong Zhang[12], Hongying Shan[13], Xujie Zhou[12], Qingwen Wang[15], Yi Sh
[1]Ministry of Education Key Laboratory of Protein Sciences, Center for Life Sciences, Collaborative Inno
Institute for Immunology, School of Life Sciences, Tsinghua University, Beijing 100084, China. [2]Depar
Center, Peking University People's Hospital, Beijing Key Laboratory for Rheumatism and Immune Diag
Tsinghua University, Beijing 100084, China. [4]Laboratory of RNA Biology, Institute of Biophysics, Chine
Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, B
Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, C
Medical University, Nanjing 211166, China. [8]Cardiovascular Research Institute, University of California
Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Peking Union Medica
China. [10]Tsinghua-Peking Center for Life Sciences, Laboratory of Dynamic Immunobiology, School of
Laboratory of Molecular Biology, National Center for Protein Science Shanghai, Institute of Biochemis
Chinese Academy of Sciences, Shanghai 200031, China. [12]Renal division, Peking University First Hosp
Renal Disease, Ministry of Health of China, Beijing 100034, China. [13]Department of Rheumatism and Im
China. [14]CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, C
Academy of Sciences, Beijing 100049, China. [15]Research Network of Immunity and Health (RNIH), Bei
100101, China. [16]BNLMS, State Key Laboratory for Structural Chemistry of Unstable and Stable Specie
Chemistry and Molecular Engineering, Center for Quantitative Biology, Peking University, Beijing 1008
Diseases, Beijing 100084, China.

*These authors contributed equally to this work.

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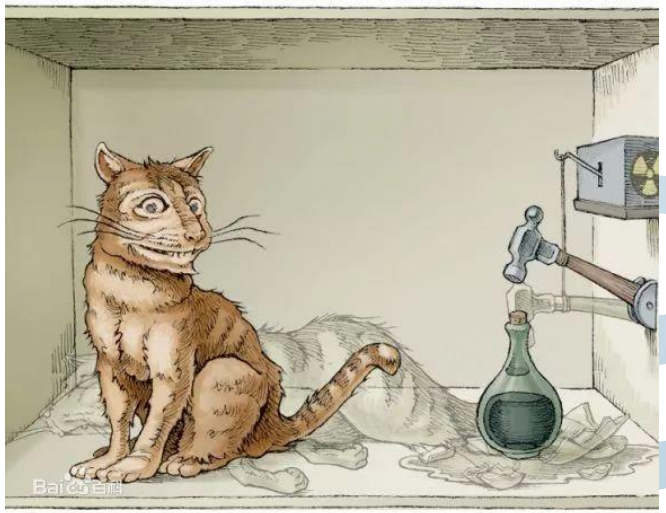
The maintenance of autoreactive B cells in a quiescent state is we identify a variant of human IgG1 (hIgG1-G396R), which posit erythematosus. In induced lupus models, murine homolog G39 numbers of plasma cells, leading to a burst of broad-spectrum of antibodies is also observed in hapten-immunized G390R mic G396R homozygous carriers. This variant potentiates the phos tyrosine (ITT) motif. This, in turn, alters the availability of phos in immunological synapses, leading to hyper-Grb2-Btk signalin



- **疾病（SLE）是切入口　展示根本/普遍的生命科学规律意义**
- **揭示了对整个人群B细胞调控的普遍规律**

自身免疫研究鉴赏评级-SS

Science

REPORTS

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An autoimmune disease variant of IgG1 modulates B cell activation and differentiation

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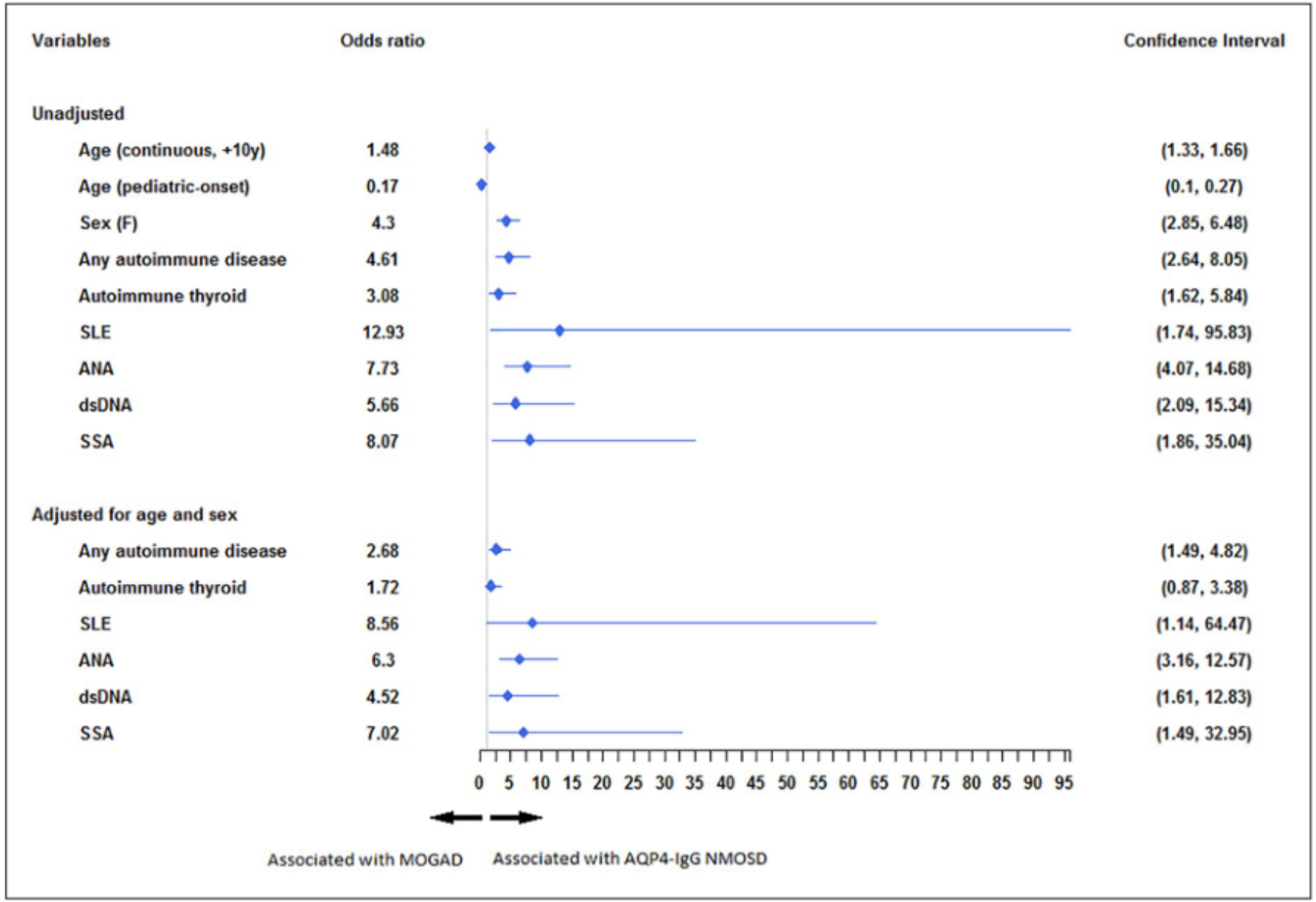
[1]Ministry of Education Key Laboratory of Protein Sciences, Center for Life Sciences, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Institute for Immunology, School of Life Sciences, Tsinghua University, Beijing 100084, China. [2]Department of Rheumatology and Immunology, Clinical Immunology

- 人类膜联免疫球蛋白IgG1重链基因IGHG1上的SNP（rs117518546）在自身免疫病（SLE）患者中显 著增加，该SNP导致人类膜联免疫球蛋白IgG1第396位甘氨酸突变为精氨酸（IgG1-G396R）。进一步的临床指标相关性分析表明，携带该SNP的患者产生更多更广泛的IgG1型的自身抗体，发生炎症反应的风险增加，疾病活动指数也更高，揭示该SNP为新的SLE易感基因位点。
- 流感疫苗免疫　携带SNP健康人　抗体滴度更高　维持更久　新冠?
- hIgG1-G396R（SNP）→IgG1 *p* ITT↑→ Grb2↑→ hyper-Grb2-Btk

自身免疫的一些普遍规律



主要内容

① 自身免疫简史


Credit: Pathology Department, Johns Hopkins University

- 诺埃尔•罗斯（Noel Rose）
- 自身免疫之父

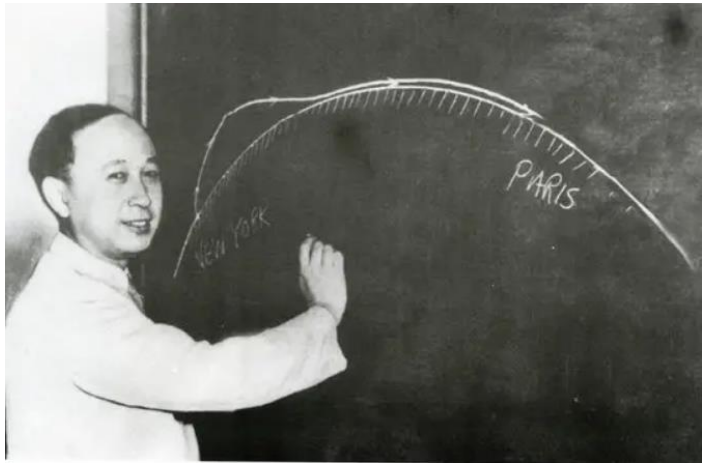
- Vanda A Lennon
- 发现NMO-IgG

② 代表性研究鉴赏

- IgG1-G396R
- rs117518546

- 知识分子专栏作家
- 免疫学通识科普

自身免疫研究的愿景



让我们消灭自身免疫认知的困苦与贫乏
为他们(病患/研究人员)带去愉悦和美丽

- 神经免疫没有边界
- 自身免疫没有边界
- 研究人员有感兴趣的方向
- 以及认可和推崇的理论

首都医科大学附属北京天坛医院

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