Collagen Antibody Induced Arthritis (CAIA) in Mice

胶原抗体诱导小鼠关节炎模型

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COLLAGEN ANTIBODY INDUCED ARTHRITIS (CAIA) MODEL

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Collagen-induced arthritis (CIA) has been extensively used as a mouse model for rheumatoid arthritis (RA). However, the CIA model requires at least 6-8 weeks to complete a typical study (1-12). To reduce this timeline, Chondrex, Inc. has developed a rapid arthritis model using monoclonal antibodies (mAbs) against type II collagen. By injecting the mAbs into mice, arthritis can be induced within a few days. Additional advantages of this CAIA model include: 1) inducing arthritis in various mouse strains, not just CIA susceptible mice, 2) quick screening and evaluation of anti-inflammatory compounds, 3) studying the roles of individual genes and their products in arthritis development using gene knockout and transgenic mice, and 4) studying various relevant inflammatory mediators and factors such as bacterial and viral toxins which may be involved in human RA as described (13-17).

胶原诱导性关节炎小鼠(CIA)作为人类类风湿关节炎模型应用广泛,但CIA引起的关节炎起病比较缓慢，造模周期较长，一般为6-8周(1-12)。Chondrex公司已开发出单一种单克隆抗体合剂诱导的小鼠关节炎模型（CAIA），明显缩短了造模周期。 与CIA 相比，CAIA模型具有以下优点: (1)可在大多数小鼠上诱发关节炎，包括CIA不敏感的小鼠；(2)CAIA造模周期短，加速筛选和评估类风湿性关节炎治疗药物；（3）应用于转基因小鼠来研究基因对关节炎发病的影响；（4）用于研究与人类类风湿性关节炎相关的各种炎症介质和因素在疾病中的作用，例如细菌和病毒毒素（13-17）。

CIA is mediated by autoantibodies to type II collagen and complement, thus arthritis can be induced by administering polyclonal antibodies (18-19) or a specific combination of monoclonal antibodies to type II collagen (mAb cocktail) (20-21). These autoreactive antibodies recognize specific antigenic determinants (arthritogenic epitopes) located in the cyanogen bromide-cleaved fragment 11 (CB11) or CB8 fragment of mouse type II collagen, depending on the MHC type (22-23).

CIA是由于自身抗体形成的免疫复合物通过激活补体而诱发关节炎症，因此研究表明多克隆胶原蛋白抗体(8-19) 或单克隆胶原蛋白抗体合剂能诱发关节炎(20-21)。根据MHC类型，这些自身反应性抗体可以识别位于小鼠II型胶原蛋白的CB11或者CB8片段中的特定抗原定簇（关节炎抗原表位）（22-23）。

Chondrex, Inc.'s mAb cocktail to induce mouse arthritis is a mixture of five unique mAbs: A2-10 (IgG2a), F10-21 (IgG2a), D8-6 (IgG2a), D1-2G (IgG2b), and D2-112 (IgG2b). Two mAbs (F10-21 and D8-6) recognize individual epitopes clustered within the 83 amino acid peptide fragment of LysC-2 (291-374) which is prepared by Endoproteinase LysC digestion, and three mAbs (A2-10, D1-2G, and D2-112) recognize the 167 amino acid peptide fragment of LysC-1 (124-290) of the CB11 fragment (124-402) of mouse type II collagen (13). These epitopes are highly conserved amino acid sequences in many different species including chicken, mouse, rat, bovine, porcine, monkey, and human (20-21).

Chondrex公司生产的能诱发小鼠关节炎的抗体合剂含有： A2-10 (IgG2a), F10-21 (IgG2a), D8-6 (IgG2a), D1-2G (IgG2b), and D2-112 (IgG2b). 其中两个单克隆抗体（F10-21和D8-6）识别在LysC-2(291-374)的83个氨基酸肽段，该肽段有LysC内切酶作用产生。 另外三个单克隆抗体（A2-10,D1-2G和D2-112） 能够识别二型胶原蛋白CB11片段（124-402）中LysC-1(124-290)的167各氨基酸肽段（13）。这些抗原表位氨基酸序列在各种物种中具有高度保守性，包括鸡，小鼠，大鼠，牛，猪，猴子和人（20-21）。

Severe and consistent arthritis can be induced in mice by combining a sub-arthritogenic dose of the mAb cocktail and Lipopolysaccharide (LPS) from *Escherichia coli (E. coli)*: O111:B4 (13). This model was developed based on the hypothesis that bacterial toxin(s), such as LPS, absorbed through the gastrointestinal tract play a synergistic and pathological role with sub-arthritogenic levels of autoantibodies to type II collagen, triggering arthritis (24). The advantages of this model over the classical CIA model are multifold. First, synchronized arthritis is induced within a few days with nearly 100% incidence. Second, a variety of mouse strains such as CIA-resistant, T-cell deficient, knockout, and transgenic mice can be used (see Table 1).

研究表明，联合注射低于致炎剂量的单克隆抗体合剂和大肠杆菌多脂（LPS）可诱发严重的小鼠关节炎（13）。通过胃肠道吸收的细菌毒素（如LPS）与低

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致炎水平的二型胶原自身抗体对引发关节炎有发协同作用（24）。这种模型相比于传统CIA 模型有多重优势。第一，起病时间短，发病率高达100%。第二，可在大多数小鼠上诱导关节炎，包括CIA不敏感的小鼠，T细胞缺陷的小鼠，特定基因敲除变异的小鼠，详情请见表二.

A typical time course study of the CIA and CAIA models are shown in Figure 1. The CAIA model can reduce the timeline of experiments down to a tenth of that of the CIA model.

图一显示CIA模型和CAIA模型特点的比较。CAIA造模周期是CIA建模周期的十分之一。

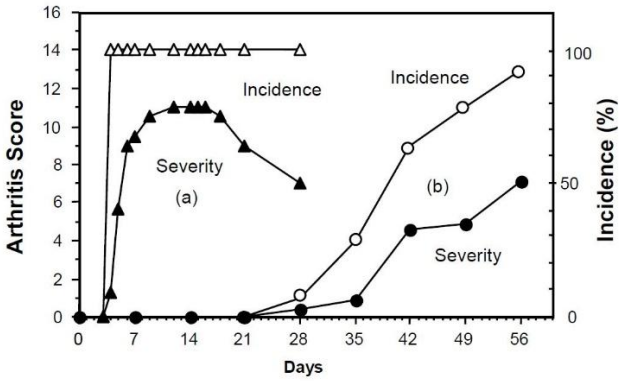

Figure 1 - CAIA vs. CIA: (a) Triangles: Arthritis developed in 100% of mice within 24-48 hours after LPS injection and reached a maximum score within 5-7 days in the CAIA model. (b) Circles: in the CIA model, it took 4 weeks for the onset of arthritis even in CIA highly susceptible strains such as DBA/1J and B10.RIII mice.

Solid markers = arthritis score (severity of arthritis)

Blank markers = incidence of arthritis (%).

图一 CAIA vs. CIA: (a)三角形：100%的小鼠在LPS注射后24-48小时即可见关节炎发作，在第5-7天病情达到高峰。（b）圆形：CIA诱发小鼠关节炎模型一般需要4周起病，即使使用CIA易感品系，如DBA/1J和B10.RIII小鼠。

实心点：病情评价打分

空心点：发病率（%）

Animal Care and Diet

动物饲养条件和饮食

It is imperative to use 7-8-week-old mice for the CAIA model. Older mice may demonstrate lower incidence and disease severity. Specific pathogen free (SPF) housing conditions are recommended over conventional housing conditions, as bacterial contamination may reduce the immune response, resulting in attenuated arthritis. Intestinal bacteria flora varies depending on animal vendors and can affect the host immune system's susceptibility to antigens such as LPS. Some mice are highly susceptible to LPS and killed by LPS injections. Chondrex, Inc. recommends testing mice for LPS susceptibility prior to running large studies. Diet considerations for mice are not necessary, however, Chondrex, Inc. recommends a high fat diet (Purina Mouse Chow 5015) for mouse inflammation studies (4). Please contact customer support at support@chondrex.com for guidance regarding animals and housing conditions.

建立CAIA模型需要选择7-8周龄小鼠。老龄鼠的发病率和病情严重程度较低。建议在无特定病原体（SPF级别）条件下饲养动物，因为细菌感染会降低宿主的免疫应答，从而减轻关节炎症。肠道菌群会影响宿主免疫系统对LPS 的易感性。LPS甚至会引起某些对LPS超级易感品系的小鼠致死。Chondrex公司建议在开展实验前先测试实验用小鼠对LPS的易感性。尽管饮食影响可以不用考虑，但是Chondrex公司建议饲喂高脂肪食物，研究表明高脂肪食物更容易引发炎症 （4）。

Mouse Strains

小鼠品系

Administering the anti-type II collagen mAb cocktail bypasses the host's need to generate autoantibodies to type II collagen. Thus, arthritis can be induced in mouse strains which lack CIA-susceptible MHC haplotypes (i.e. H-2q and H-2r). All mouse strains with normal inflammatory responses including complement activation should be susceptible to CAIA. Table 1 lists the mouse strains that have been tested to date.

注射抗二型胶原单克隆抗体合剂可以绕过宿主生成抗二型胶原自身抗体的需求，所以可以诱发MHC （例如H-2q和H-2r）缺陷的小鼠产生关节炎.所有能产生正常炎症反应和补体激活的小鼠品系都应该对CAIA敏感。表一为目前为止测试过的小鼠品系。

DBA/1 (H-2q) and B10.RIII (H-2r) mice are susceptible to both CIA and CAIA (13).

DBA/1 (H-2q) and B10.RIII (H-2r) 小鼠对CIA和CAIA均有较高的敏感性（13）。

BALB/c (H-2d) mice, which are resistant to CIA, are highly susceptible to CAIA and are the most commonly used strain (13, 25-27), being readily available.

BALB/c (H-2d) 小鼠对CIA具有抗性，但对CAIA有较高敏感性，是目前最常用的品系（25-27）。

C.B-17 scid/scid mice are T-cell deficient mice which can be used for CAIA as T-cells are not required for antigen recognition for antibody production in arthritis development (17). These mice may even develop more severe arthritis than T-cell normal strains (unpublished data), as T-cells may play roles in down-regulating

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inflammation during healing as well as in up-regulating inflammatory reactions.

T细胞缺陷的C.B-17 scid/scid 小鼠可用于CAIA，因为在炎症发生的过程中，不需要T细胞识别抗原来产生抗体（17）。这中品系小鼠相比正常T细胞的小鼠，会产生更严重的关节炎症， T细胞在愈合过程中有调节炎症的作用。

SWR (H-2q) mice have a CIA-susceptible haplotype but are resistant to CIA and CAIA due to a C5 deficiency. Other C5 deficient mouse strains, B10.D2/oSn and NOD/LtSz scid/scid, are also apparently resistant to CAIA (12,19, 27).

SWR（H-2q）小鼠具有CIA易感基因型，但由于C5缺陷，对CIA 和CAIA具有抗性。其他C5缺陷小鼠，例如B10.D2/oSn 和 NOD/LtSz scid/scid 对 CAIA 具有抗性（12,19,27）。

Nude mice are resistant to CAIA (28) for unknown reasons despite nude rats being highly susceptible to antibody-induced arthritis (29). Nude mice may lack select pro-inflammatory cytokine expression.

尽管裸大鼠对CAIA具有高易感性， 裸小鼠对CAIA具有抗性（29）。裸小鼠可能缺乏特定的促炎细胞因子的表达。

C57BL/6 mice are most commonly used as parent mice for gene knockout and transgenic mice. Although wild type C57BL/6 mice are apparently low responders to LPS, these mice also develop severe arthritis in CAIA with LPS. However, a higher dose of the mAb cocktail is required such as 5 mg/mouse instead of 1.5 mg/mouse (21, 30). C57BL/6-backcrossed to 129/Sv mice are commonly used for creating gene knockout mice. Some of these backcrossed mice respond to LPS, thus severe arthritis can be induced with an ordinary 1.5 mg/mouse dose (30-31).

C57BL/6小鼠是转基因小鼠模型中最常用的品系。尽管C57BL/6小鼠对LPS不敏感，但CAIA联合LPS 会使这些小鼠产生严重的关节炎症。在这种品系的小鼠中建模需要使用高剂量单克隆抗体合剂，每只小鼠需要5mg (21,30).C57BL/6 与129/Sy小鼠杂交用于建立基因敲除小鼠。一些杂交小鼠会对LPS有应答，所以1.5mg每只小鼠的剂量一会产生严重的关节炎症（30-31） 。

The following gene knockout mice have been used to study the role of genes in the CAIA model (29-39).

以下基因敲除小鼠用于基因对CAIA模的影响 (29-39).

1) NOS2 knockout mice (30)
2) Osteopontin knockout mice (31)
3) COX-1 and COX-2 knockout mice (32)
4) MMP-2 (gelatinase A) and MMP-3 (gelatinase B) knockout mice (33)
5) $P2X_7$ receptor knockout mice (34)
6) c-Jun N-Terminal Kinase knockout mice (35)
7) Prostaglandin E2 receptor knockout mice (36)
8) CD69 null mice (37)

Table 1 - Mouse Strains Commonly Used for CIA and CAIA

表一-用于胶原 CIA 及 胶原蛋白抗体诱导（CAIA ）的关节炎动物模型研究的常用小鼠品系

Mouse Strain	H-2 Type	CIA Susceptibility	Reference	CAIA Susceptibility	Ref	Note
DBA/1	q	High	2, 4, 5	High	13, 20	INFγ high
B10.Q	q	High	5	(High)		
B10.G	q	High	5	(High)		
NFR/N	q	High	37	(High)		
SWR	q	Resistant	12	Resistant		C5 deficient
B10.RIII	r	High	5	High	13	Low response: chick and human type II
B10	b	Low	9	(High)		* Need alternative immunization
C57BL/6	b	Low	9	Moderate - High	8, 17, 29	LPS low responder – * Need alternative immunization
C57BL/6 beige	b	Resistant	19	Resistant		PMN mutation
C57BL/6 x 129/Sv	b	Low	9	Moderate - High	29, 30	* Need alternative immunization
129/Sv	b	Resistant	9	High	26	
B10.D2/nSn	d	Resistant	19	High	19	
B10.D2/oSn	d	Resistant	19	Resistant	19	C5 deficient
Balb/c	d	Resistant		High	13	
Balb/c nu/nu	d	Resistant		Resistant	27	B & T cell deficient
C3H/He	k	Low	38	(Low)		
B10.S	s	Resistant	5	?		
SJL/1	s	Moderate	2	(High)		
C.B-17 scid/scid		Resistant		High	17	B & T cell deficient

(Parentheses-assumed, but not yet tested)

*Develops arthritis by alternative immunization with Complete Freund's Adjuvant containing 5 mg/ml *M. tuberculosis**需要含结核杆菌的 5mg/ml CFA佐剂诱导关节炎

PROTOCOL TO INDUCE CAIA

CAIA实验方案

Chondrex, Inc. recommends administering the mAb cocktail intravenously (i.e. tail vein). Intraperitoneal (IP) injection can also be used in CAIA susceptible strains; however, the severity of arthritis tends to be lower and the period of active inflammatory arthritis shorter. Individual investigators must determine the best protocol for their own experimental purposes.

Chondrex公司建议尾静脉注射单克隆抗体合剂。对于易感品系，可采用腹腔注射，但是通过腹腔注射CAIA

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诱发的炎症严重程度往往较低，关节炎持续时间也较短。请根据实验目的选择合适的实验方案。

Bacterial toxins such as LPS (B-cell mitogen), Staphylococcal enterotoxin B (T-cell mitogen), and *Mycoplasma arthritidis* mitogen (T-cell mitogen) act synergistically with antibodies to type II collagen in arthritis development. Thus, the mAb dose required for inducing arthritis can be reduced in the presence of these toxins. For example, injecting 1.5 mg/mouse of the mAb cocktail on day 0 followed by an LPS injection (25-50 µg) on day 3 can induce arthritis in nearly 100% of CAIA susceptible mice, such as Balb/c, DBA/1, B10.RIII, and C.B-17 scid/scid mice. Inject 5 mg/mouse for CAIA susceptible C57BL/6 mice. Arthritis progresses rapidly, and acute inflammation peaks on day 7-10 and persists for 2 weeks. Arthritis can be further exacerbated by an additional LPS injection (25-50 µg) on day 10 or 14. The resulting joint destruction is permanent, leading to ankylosis even though active inflammation declines after 3 weeks. Table 3 references compounds which have successfully blocked inflammation in the CAIA model.

细菌毒素LPS（B细胞分裂素）， MAM(支原体产生的T细胞分裂素)或SEB(金黄色葡萄球菌产生的T 细胞分裂素)和胶原抗体在诱发关节炎中具有协同效应。在这些毒素的存在下，诱导关节炎的抗体合剂的量可降低。例如，每只小鼠初次免疫注射1.5mg抗体合剂后第三天注射25-50µgLPS，对于易感品系小鼠（Balb/c, DBA/1, B10.RIII, and C.B-17 scid/scid mice），关节炎的发生率高达100%。在C57BL/6小鼠尾部静脉注射5mg抗体合剂，关节炎在初次免疫后第7-10天达到最严重， 可维持两周。在初次免疫第10或14天注射25-50µgLPS, 关节炎会持续恶化。尽管三周后炎症反应有所缓解，关节破坏是永久性的，甚至导致关节强直。

Table 2. Arthrogen-CIA Arthritogenic Monoclonal Antibody 5-Clone Cocktail Kit

表二 Arthrogen-CIA 致关节炎单克隆抗体五克隆混合物试剂盒

Catalog Number	Quantity
53100	mAb Cocktail: 10 mg/ml x 10 ml LPS: 0.5 mg/ml x 7.5 ml
53040	mAb Cocktail: 10 mg/ml x 4 ml LPS: 0.5 mg/ml x 3.5 ml
53010	mAb Cocktail: 10 mg/ml x 1 ml LPS: 0.5 mg/ml x 1.5 ml

The optimal dosages for mAb cocktails and LPS depend on several factors, including the mouse strain, animal vendor, and housing environment.

单克隆抗体混合物和脂多糖（LPS）的最佳剂量取决于多重因素，包括小鼠品系，动物供应商以及饲养环境等。

1) High doses of LPS, even as low as 50 µg per mouse, can be lethal depending on the health of the animals. Chondrex, Inc. recommends performing a preliminary pilot study using a small number of mice to test LPS dosages of 10, 25, and 50 µg without any antibody administration.

高剂量脂多糖（LPS），即使剂量低至每只小鼠 50 µg，也可能因动物健康状况不同而导致死亡。Chondrex, Inc. 建议先使用少量小鼠进行预实验，在不注射任何抗体的情况下，分别测试 10、25 和 50 µg 的 LPS 剂量。

2) Susceptibility to CAIA also varies significantly. A pilot study is recommended to identify the ideal dose to ensure the desired disease severity before proceeding with a large-scale study.

小鼠对CAIA的易感性也存在显著差异。建议在开展大规模实验前，先进性预实验以确定合适剂量，从而确保达到预期的疾病严重程度。

Table 3 - Compounds that Have Successfully Blocked Inflammation in the mAb-Induced Arthritis Model.

表三 成功阻断单克隆抗体诱发的关节炎的药物

Compound	Class	Reference
Oncostatin M	Cytokine	25
Anti-Integrins α1β1, 2β1	Adhesion Molecule	26
Chemically Modified Tetracycline (CollaGenex)	Matrix Inhibitor Metalloproteinase	27
Anti-CD44 (IM7 Clone)	Adhesion Molecule	Unpublished Data
Dexamethasone (0.15 –0.5 mg/kg)	Glucocorticoid	Unpublished Data
Anti-IL-1β Antibody	Cytokine	17
Anti-TNF-α Antibody	Cytokine	17
Anti-MIP-1α Antibody	Cytokine	17
TACE Inhibitor	TNF Converting Enzyme Inhibitor	37
Methotrexate (0.25 mg/kg, single IM injection) - Effective in p53 knockout mice - Not effective in Balb/c mice	Anti-proliferation Communication	Unpublished Data

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EVALUATING ARTHRITIS

关节炎评估

Disease can be assessed by qualitative clinical score or by determining paw thickness using a Mitutoyo loop handle dial thickness gauge with a round disc. Unlike rat paw volume, mouse paw volume cannot be determined with a plethysmograph because the mouse paw is too small. Chondrex, Inc. provides a scoring system (Table 4) and a supplemental flyer (please visit www.chondrex.com for more information).

关节炎可通过临床评分来定性评估或用测厚仪来测量爪子厚度来评估。由于小鼠的爪子太小，因此无法像测量大鼠爪子体积那样通过浸没法测定小鼠爪子体积。Chondrex公司提供以下评分系统（表二）。

Table 4 - Qualitative Scoring System to Assess Severity of Paw Inflammation

表二 关节炎炎症程度的临床评分

Score 得分	Condition 发病情况
0	Normal 正常
1	Mild, but definite redness and swelling of the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits 轻度的、踝关节、腕关节发红、肿胀
2	Moderate redness and swelling of ankle or wrist 踝关节或腕关节中度发红肿胀
3	Severe redness and swelling of the entire paw including digits 爪子严重发红、肿胀，包括指端
4	Maximally inflamed limb involving multiple joints 四肢最大程度发炎，包括多关节

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