2019-05-25

病原微生物感染与宿主免疫应答

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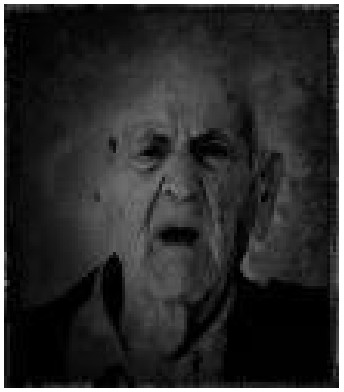
中国科学院微生物研究所

生理性衰老是不可避免的过程

Baby

Adult



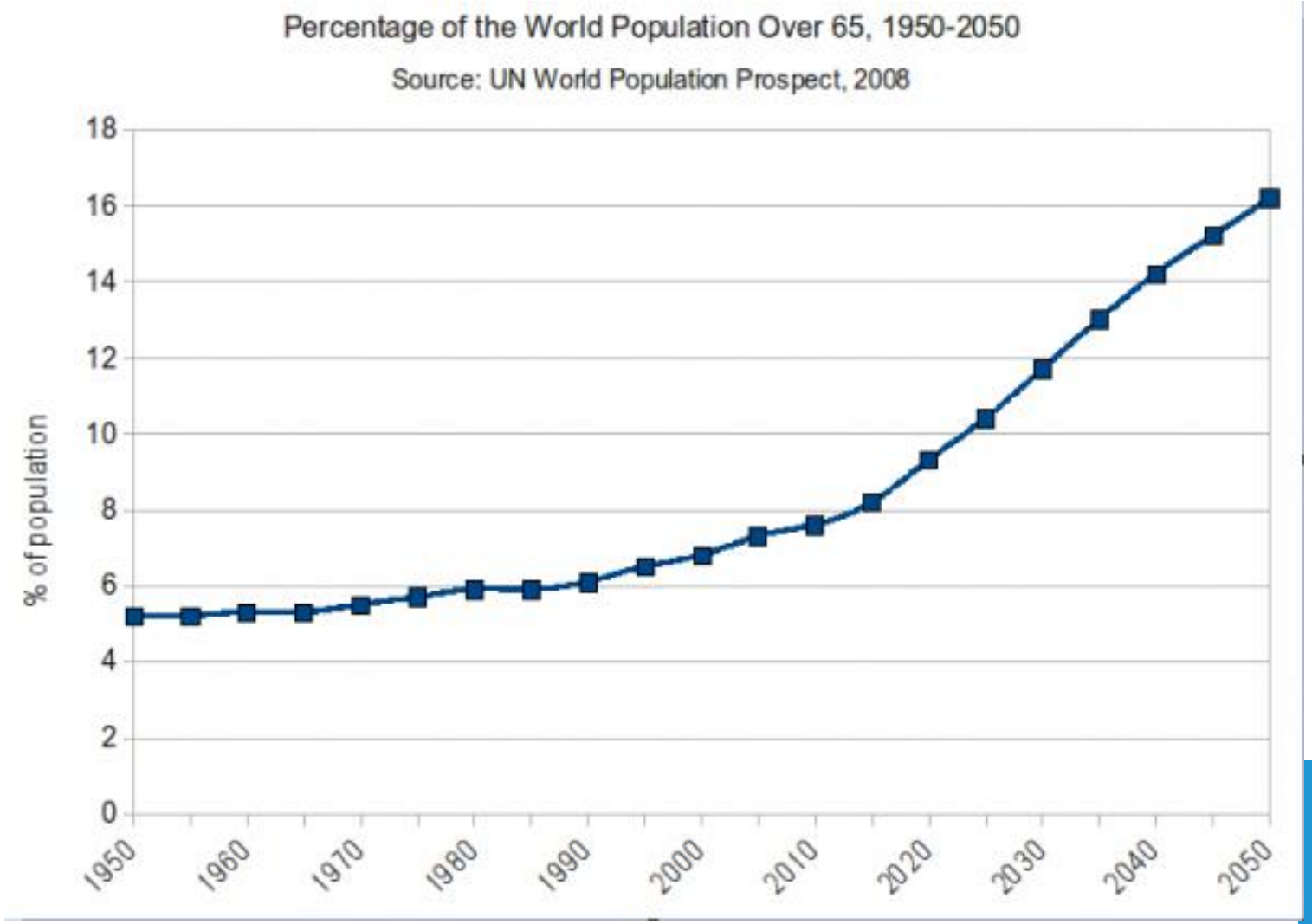
Aged

Decreased efficacy to vaccination

More vulnerable to tumor

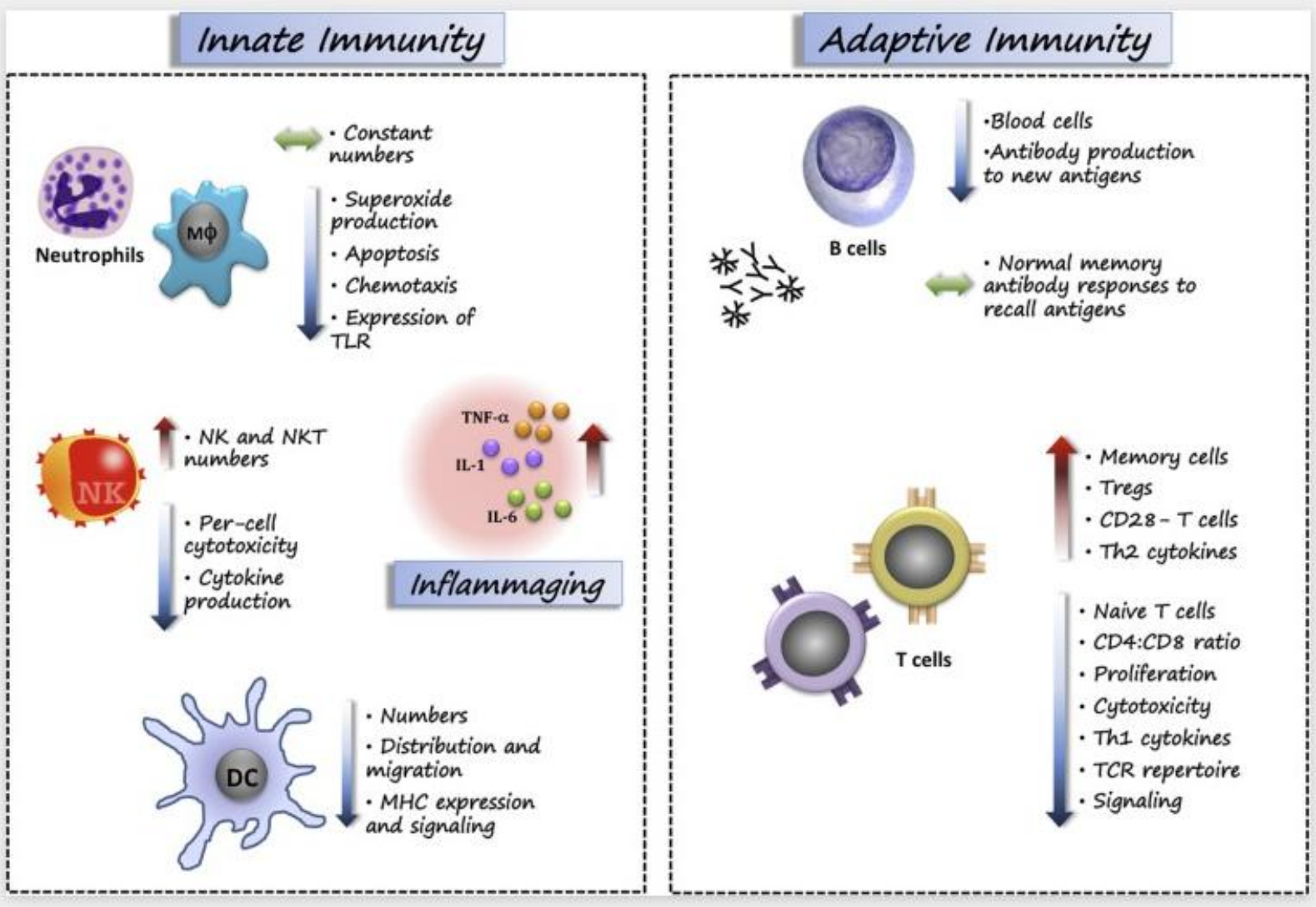
More susceptible to infectious diseases:
H5N1, West Nile virus (WNV), severe acute respiratory syndrome (SARS)

世界人口老龄化



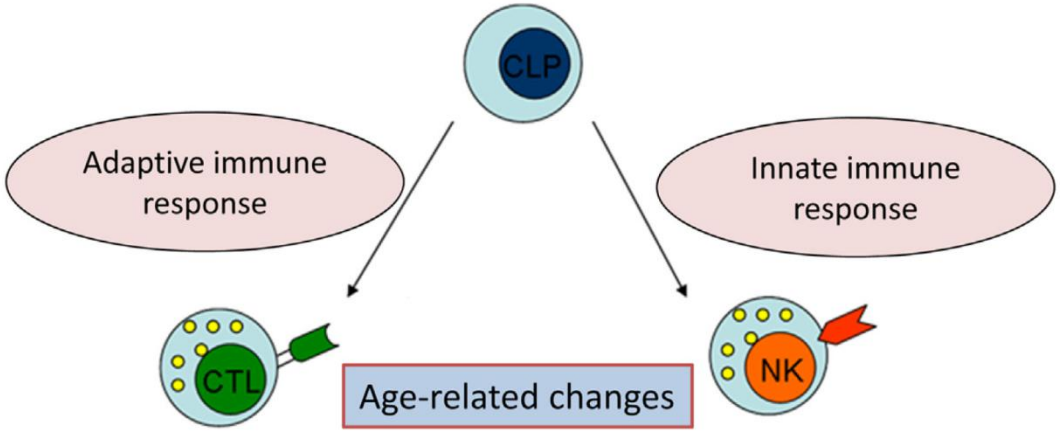
World Health Organization

免疫衰老



Mechanisms of aging and development,Vol.158,2016,27-37

免疫细胞功能随衰老改变

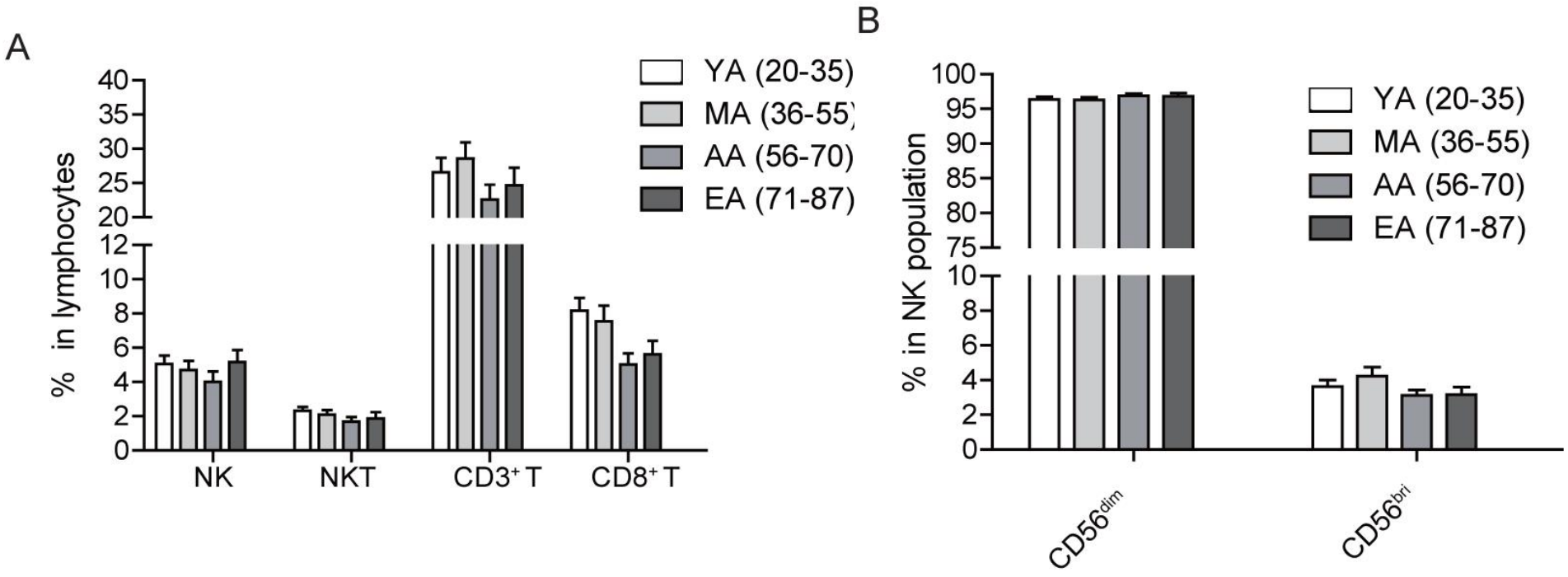


T cell compartment
Decline in naïve T cell production and ↓ lymphocyte numbers
Failure of homeostatic mechanisms:
Contraction in T cell receptor diversity
Imbalance of functional T cell subsets
Accumulation of non-functional memory T cells
Phenotype changes:
↑CD28– cells
↑ KLRG-1 + cells
↑CD152 + cells
↑ CD45RO+ cells
↑ surface expression of NK cell-associated receptors
↑ CD57+ cells
Decline in CD8 T cell function:
Failure in T cell activation and signaling
Failure in T cell proliferation (cellular senescence, low telomeres)
↓IFN-γ

NK cell compartment
Increased numbers of NK cells
Remodelling of NK cell subsets:
↓ CD56bright
↑ CD56–
Phenotype changes:
↓ NKp30 and NKp46
↓ DNAM-1
↓ NKG2A
↑KIR?
↑NKG2C
↑CD57
Decline in NK cell function:
Impaired cytotoxicity (single-cell level)
↓ Cytokine production
↓ Responsiveness to cytokines
Preserved ADCC

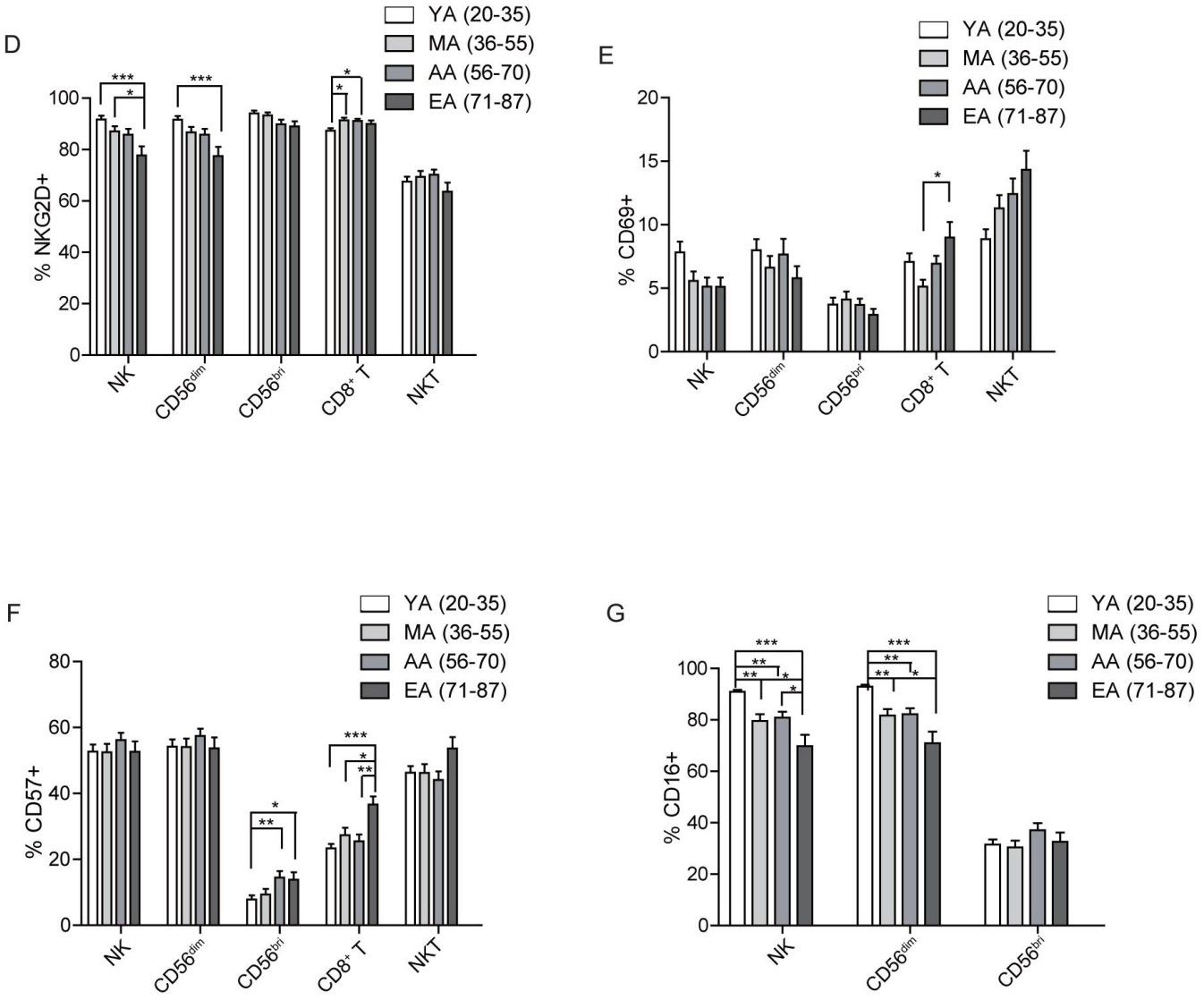
Maturitas, 2015

外周血淋巴细胞比例随年龄变化没有显著差异



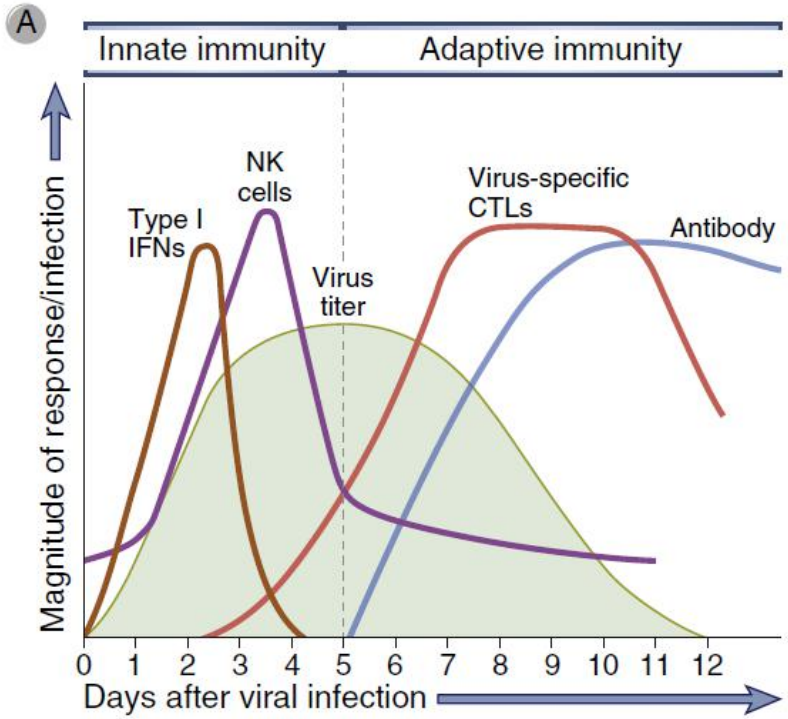
Wang, *et al*. 2017. *Oncotarget*

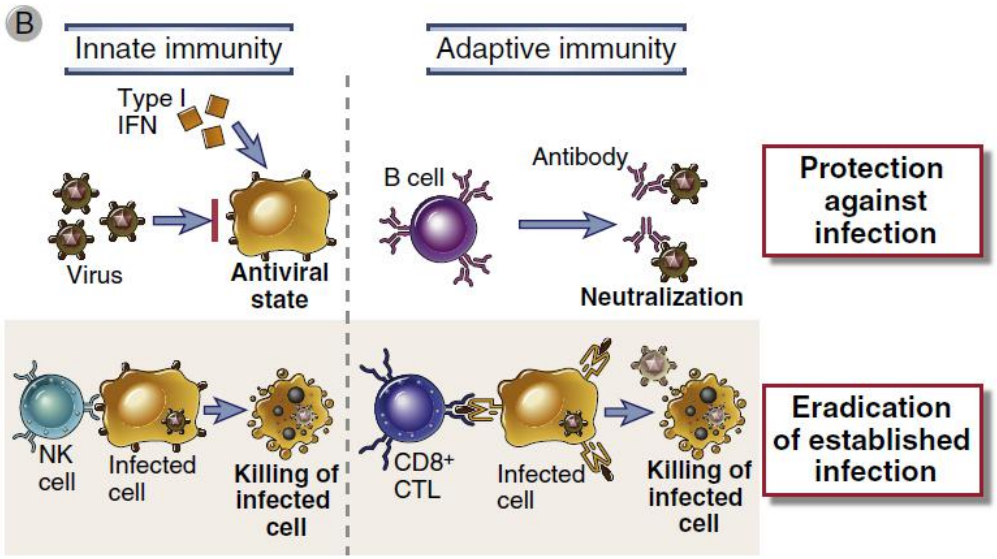
外周血淋巴细胞表面分子表达水平随年龄变化



Wang, *et al*. 2017. *Oncotarget*

抗病毒免疫应答





Cellular and Molecular Immunology. 8th edition

衰老研究动物模型

自发性动物模型

诱发性动物模型

转基因动物模型

自发性动物衰老模型

1. 快速衰老小鼠模型

（Sensecence Accelerated Mouse, SAM）

SAM种系寿命及老化病态特征

$(\bar{X} \pm s)$

种系	存活时间(天)	老化病态特征
SAM-R	526±17.5	
SAM-R/1	568±18.9	高龄化非胸腺性淋巴瘤
SAM-R/2	492±16.4	
SAM-R/4	519±17.3	高龄化的学习、记忆障碍
SAM-P	358±11.9	
SAM-P/1	374±12.5	多发性老化淀粉样变
SAM-P/2	304±10.1	老化淀粉样变及继发淀粉样变
SAM-P/3	507±16.9	变形性下颌关节炎
SAM-P/6	321±10.7	老化性骨质疏松症
SAM-P/7	336±11.2	老化淀粉样变，胸腺瘤
SAM-P/8	364±12.1	学习、记忆障碍
SAM-P/9	323±10.8	白内障
SAM-P/10	333±11.1	伴随脑萎缩的学习、记忆障碍

自发性动物衰老模型

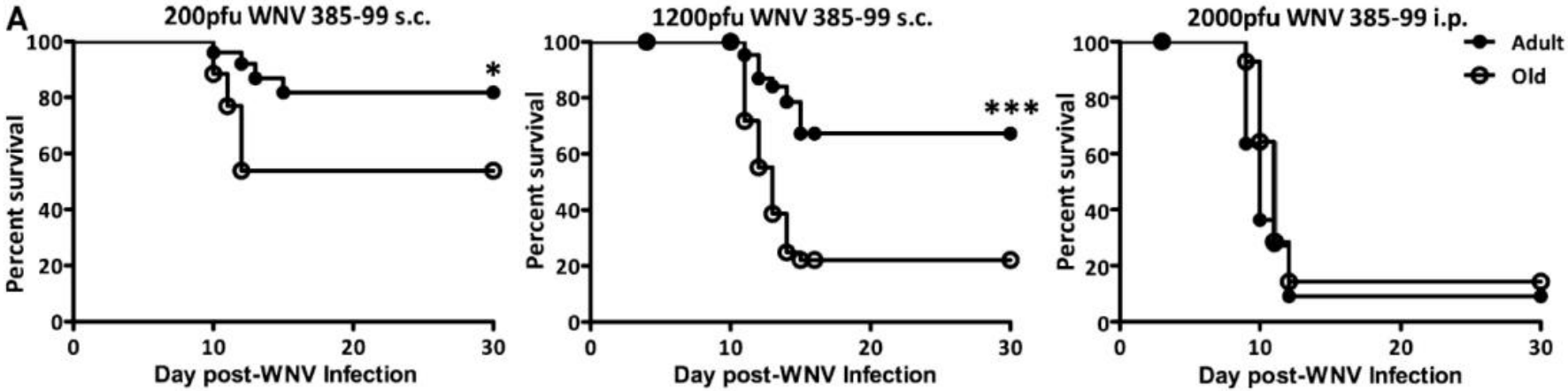
2. 自然衰老动物模型

小鼠：12-30月龄

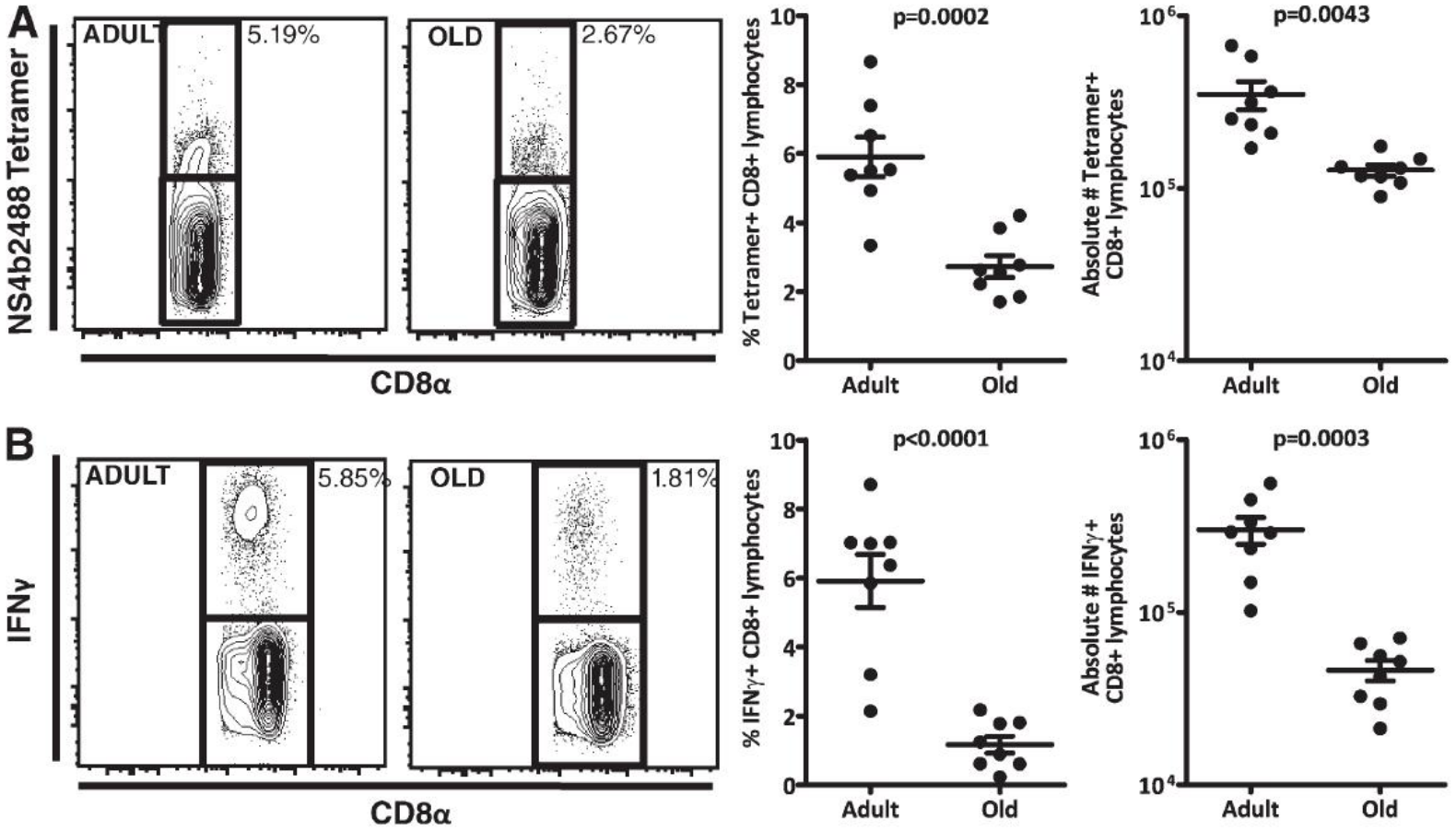
大鼠：21-26月龄 衰老早期
30-32月龄 衰老晚期

Key role of T cell defects in age-related vulnerability to West Nile virus

James D. Brien,[1,2,3] Jennifer L. Uhrlaub,[1,2,4,5] Alec Hirsch,[1,2]
Clayton A. Wiley,[6] and Janko Nikolich-Žugich[1,2,4,5]



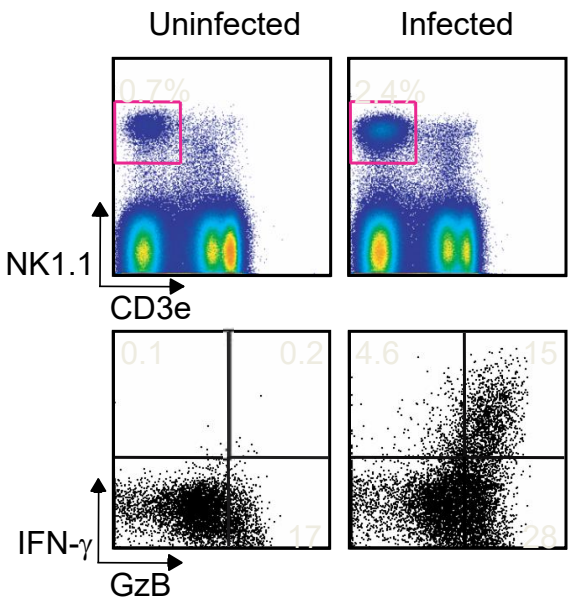
T细胞功能缺陷导致老年小鼠对西尼罗病毒敏感



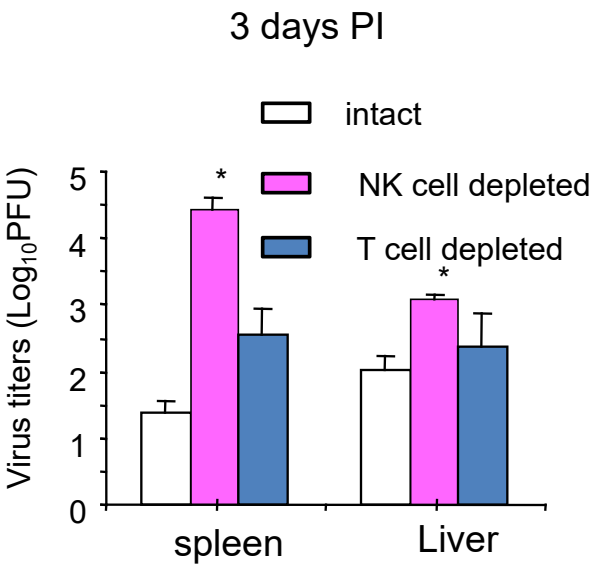
JEM, 2009

NK细胞抗痘病毒的作用机制

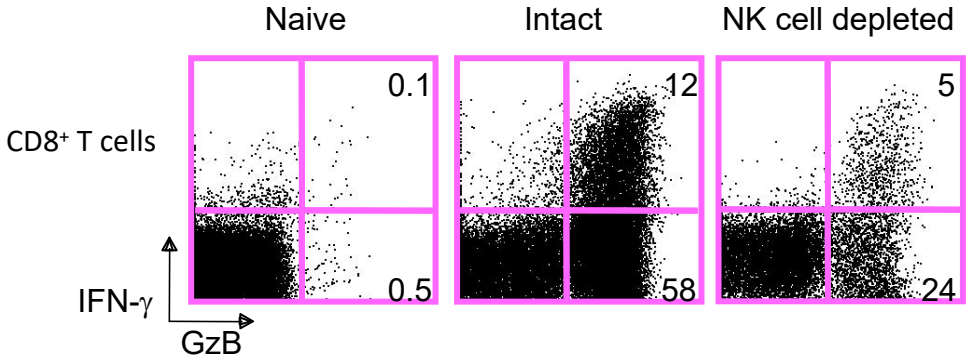
NK细胞 ➡局部淋巴结



控制病毒的早期扩散

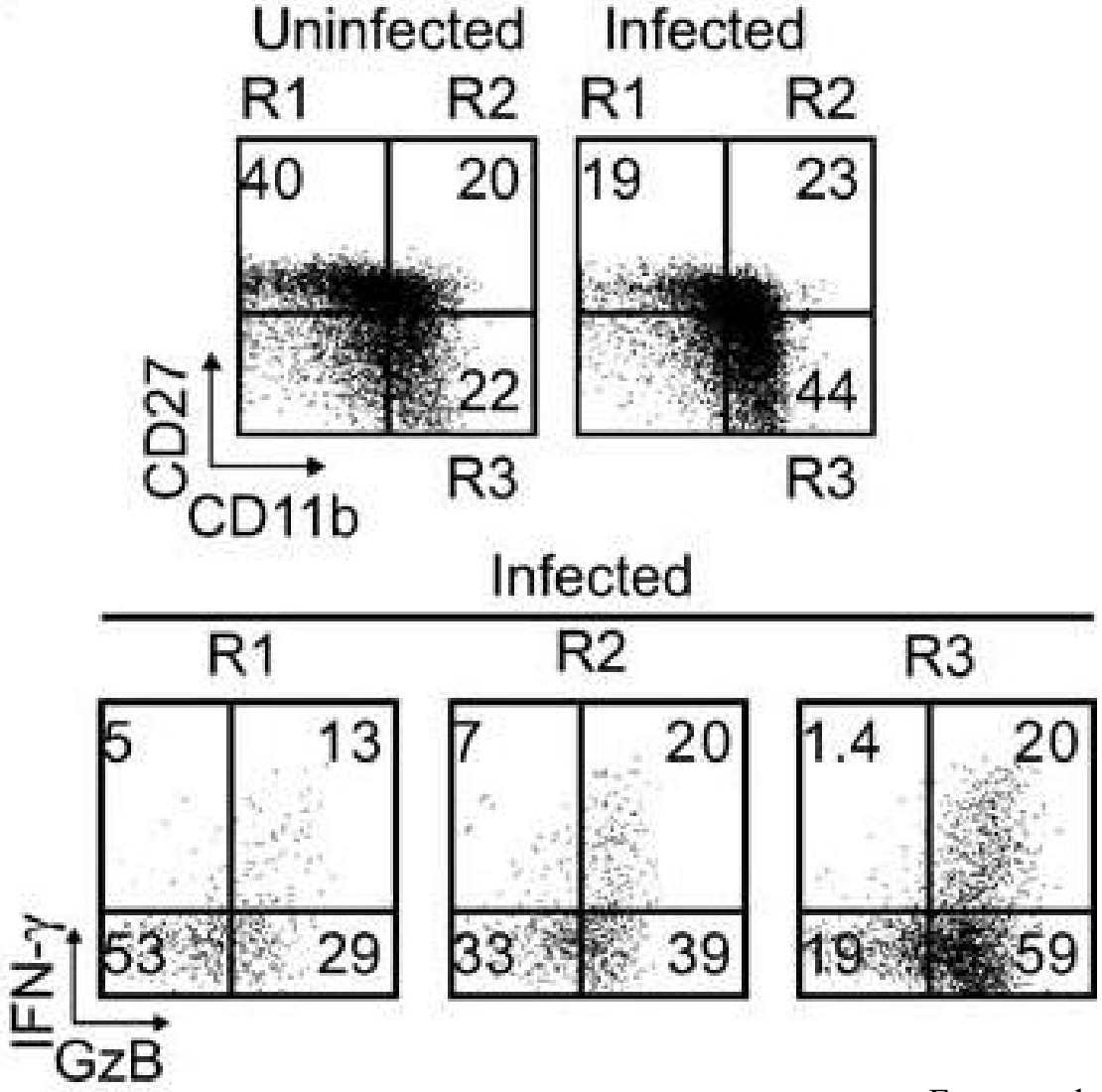


调控CD8⁺ T细胞反应



Fang, et al. 2008. *Plos Pathogens*

R3 ($CD27^{-}CD11b^{+}$) NK 细胞杀伤靶细胞能力强



Fang, et al. 2008. *Plos Pathogens*

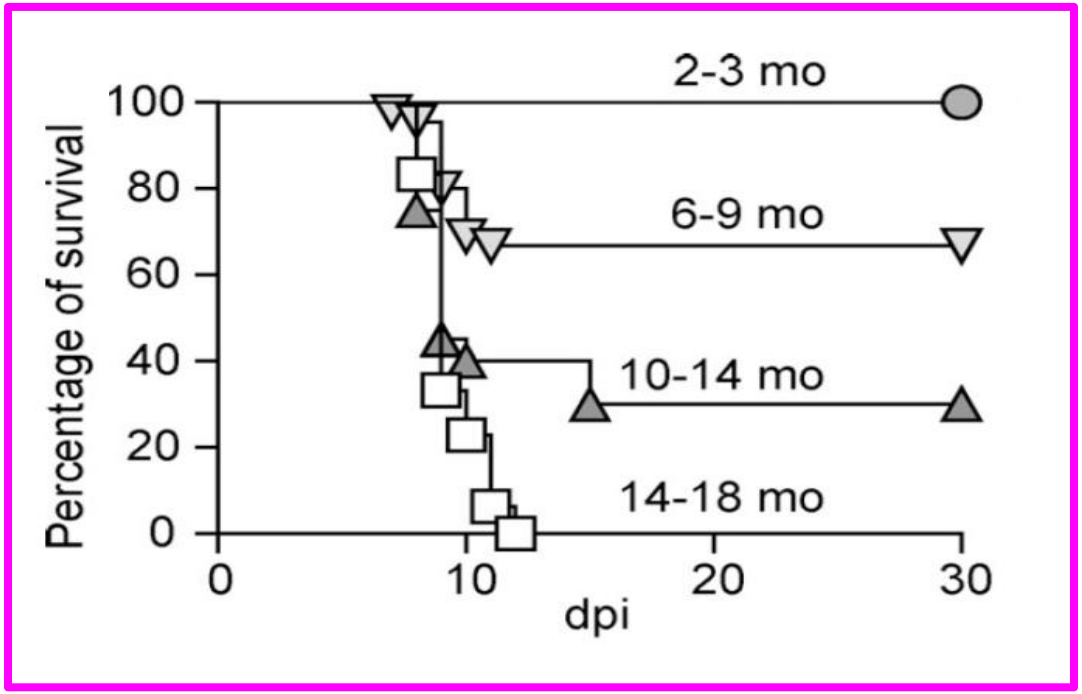
Published September 27, 2010

JEM

Article

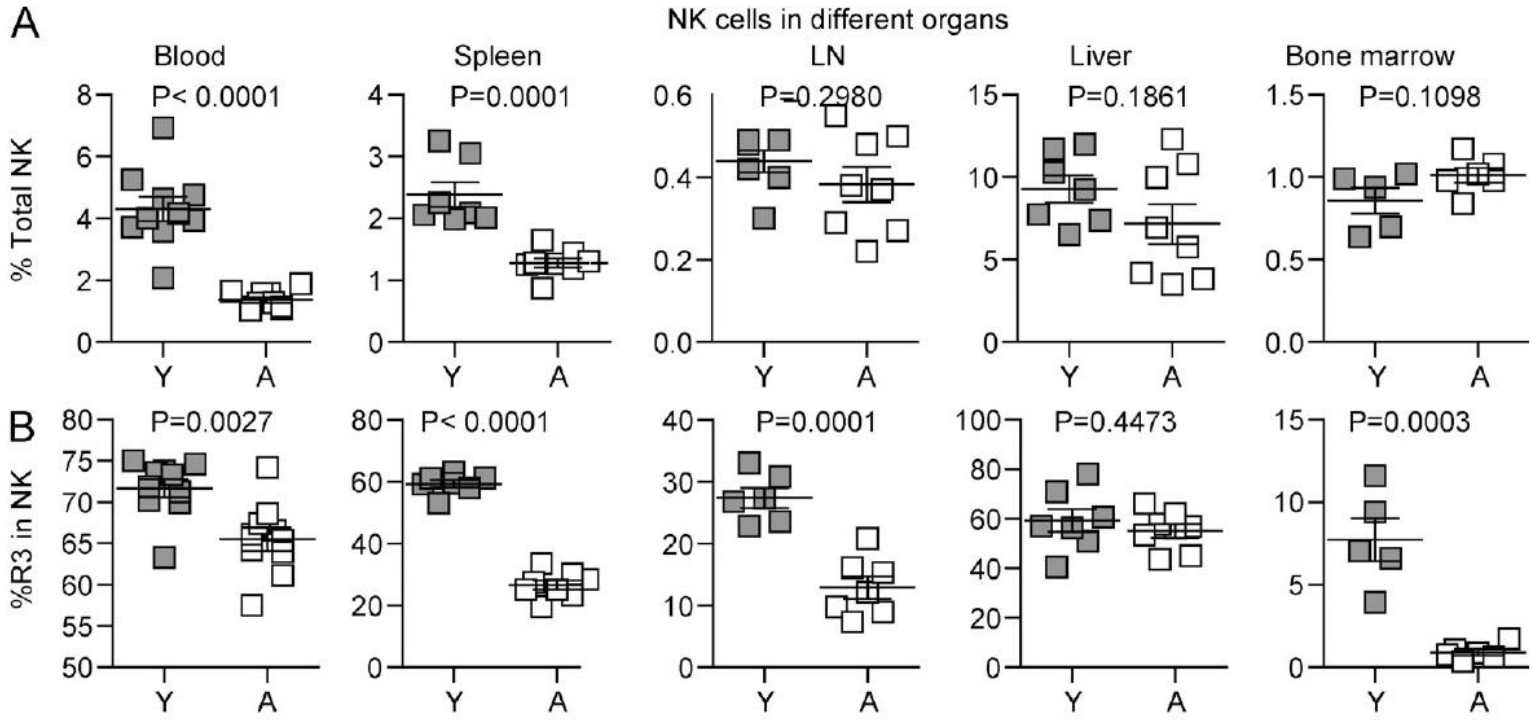
Age-dependent susceptibility to a viral disease due to decreased natural killer cell numbers and trafficking

Min Fang, Felicia Roscoe, and Luis J. Sigal



Fang, *et al.* 2010, *JEM*.

NK细胞随衰老出现发育分化缺陷

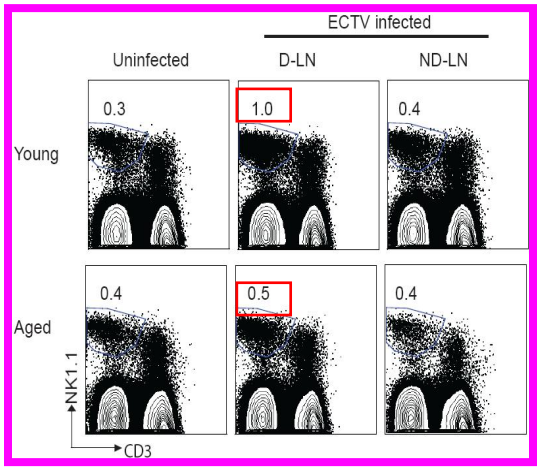


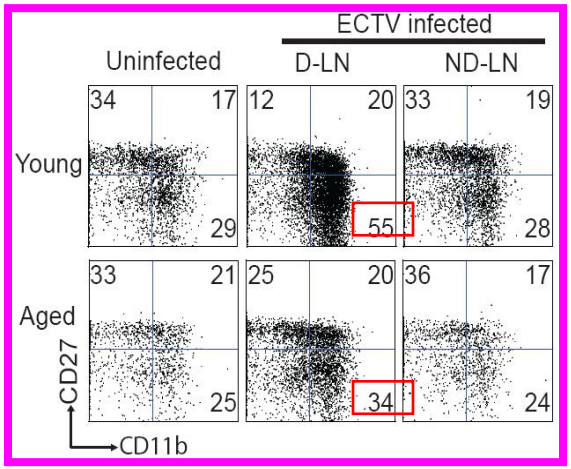
总NK细胞比例在血液、脾脏 ↓

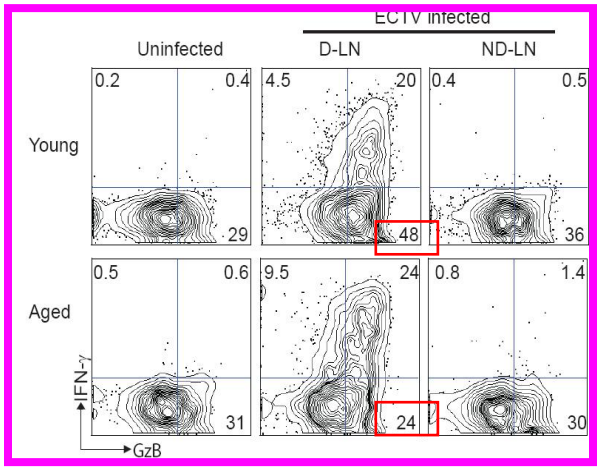
成熟的NK细胞比例在血液、脾脏、淋巴结尤其是骨髓 ↓

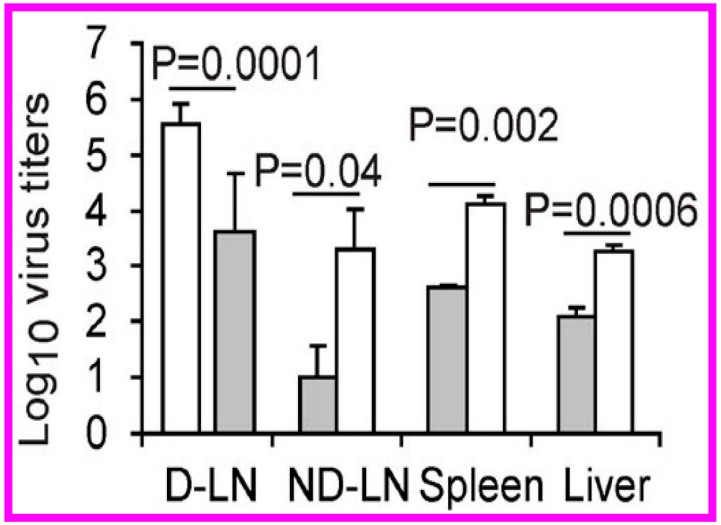
Fang, *et al.* 2010, *JEM*.

NK细胞的功能缺陷导致老年小鼠丧失对痘病毒的抵抗能力



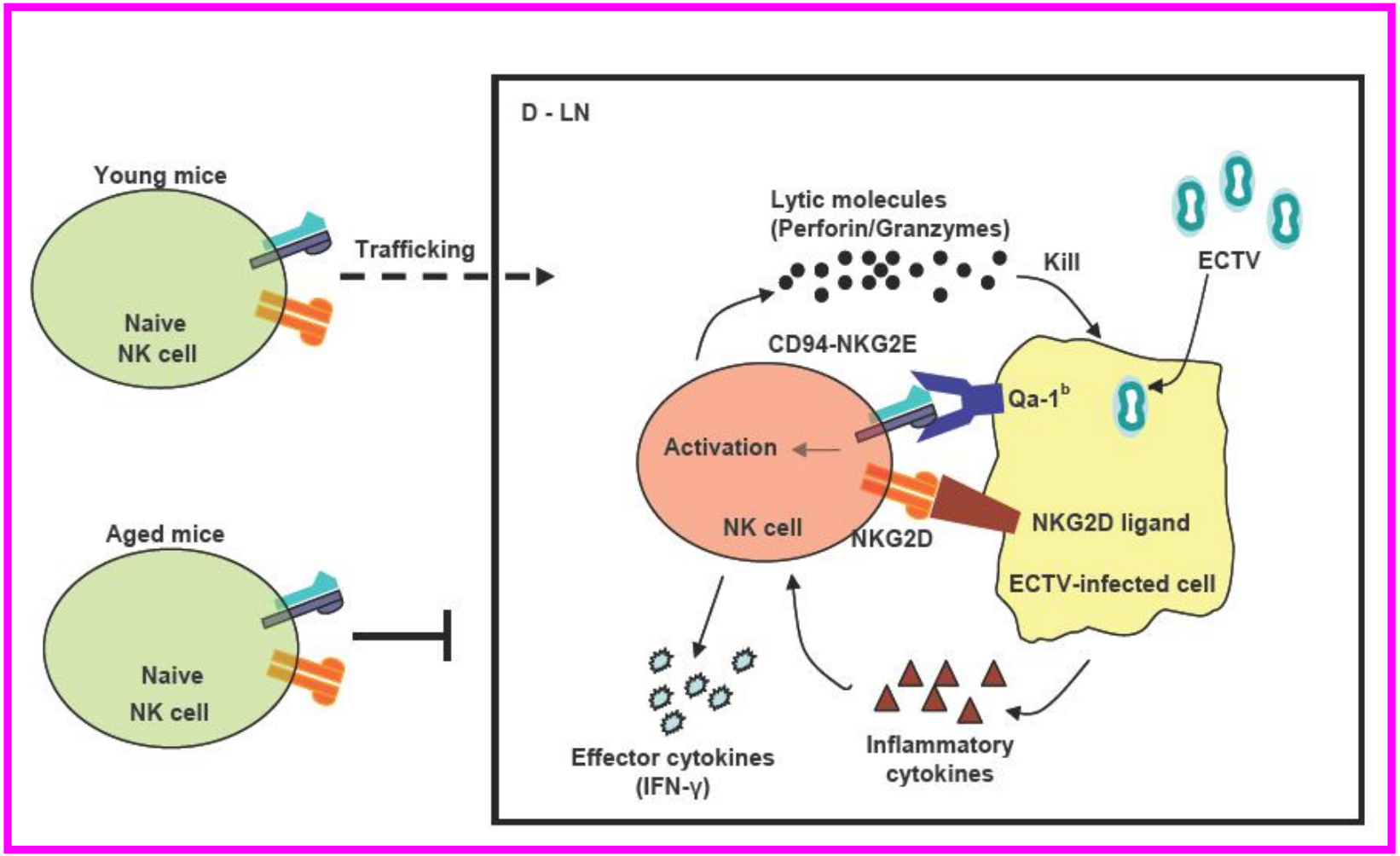






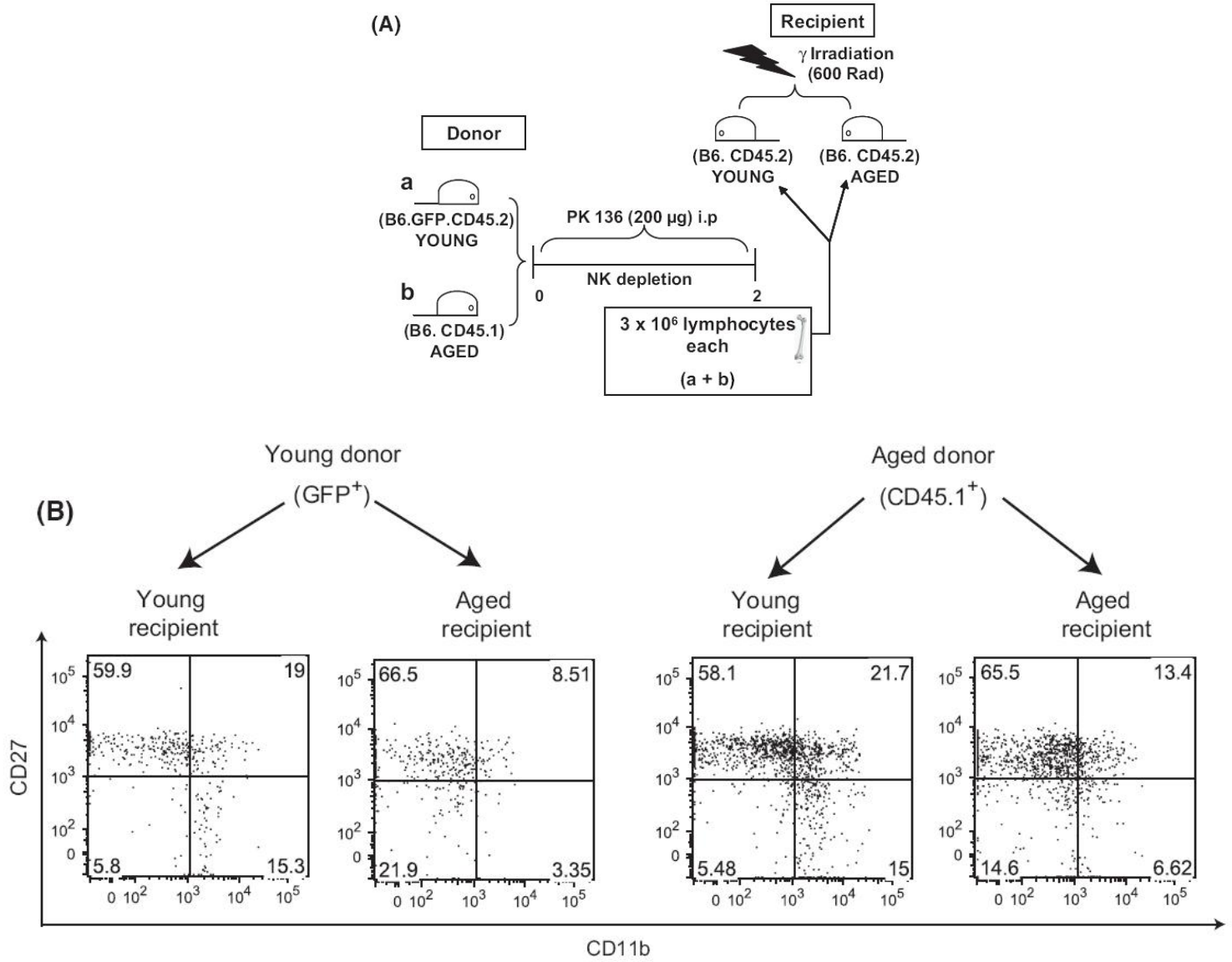
Fang, *et al.* 2010, *JEM*.

NK细胞对痘病毒的特异性反应



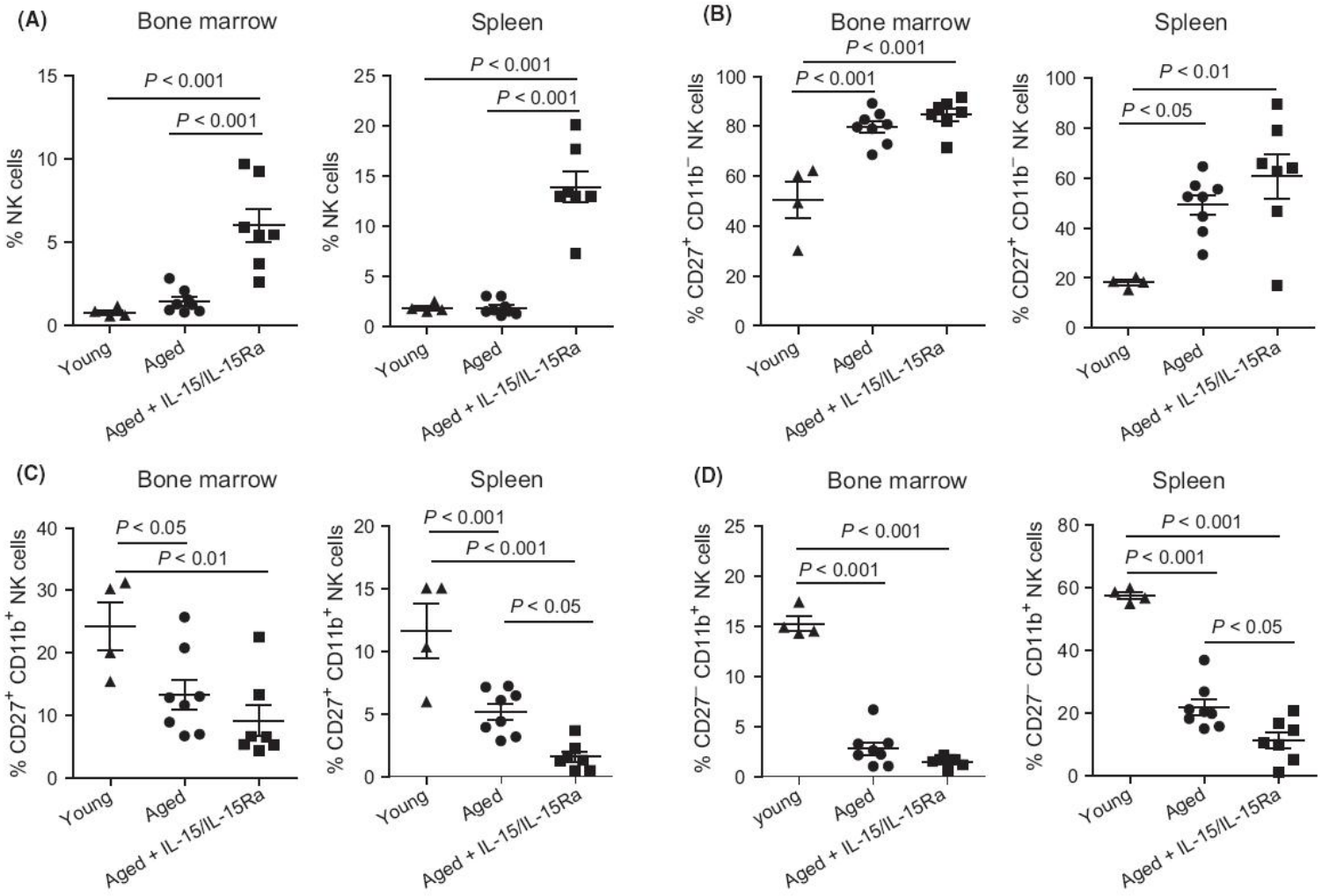
Immunity, 2011; JEM, 2010; Plos Pathogen,2008

老年小鼠的骨髓微环境导致NK细胞发育分化缺陷



Nair, *et al.* 2015, *Aging cell*.

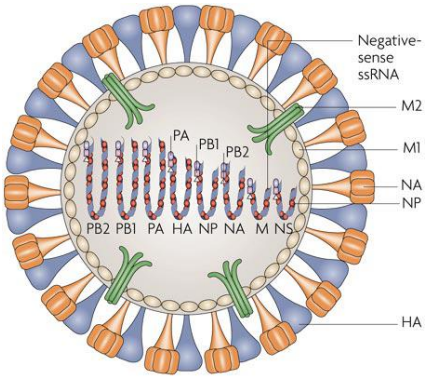
IL-15/IL-15Ra处理不能增加老年小鼠中成熟NK细胞比例

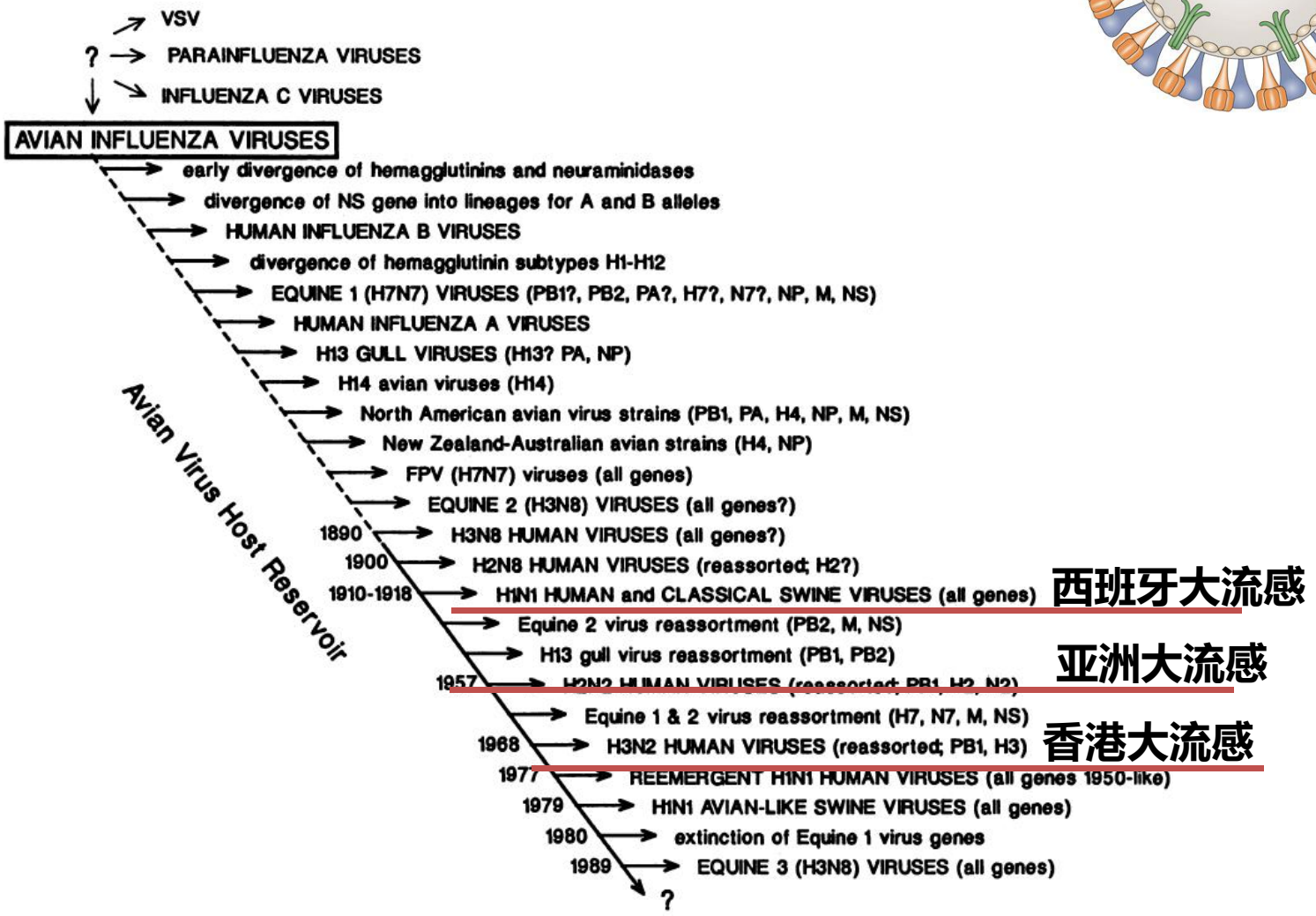


Nair, *et al.* 2015, *Aging cell*.

年龄对小鼠抗流感病毒感染的影响？

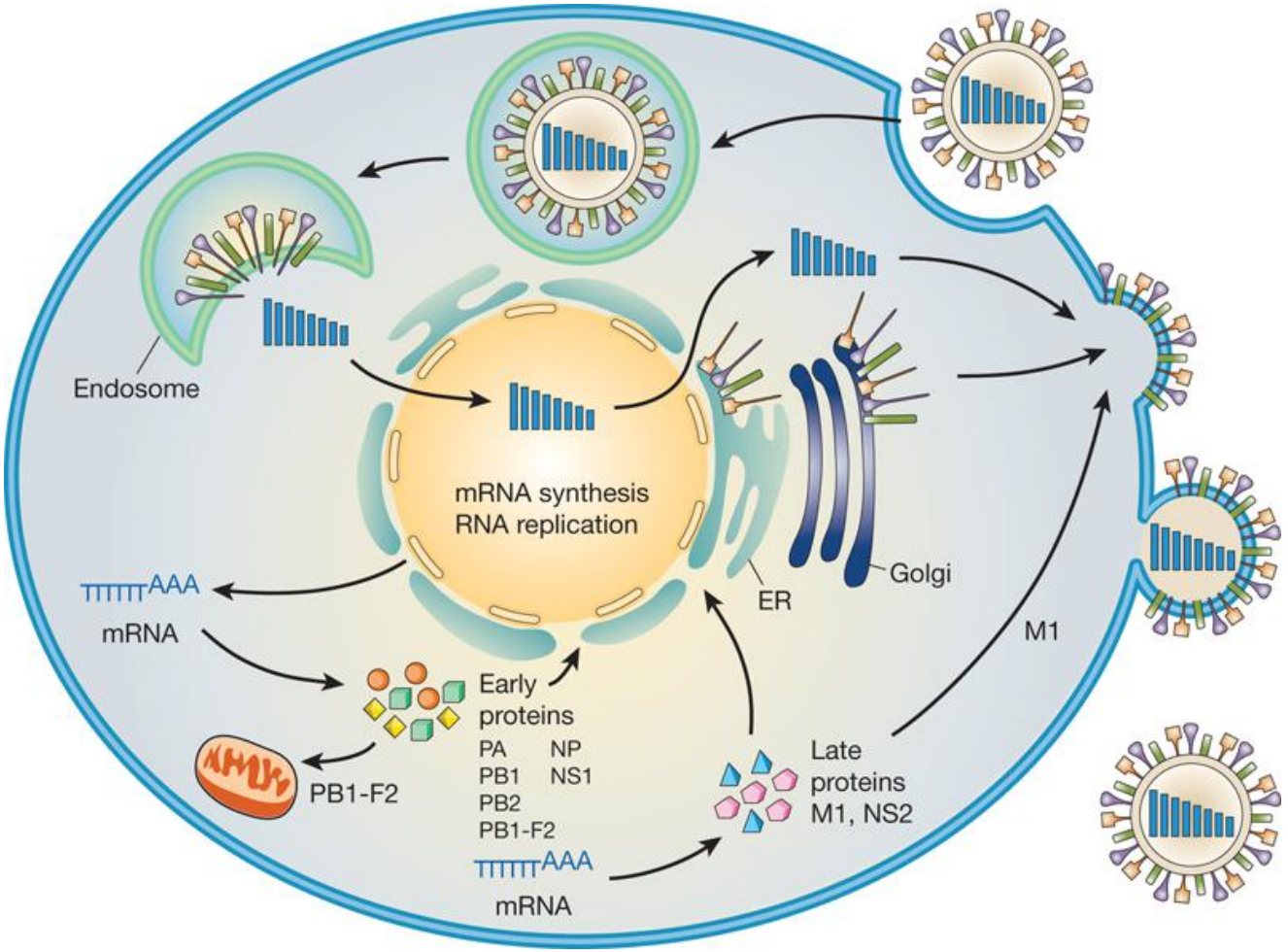
流感病毒严重威胁人类健康





1997-香港禽流感病毒 H5N1，2009-北美H1N1，2013-中国大陆H7N9

流感病毒生命周期



Nature 2009;459:931.

流感病毒高度变异

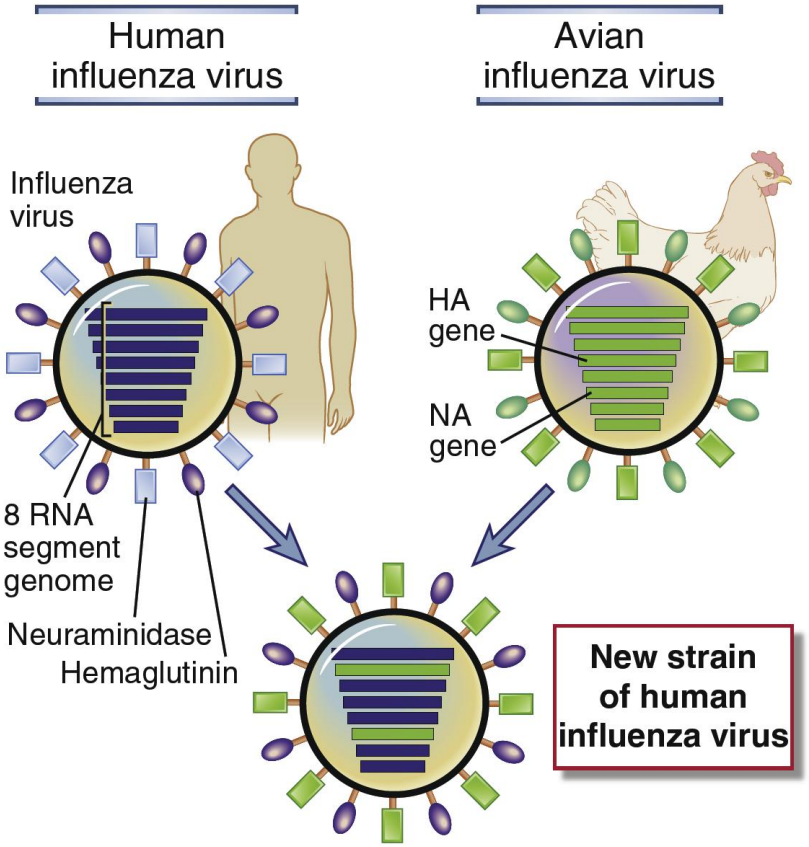


FIGURE 16-8 Generation of new influenza virus strains by genetic recombination (antigenic shift). The genome of

Cell Mol Immunol, 8th Edition

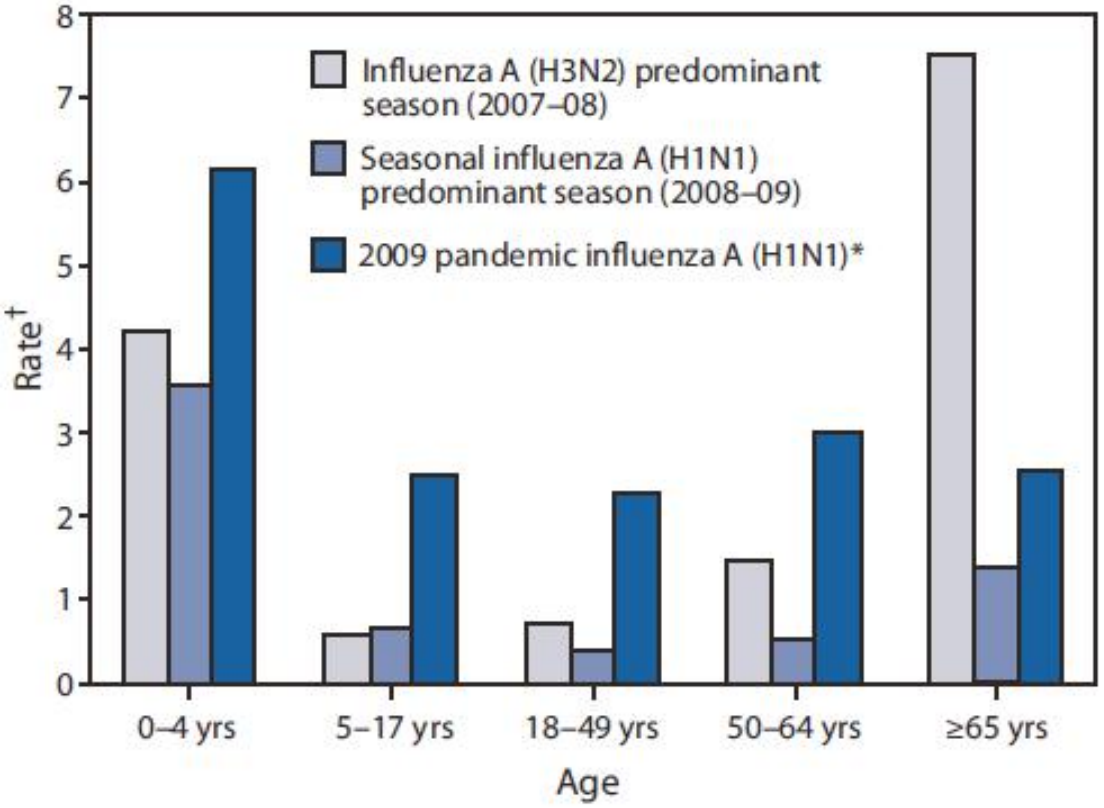
Antigenic shift and drift

Antigenic drift: Small changes in the genes of influenza.

These changes usually produce viruses that are pretty closely related to one another with shared antigenic properties and an immune system exposed to an similar virus will usually recognize it and respond.

But these small genetic changes can accumulate over time and result in viruses that are antigenically different. When this happens, the body's immune system may not recognize those viruses.

重症流感感染呈现出一定的年龄差异



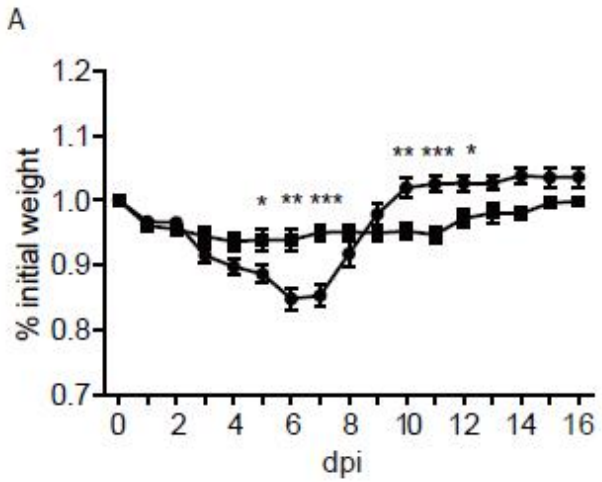
The median age of individuals confirmed infection with H7N9 was **63** years old, while with H5N1 infection was **26** years old and with 2009 pandemic H1N1 infection was **25** years old.

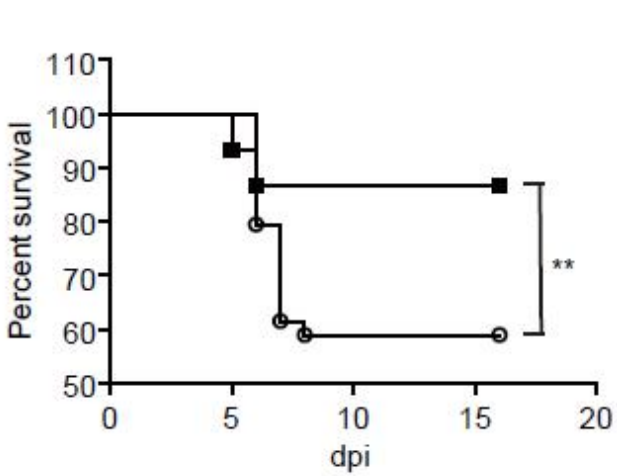
Centers for disease control and prevention, 2014

Wang, et al. Clin Infect Dis, 2014;.

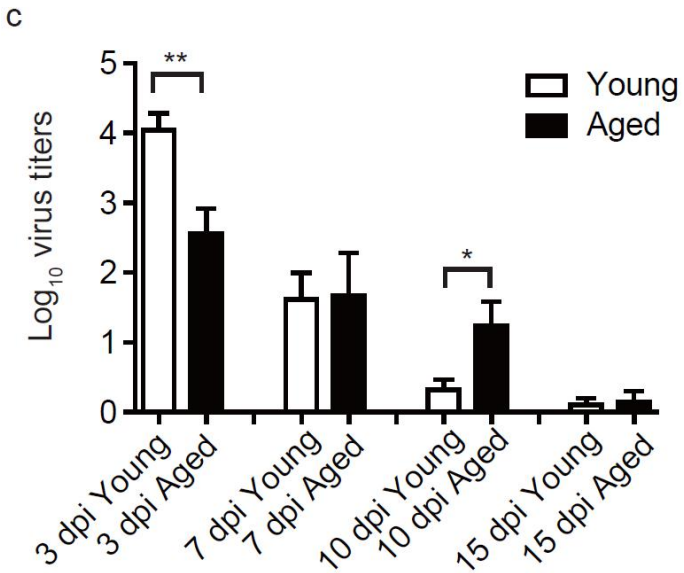
Cowling, et al. Lancet, 2013.

老年小鼠对流感病毒感染抵抗力更强





i.n.10^3pfu/mouse

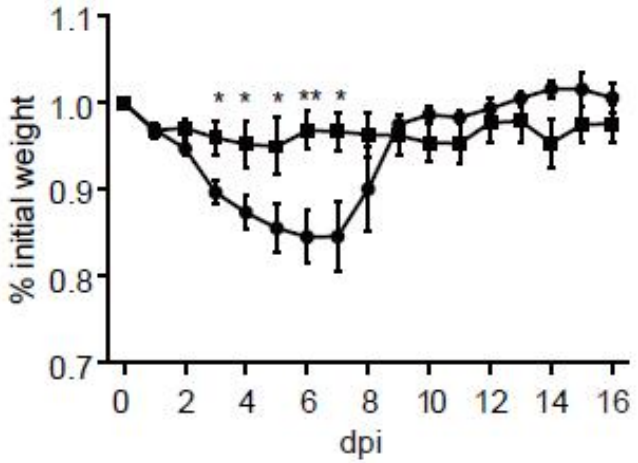


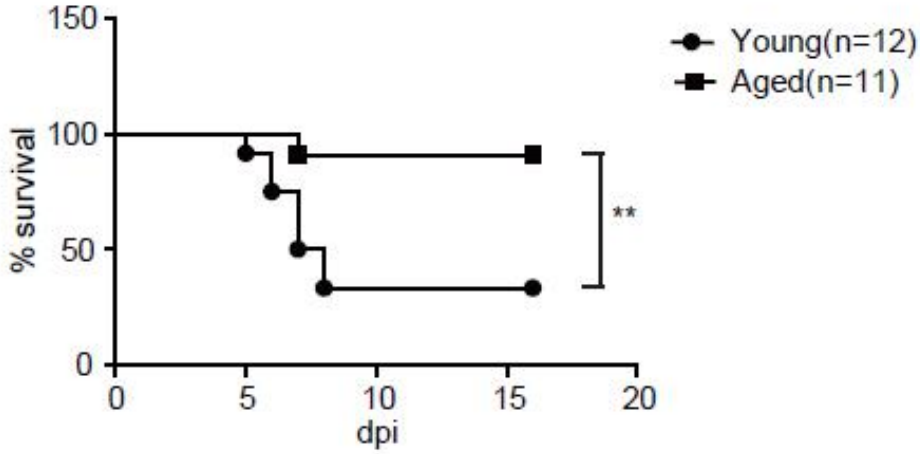
Lu, *et al.* Aging Dis, 2018

老年小鼠对流感病毒感染抵抗力更强

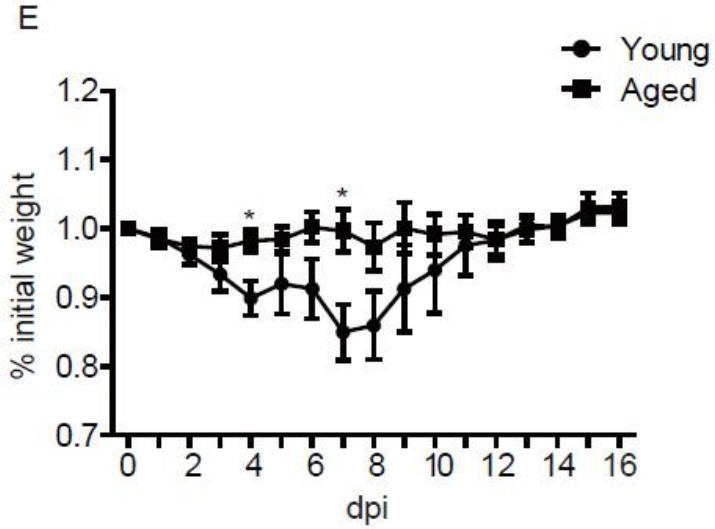
D

10^4 pfu PR8





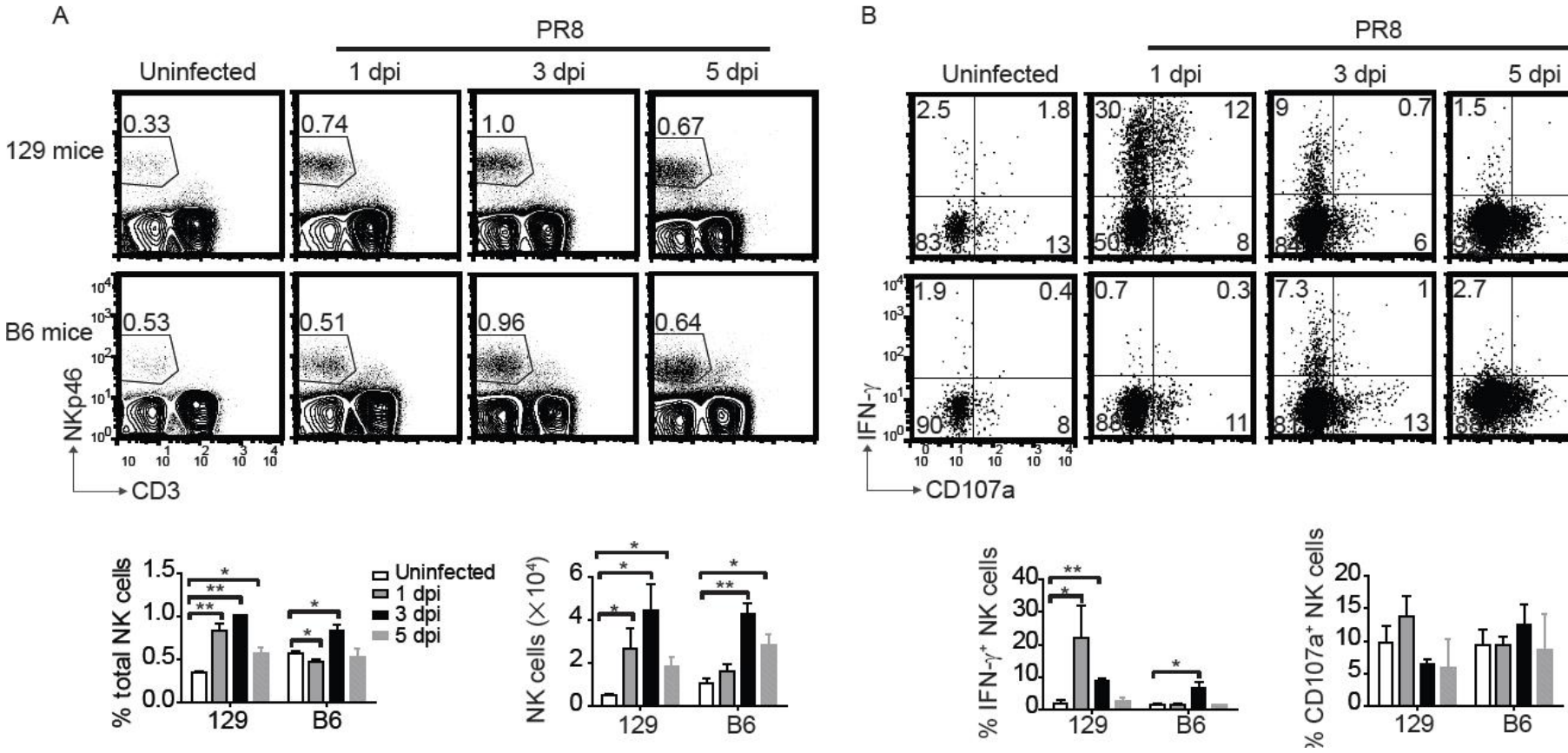
E



Young 10^3 pfu PR8;
Aged 1.7X10^3 pfu PR8

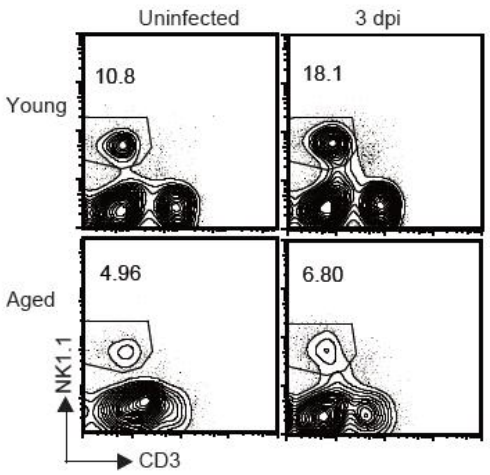
Lu, *et al.* Aging Dis, 2018

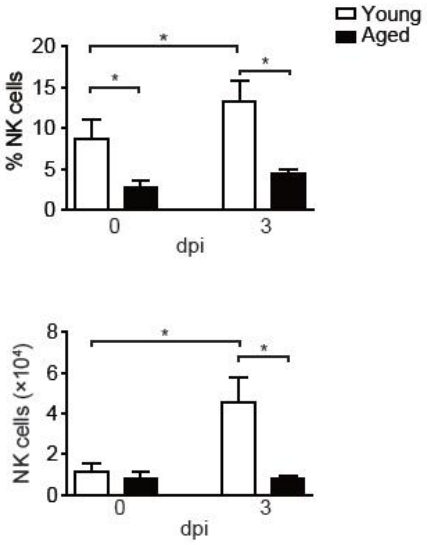
NK细胞在流感病毒感染中的作用与NK细胞活化的速度和强度相关

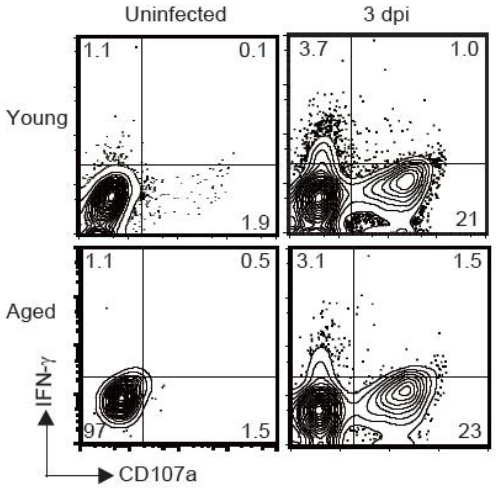


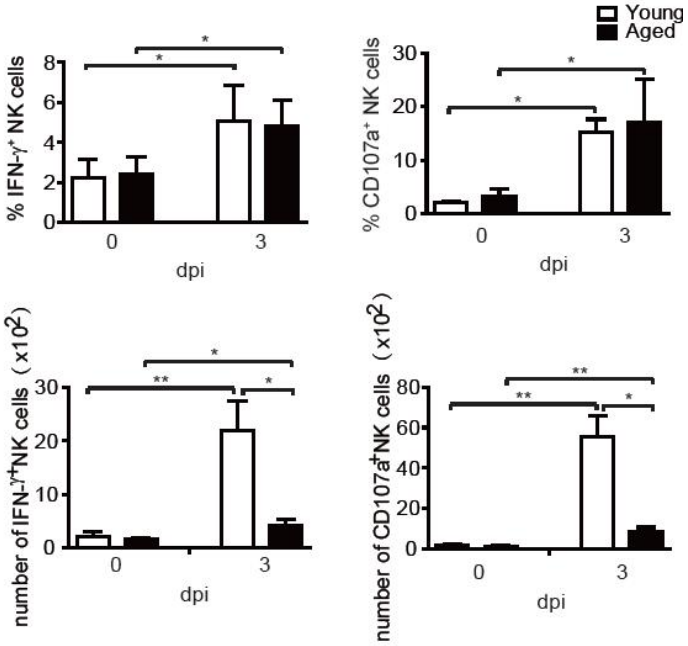
Zhou, *et al*. 2016. *J Immunol*

老年小鼠在IAV感染后NK细胞的免疫应答下降



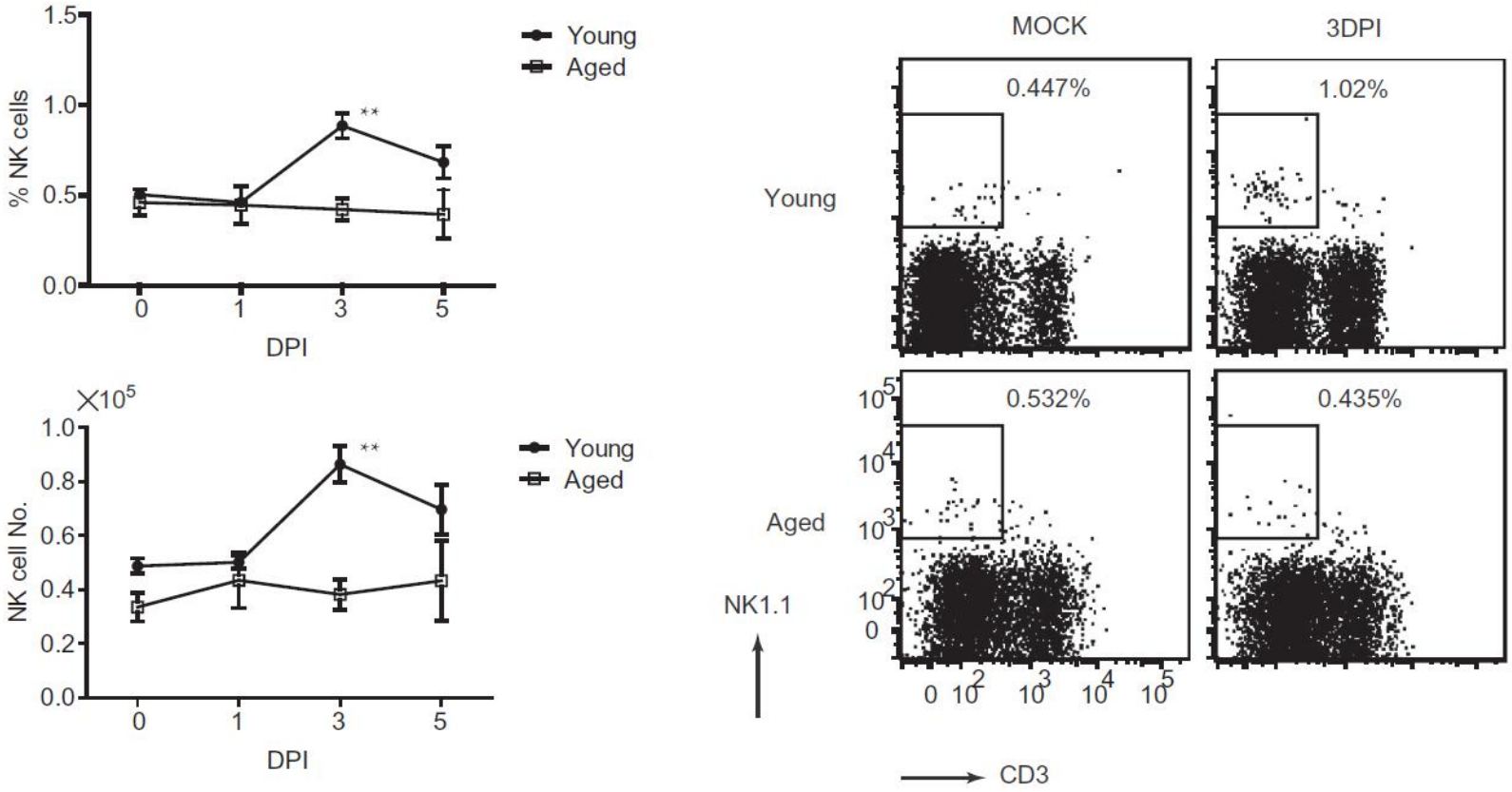






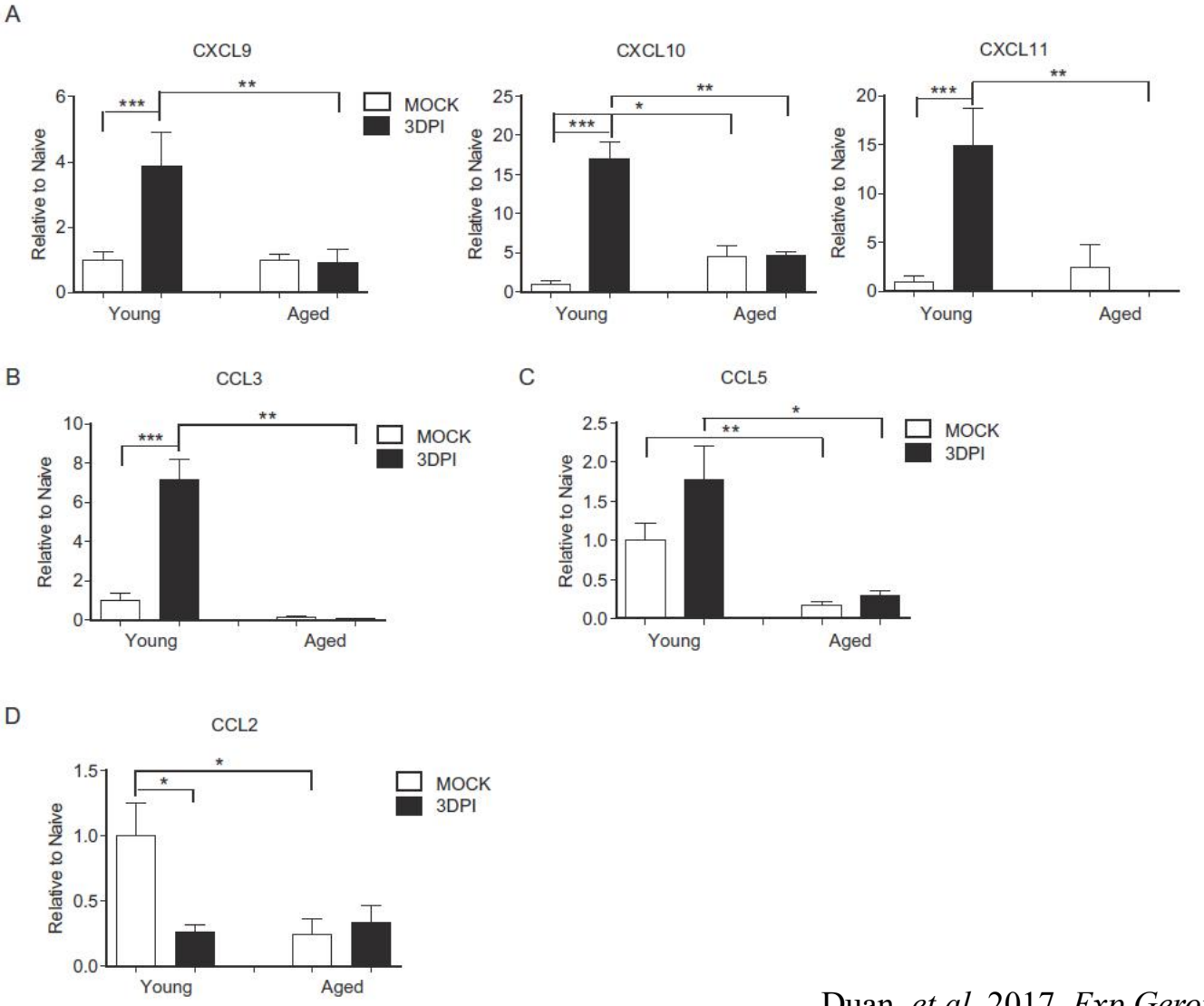
Lu, *et al.* Aging Dis, 2018

老年小鼠感染IAV后NK细胞到引流淋巴结的迁移存在缺陷



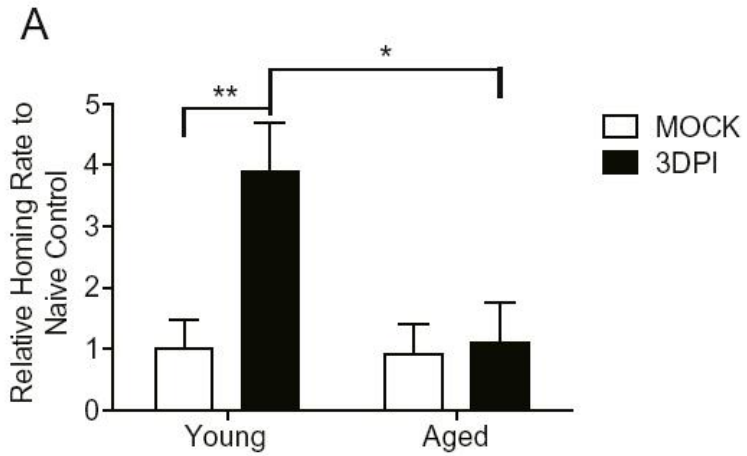
Duan, *et al*. 2017. *Exp Gerontol*

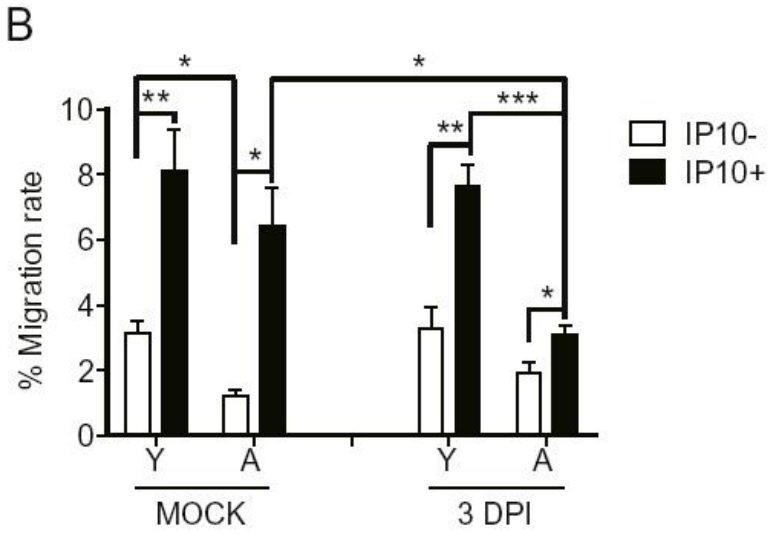
老年小鼠感染IAV后引流淋巴结中趋化因子水平低

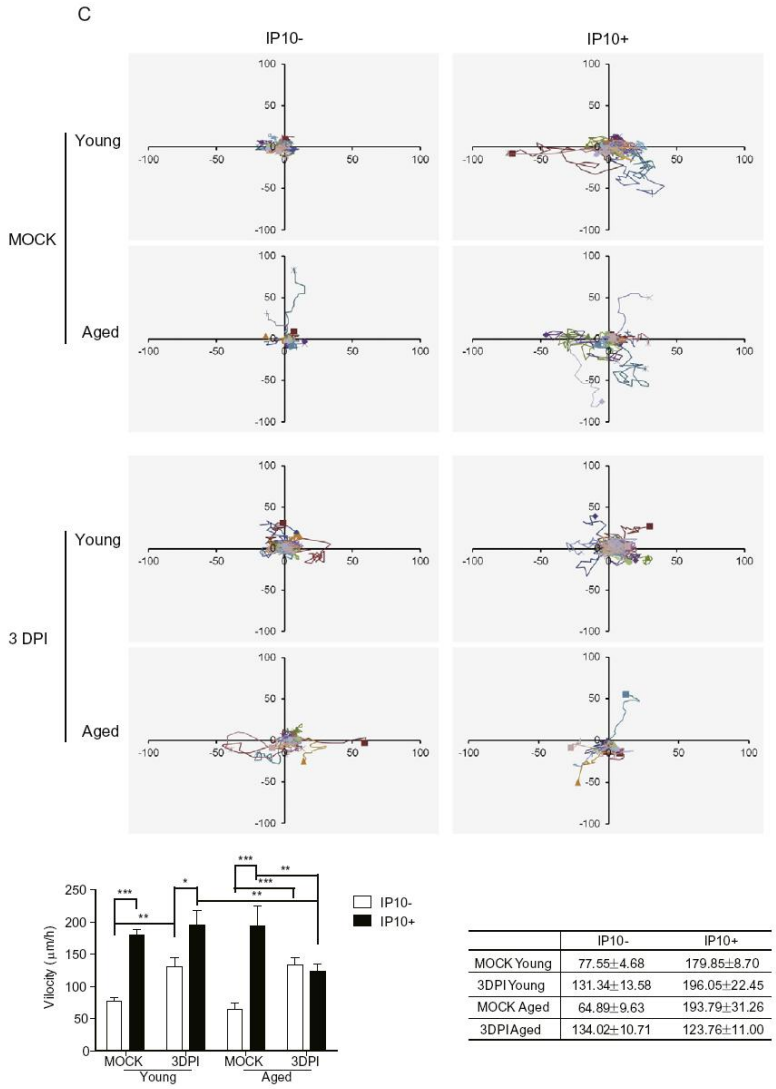


Duan, *et al*. 2017. *Exp Gerontol*

NK 细胞随衰老出现内在迁移缺陷



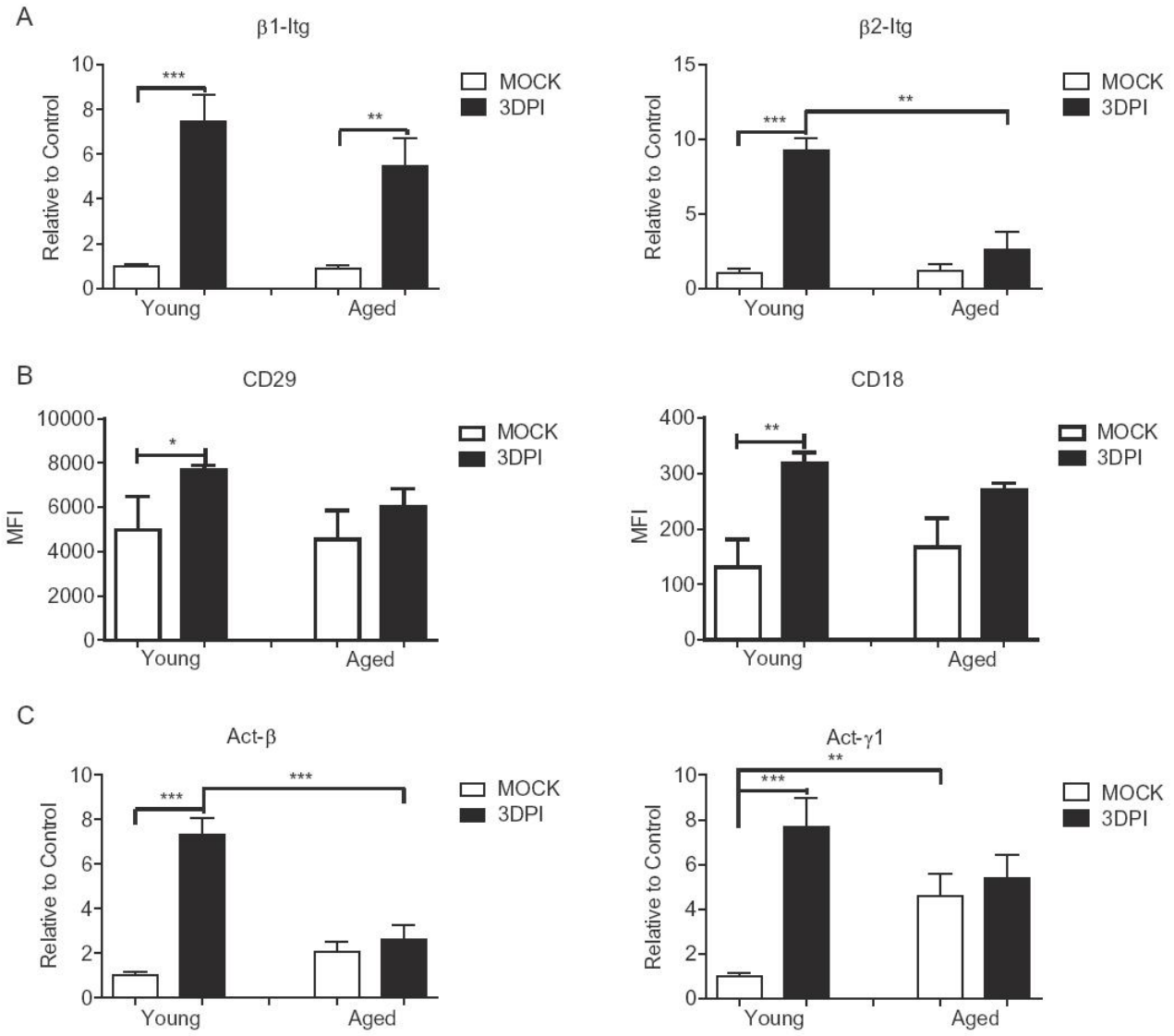




	IP10-	IP10+
MOCK Young	77.55±4.68	179.85±8.70
3DPI Young	131.34±13.58	196.05±22.45
MOCK Aged	64.89±9.63	193.79±31.26
3DPI Aged	134.02±10.71	123.76±11.00

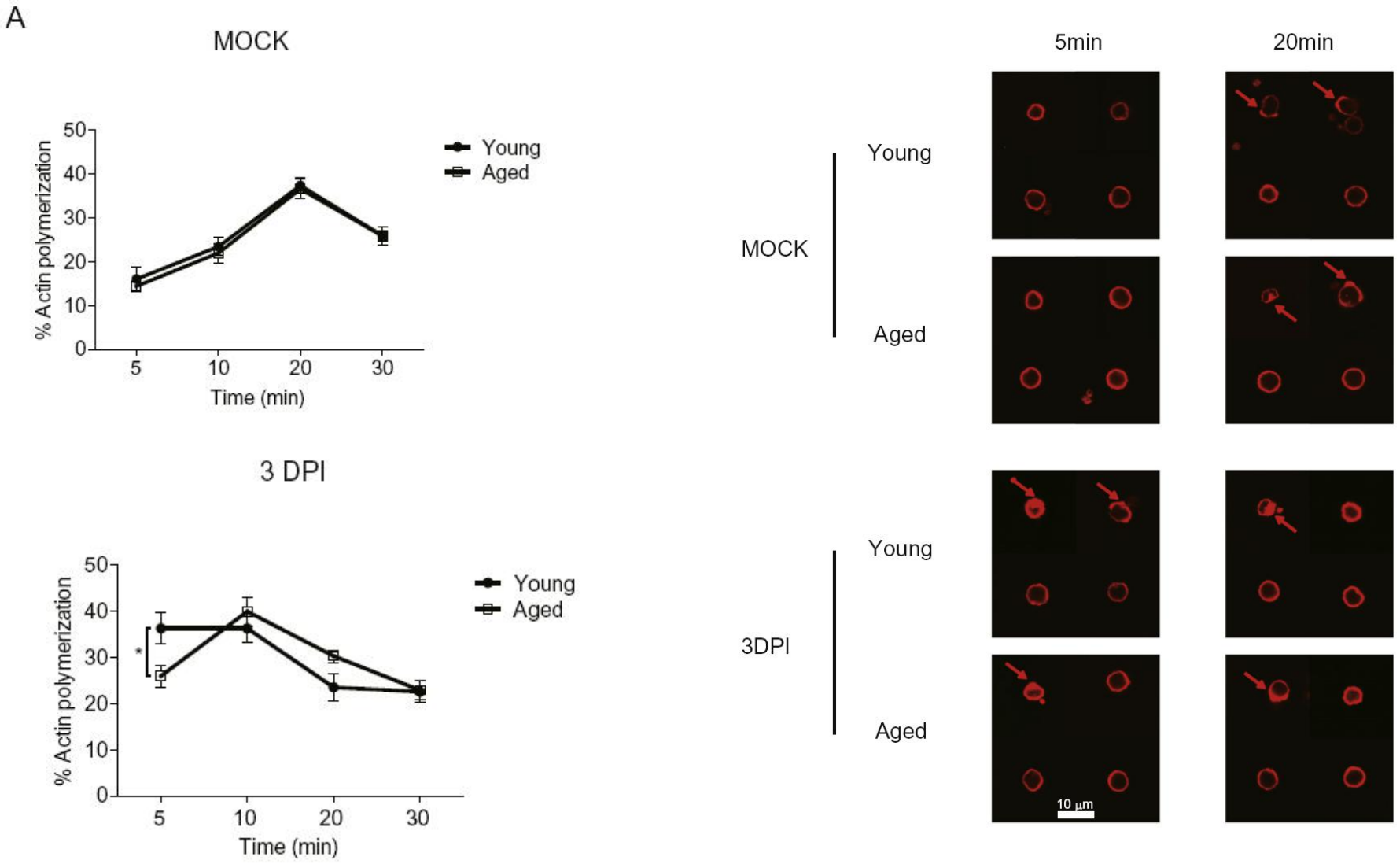
Duan, *et al*. 2017. *Exp Gerontol*

IAV感染后老年小鼠中NK细胞Actins 和 Integrins表达低



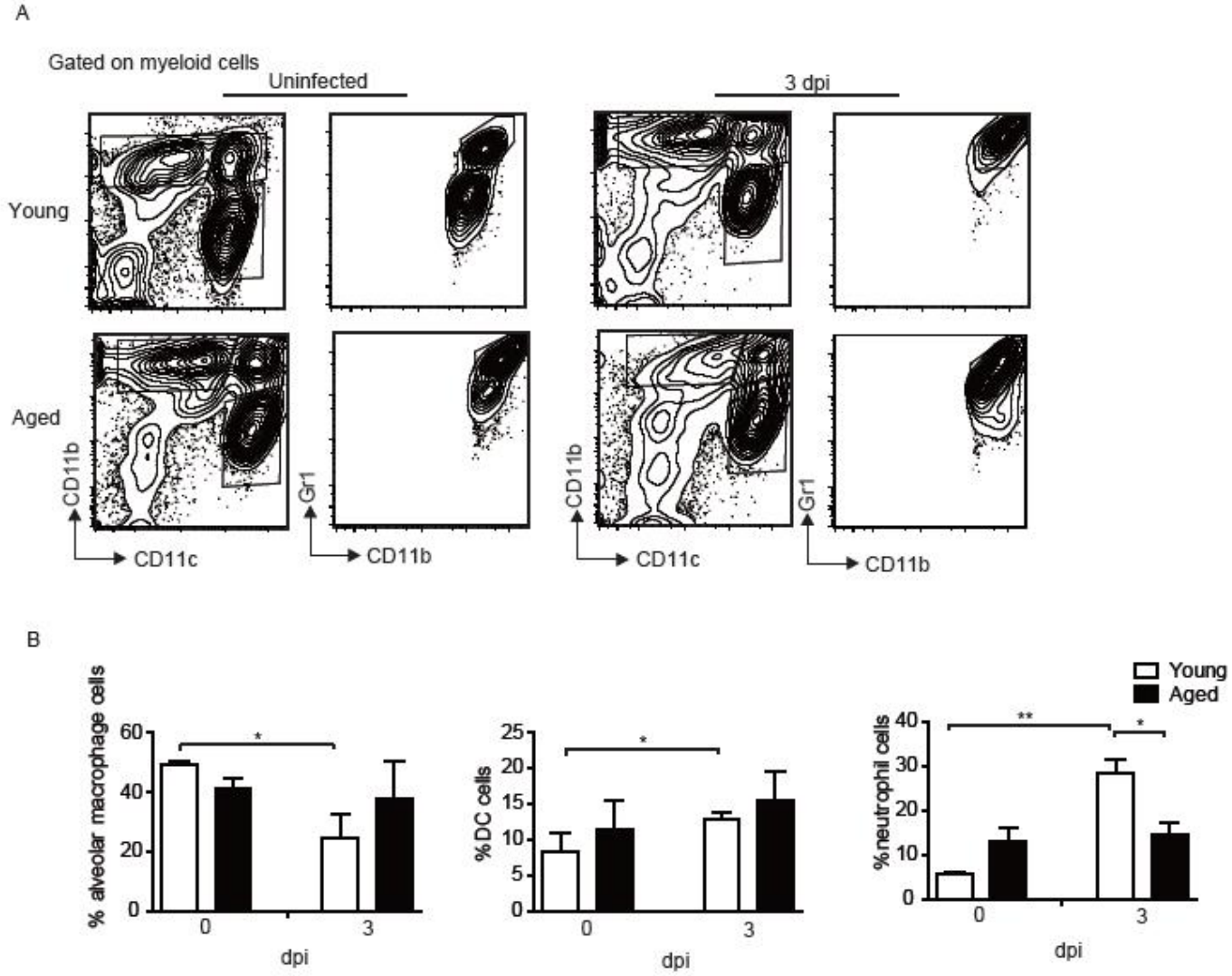
Duan, *et al*. 2017. *Exp Gerontol*

老年NK细胞在IAV感染后Actin Polymerization 存在缺陷



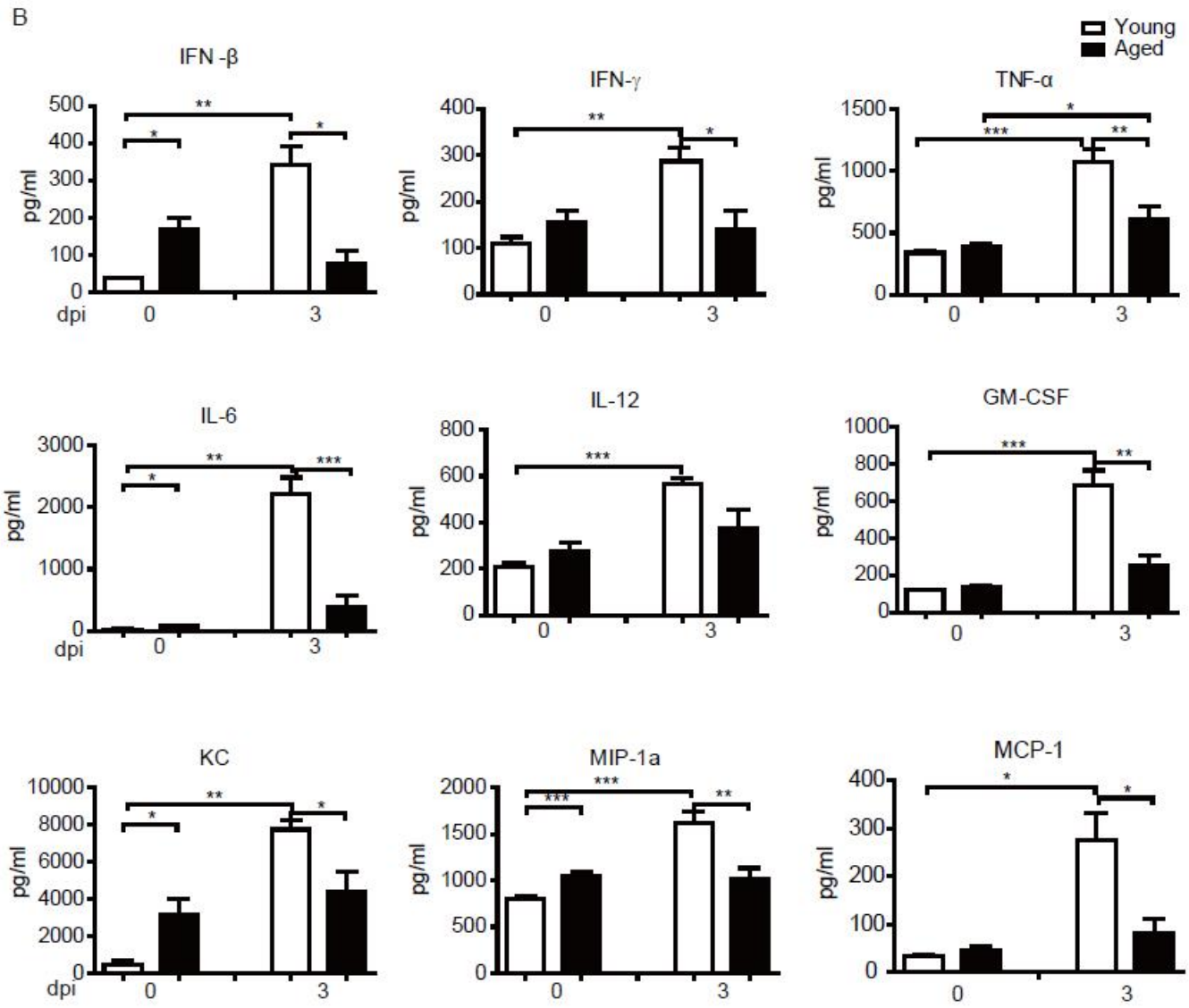
Duan, *et al*. 2017. *Exp Gerontol*

中性粒细胞和DC细胞在老年小鼠肺组织中的聚集减少



Lu, *et al.* Aging Dis, 2018

老年小鼠在感染早期肺部细胞因子和趋化因子水平低



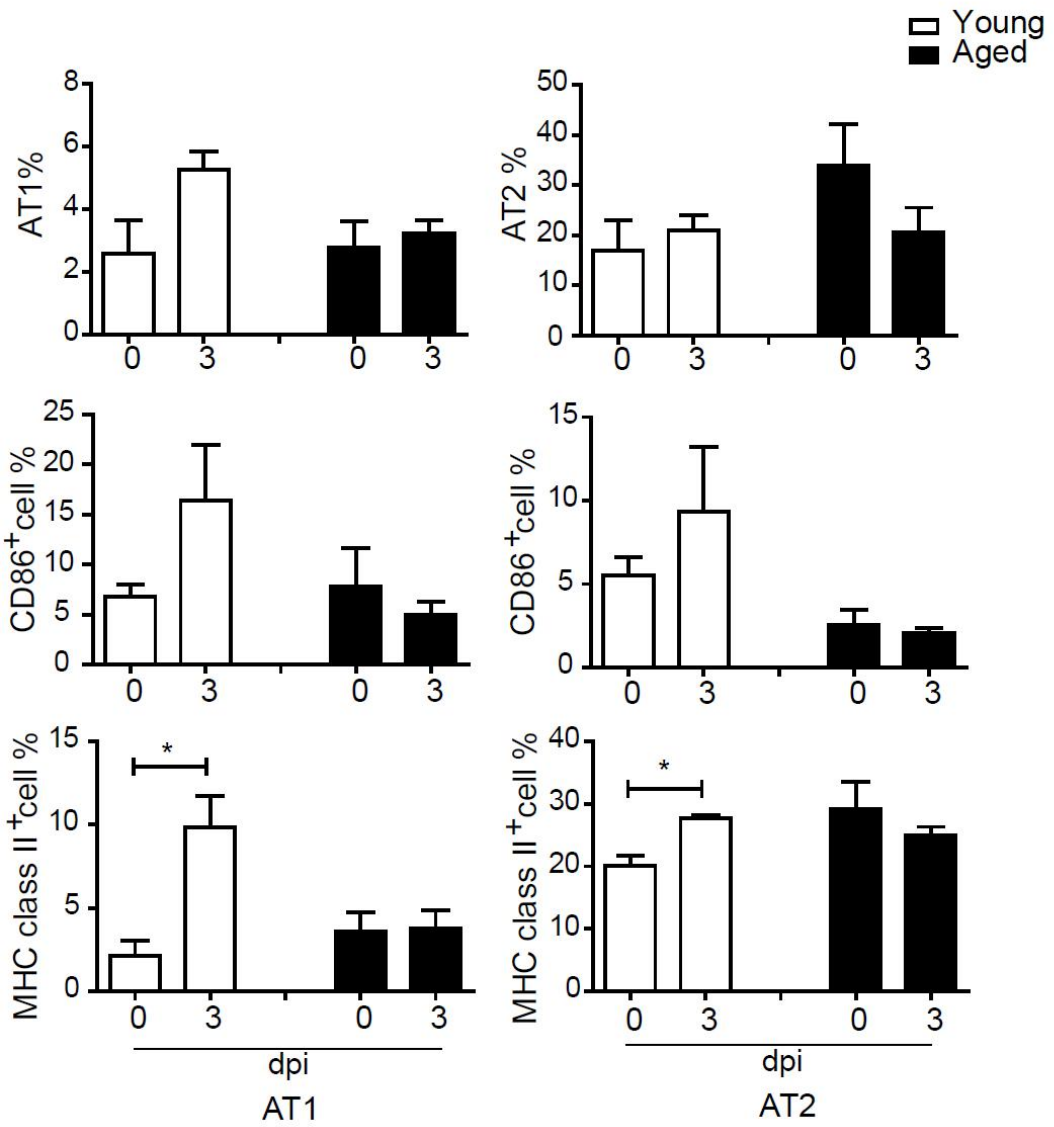
Lu, *et al.* Aging Dis, 2018

小结：

1. 老年小鼠对流感病毒感染的天然免疫应答减弱

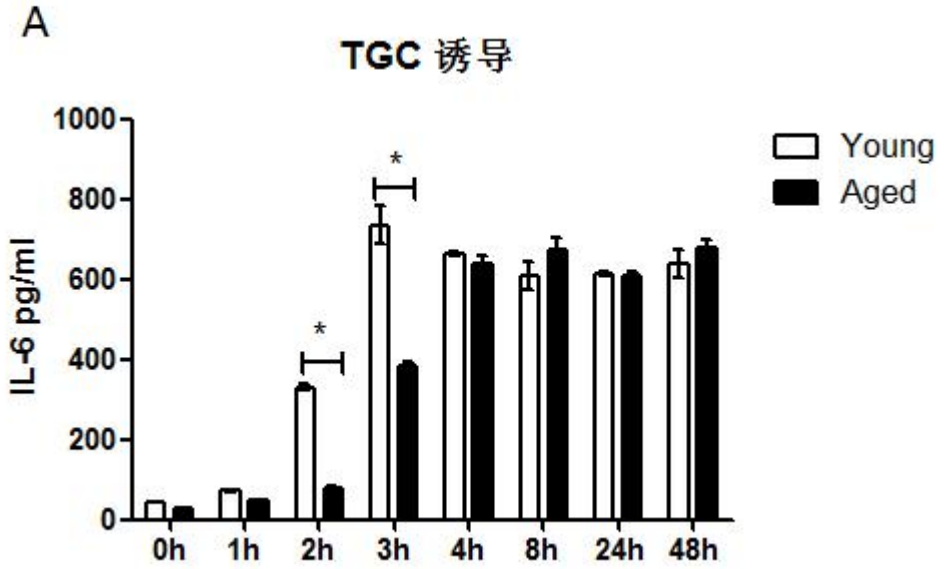
2. NK细胞内源性和淋巴结分泌的趋化因子等外源性因素的双重影响造成老年NK细胞的迁移障碍。

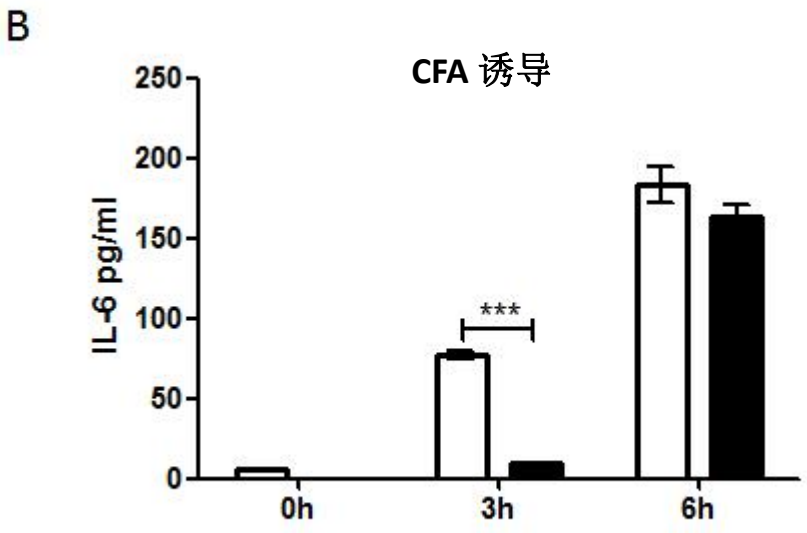
流感病毒感染后肺泡上皮细胞在老年小鼠中呈现不同的变化趋势



Unpublished data

老年小鼠的腹腔巨噬细胞的应答能力低于年轻小鼠

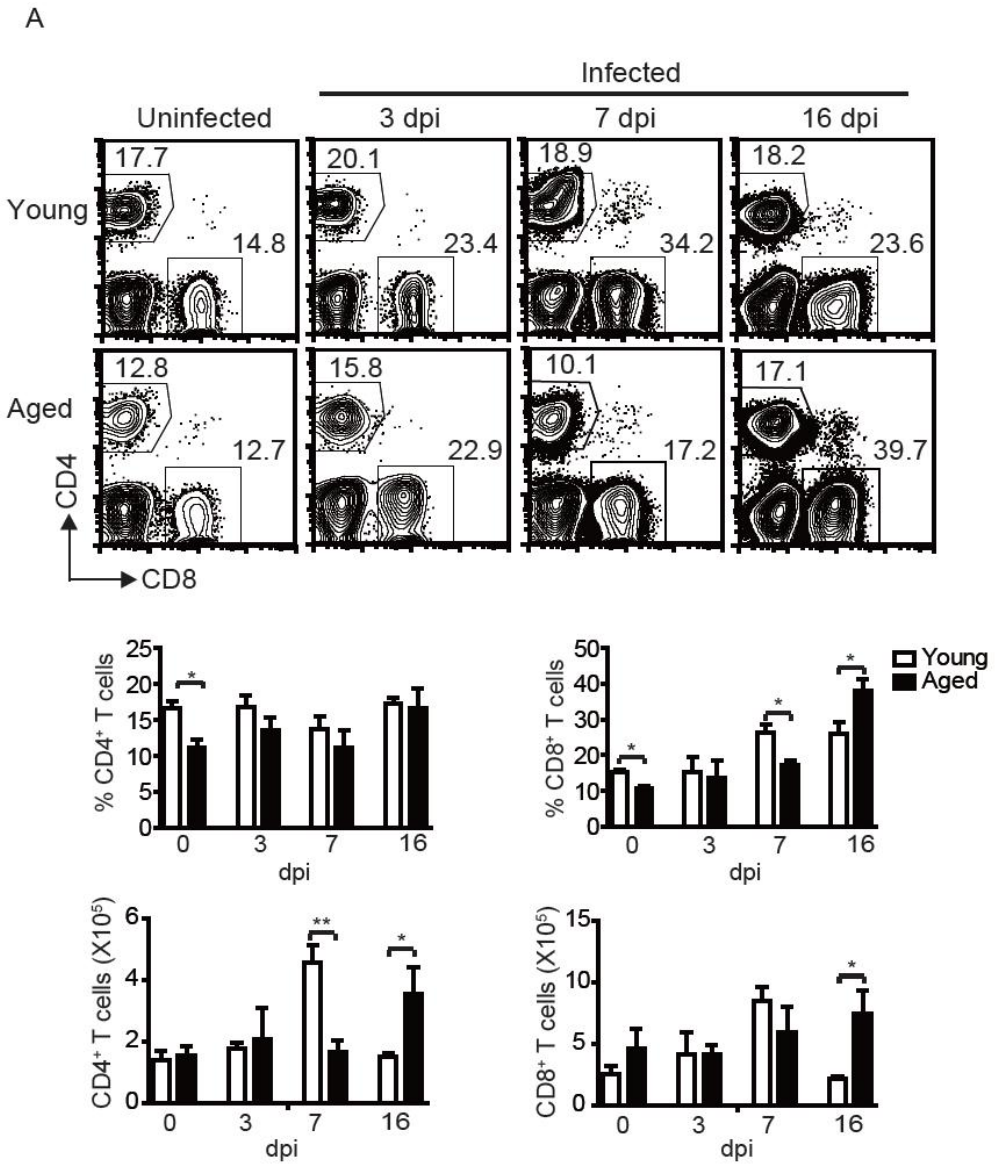




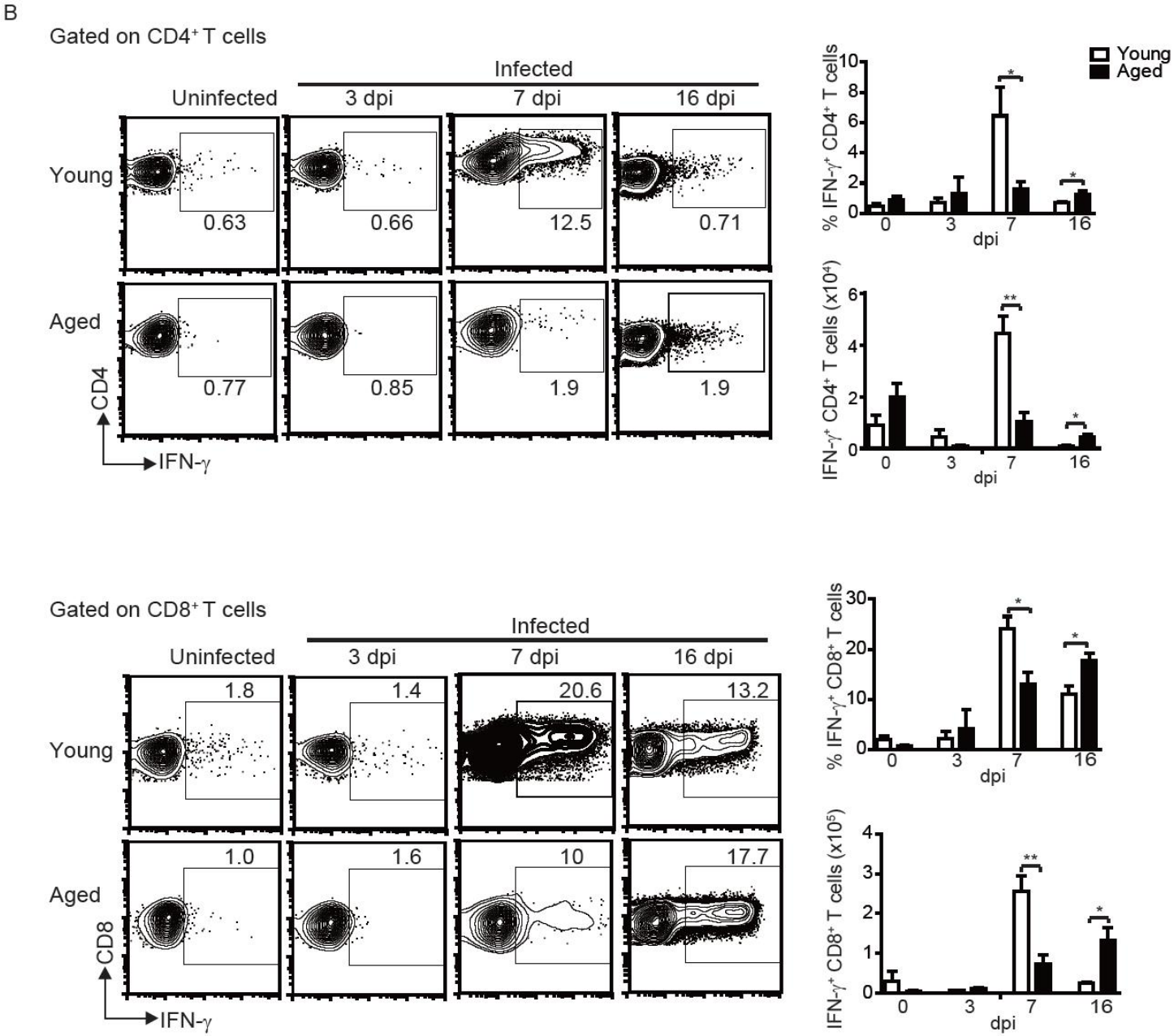
Unpublished data

抗病毒特异性免疫应答？

老年小鼠在IAV感染后T细胞免疫应答降低且滞后

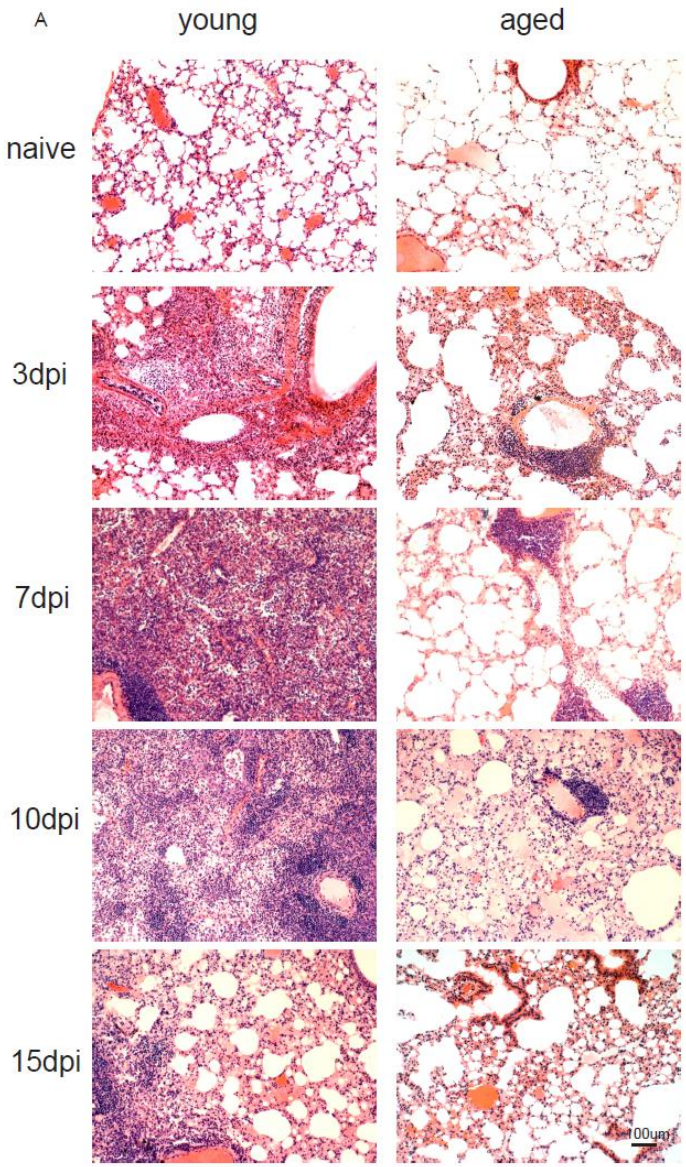


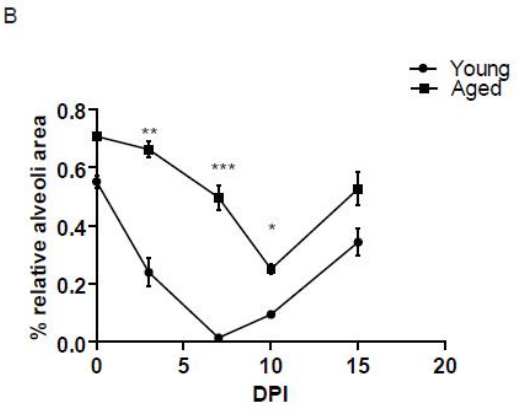
Lu, *et al.* Aging Dis, 2018

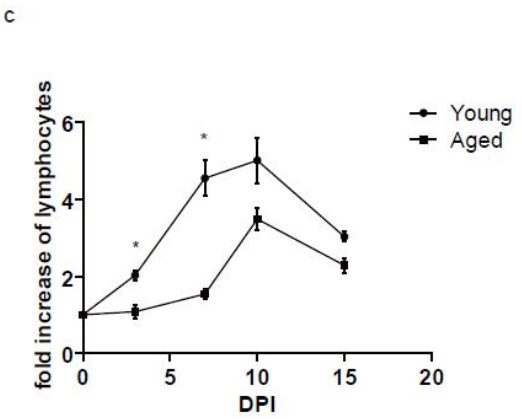


Lu, *et al.* Aging Dis, 2018

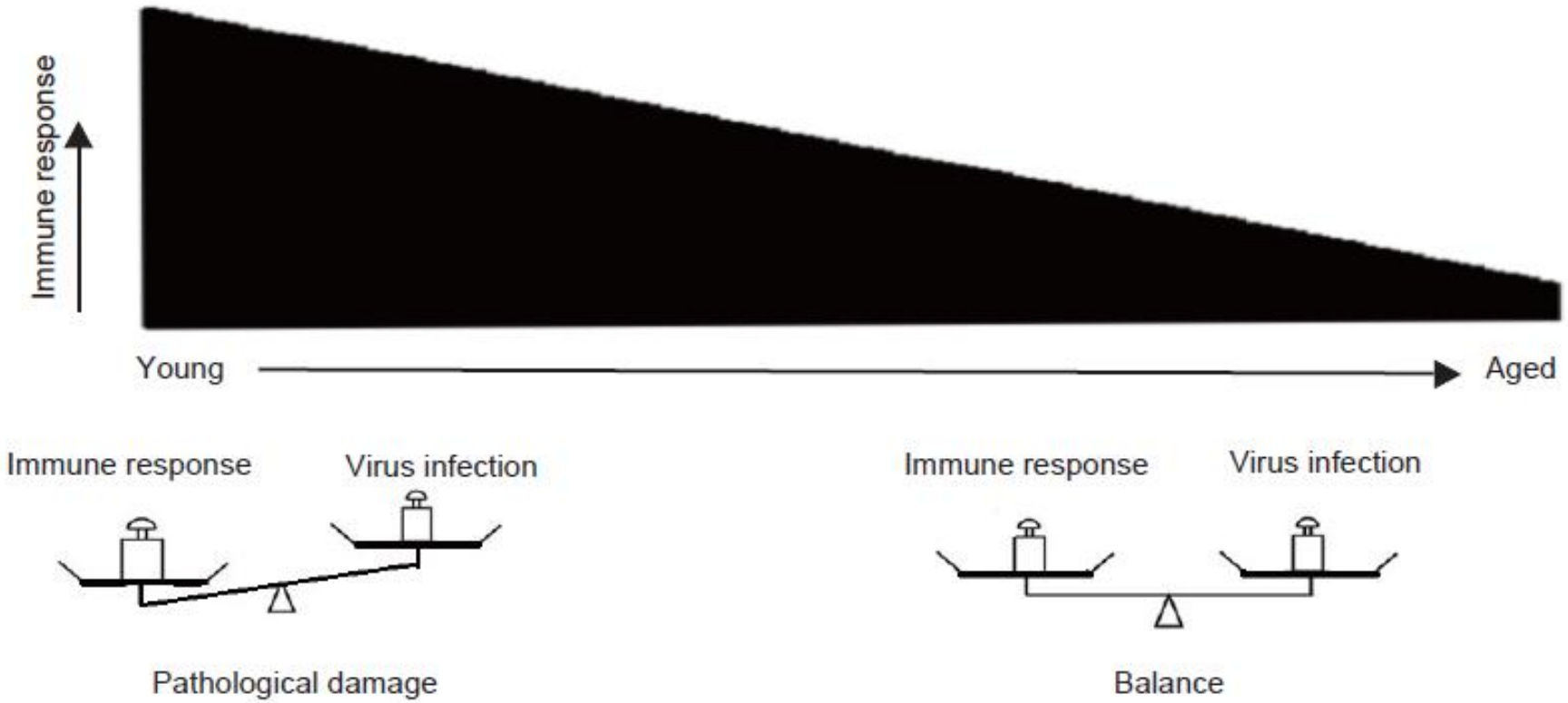
老年小鼠肺部病理损伤显著低于年轻小鼠







Lu, *et al.* Aging Dis, 2018



免疫应答随年龄增大而逐渐降低

Young：快速而强烈的免疫反应造成严重的肺部病理损伤

Aged： 缓慢而温和的免疫反应最终清除病毒且病理损伤较低

Lu, *et al.* Aging Dis, 2018

几点思考：

1. 感染的最终结果取决于病毒毒力、感染路径和宿主的免疫状态

2. 免疫应答是一把双刃剑，既能有效清除病毒同时病理损伤低的免疫应答对宿主最有利

3. 免疫衰老影响到免疫系统的多个方面，整体上免疫应答水平随衰老下降

4. 弱的免疫应答在病毒感染中并不总是坏事，与病毒的毒力、感染路径等密切相关

5. 病毒性疾病的治疗要考虑到患者年龄、免疫状态等因素

致　谢！

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