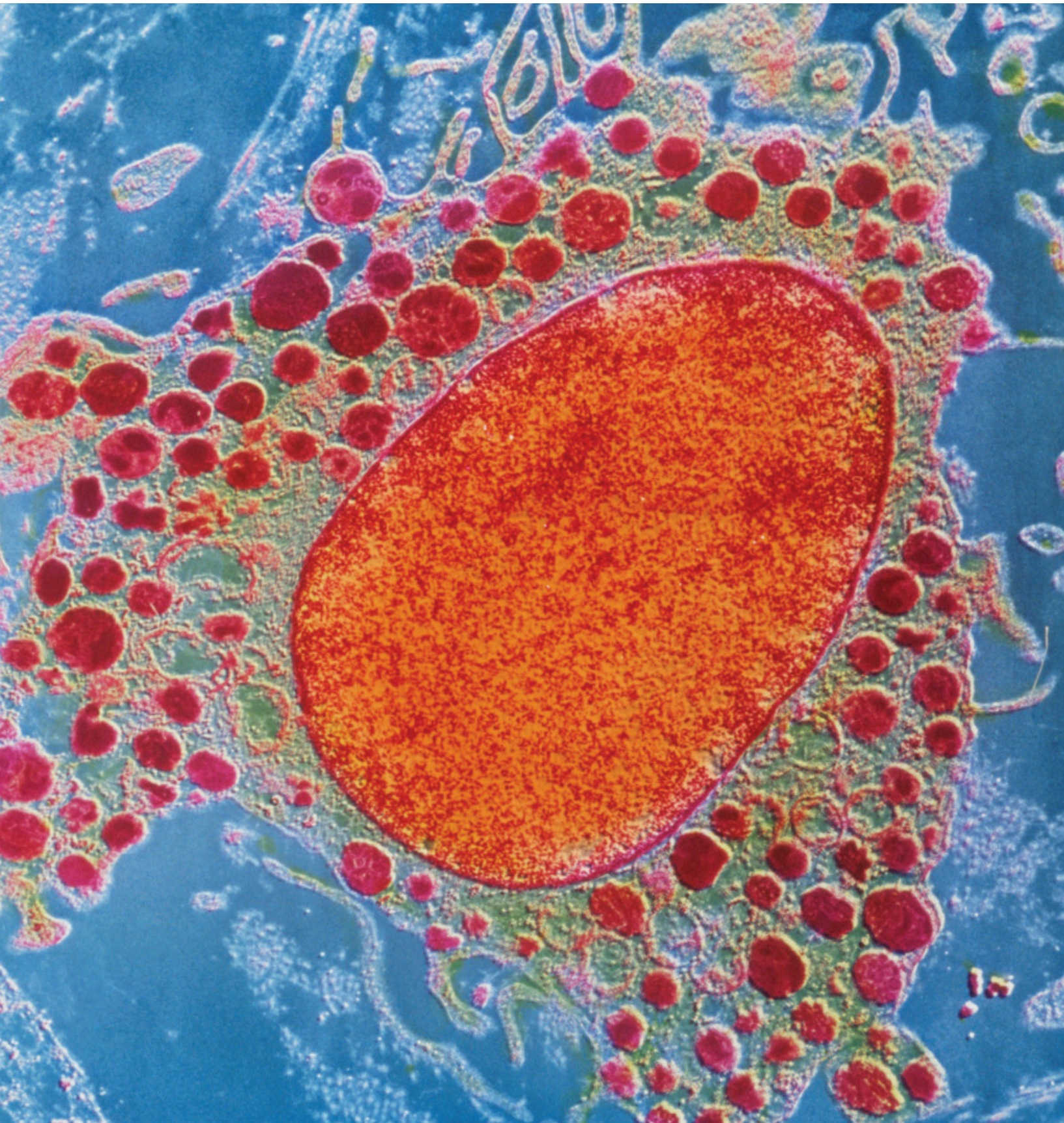
免疫学研究综述

近期以Illumina®技术为特色的免疫学研究论文综述



目录

本文档强调了近期的一些能证明 Illumina 技术在免疫学研究中应用的文献。如欲深入了解本文所引用的平台和检测，请访问 www.illumina.com。

简介

免疫学是开展进入体内的外来或“非自身”物质的识别和处理相关研究。这些物质通常是威胁生命的传染性微生物[1]或癌症[2]，但不幸的是，有时也是挽救生命的移植体[3]。身体也可能受骗，调动针对自身的免疫反应，从而形成自身免疫性疾病。美国国立卫生研究院（NIH）估计，大约 2350 万名美国人患有自身免疫性疾病，且患病率还在上升。[4]近期，关于自身免疫性疾病治疗的进展充分说明了免疫学的进步对人类健康和疾病的影响。

新一代测序技术已被证明是一种强大的工具，能够定位大量的免疫细胞组库，这些细胞能够识别看似无限的目标。[5]免疫组库测序让研究人员能够鉴定那些易患恶性血液病、自身免疫性疾病和过敏的个体中特异性受体变异。[6]这种方法正在迅速引起转化科学家的注意，他们试图改善患者治疗方式。血液病催生了免疫组库测序工作，并证明了免疫组库测序在造血干细胞移植上的可靠性、经济性和医学价值。[7]

主要组织相容性复合物（MHC）是一段编码高度可变的细胞表面蛋白库序列。这些蛋白将外来抗原呈递给 T 细胞。细胞表面分子的编码库实现了免疫识别和外来物质的清除。在实体器官移植[8]和造血干细胞移植[9]时，人们通常评估此位点上的基因，以便将患者与捐赠者相匹配。通过比较健康和患病个体中这些基因的变异，研究人员如今能够阐明疾病易感性的根本原因（即血液学、自身免疫、过敏、超敏、慢性炎症、传染病）。[10]

Illumina 新一代测序的发展为研究界提供了人类免疫反应中所需要的高质量、高通量和长读长的数据，并以高分辨率的形式进行定位。新方法（如 phase-defined 测序和单细胞测序）的出现有望加速该领域的认识。

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4. The Cost Burden of Autoimmune Disease: The Latest Front in the War on Healthcare Spending. 1–14 (www.diabetesed.net/page/_files/autoimmune-diseases.pdf)
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6. Robins H. (2013) Immunosequencing: applications of immune repertoire deep sequencing. Curr Opin Immunol 25: 646-652
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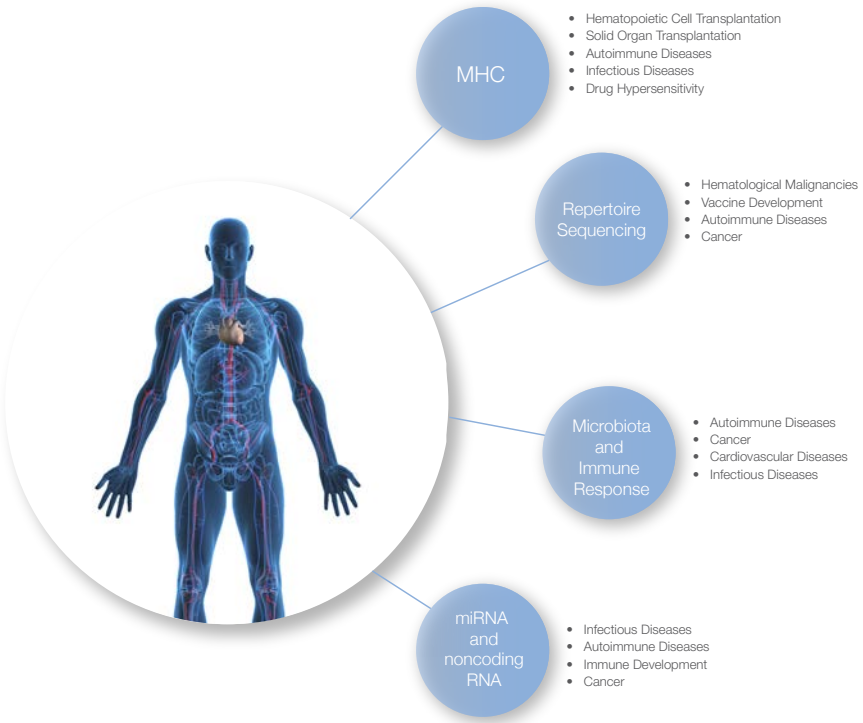

新一代测序让研究人员能够在这些应用（以蓝色表示）中产生重大影响。最右侧的列表表示通过这些应用着手解决的一些人类健康和疾病问题。

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Georgiou G., Ippolito G. C., Beausang J., Busse C. E., Wardemann H., et al. (2014) The promise and challenge of high-throughput sequencing of the antibody repertoire. Nat Biotechnol 32: 158-168

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Bronevetsky Y. and Ansel K. M. (2013) Regulation of miRNA biogenesis and turnover in the immune system. Immunol Rev 253: 304-316

De Santis D., Dinauer D., Duke J., Erlich H. A., Holcomb C. L., et al. (2013) 16(th) IHIW : review of HLA typing by NGS. Int J Immunogenet 40: 72-76

Finn J. A. and Crowe J. E., Jr. (2013) Impact of new sequencing technologies on studies of the human B cell repertoire. Curr Opin Immunol 25: 613-618

Robins H. (2013) Immunosequencing: applications of immune repertoire deep sequencing. Curr Opin Immunol 25: 646-652

Shay T. and Kang J. (2013) Immunological Genome Project and systems immunology. Trends Immunol 34: 602-609

Warren E. H., Matsen F. A. t. and Chou J. (2013) High-throughput sequencing of B- and T-lymphocyte antigen receptors in hematology. Blood 122: 19-22

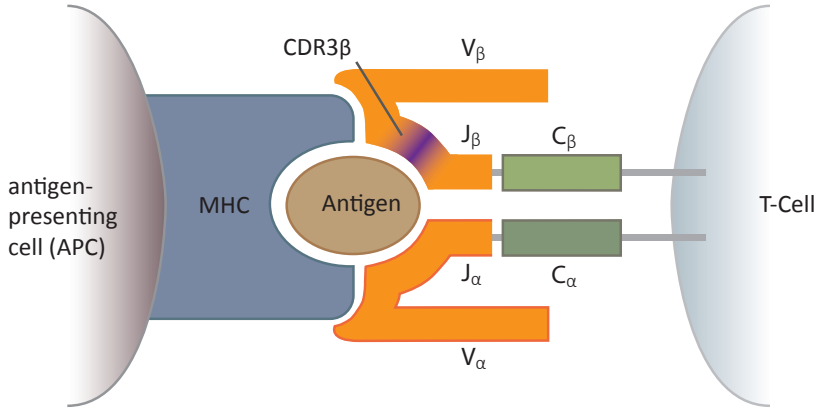
Woodsworth D. J., Castellarin M. and Holt R. A. (2013) Sequence analysis of T-cell repertoires in health and disease. Genome Med 5: 98

适应性免疫

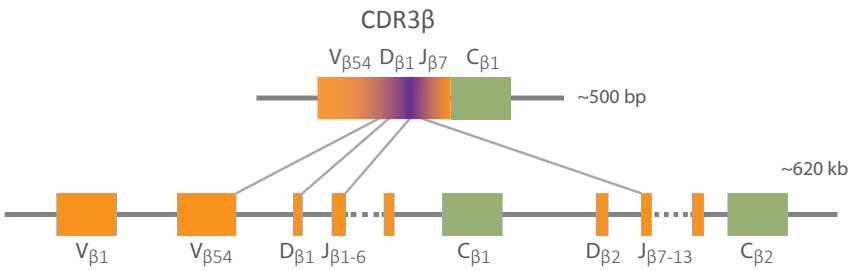
淋巴细胞受体的免疫组库测序

B 细胞和 T 细胞构成了免疫系统的适应性分支，并能够鉴定种类繁多的抗原。B 细胞和 T 细胞受体上免疫球蛋白分子的独特组合形成了这个多样的识别元件库。抗原的成功识别引发了效应应答以及记忆应答。效应应答包括 CD8+ T 细胞，它们清除外来抗原的细胞，以及 CD4+ T 细胞，它们分化成几种不同类型的效应细胞，包括那些能进一步激活巨噬细胞、细胞毒性 T 细胞和 B 细胞的细胞。[11,12]B 细胞的效应应答涉及到浆细胞，它们分泌抗体，能够中和或清除外来物质。[13] 当 B 细胞和 T 细胞暴露在外来抗原下而被激活时，记忆应答发生。[14] 这些细胞的激活导致特定抗原受体的增殖和保存，这使得二次暴露在外来抗原下产生了强大的免疫反应。[15]

与体细胞相比，B 细胞和 T 细胞是独特的，其发育和成熟是由生殖细胞系中未编码的 DNA 序列决定的。相反，在成熟过程中，这些细胞经历了可变区（V）、多样区（D）和接合区（J）基因片段的重排，以便形成独特的序列，这些序列编码 B 细胞免疫球蛋白的重链、αβ T 细胞受体的 β 链和 γδ T 细胞受体的 δ 链的受体结构。



T 细胞受体 - 抗原 - 肽段 -MHC 相互作用和 T 细胞受体（TCR）基因重排。(a) 抗原呈递细胞呈递结合到主要组织相容性复合物（MHC）上的肽段抗原。TCR（橙色）与抗原和 MHC 结合。如果结合亲和力足够高，则 T 细胞被激活。互补决定区 3（CDR3）结构域以紫色显示。[16]



TCR-β VDJ 基因重排导致 TCR 多样性简图。TCR-β 基因座位于 7 号染色体上，长度约为 620 kb。最初两个 D 区域中的一段序列与 13 个 J 区域中的一段序列（两个都随机选择）连接，接着将 DJ 区域与 50 多个 V 区域中的一段序列（也是随机选择）连接，产生最终的 VDJ 区域，其长度约为 500 bp。基因片段连接的机制也引入了 bp 多样性，这与片段的组合选择一起带来 TCR 多样性。一个完全类似的过程也发生在 TCR α 链上，但不包括 D 基因片段。

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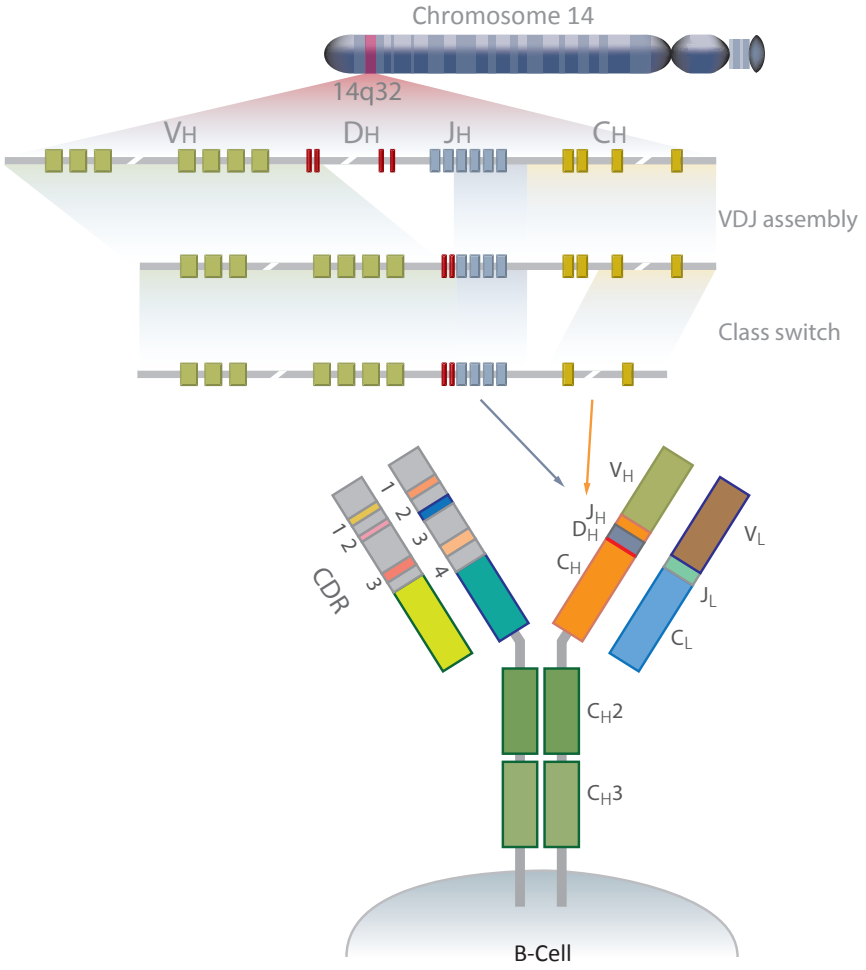
B 细胞中的 VDJ 重排产生了免疫球蛋白分子的可变重链。这种免疫分子表达在 B 细胞的表面，也可作为抗体分泌。



抗体重链库主要是由可变区 (V)、多样区 (D) 和接合区 (J) 基因片段的体细胞重排形成的。非模板核苷酸（以红色表示）也可加入。重链的抗原结合位点是由高变互补决定区（CDR-H1、H2 和 H3）和骨架区 3（FR3）的并列形成的。在 IgH 重排后，轻链（IgL）的重排也随之而来，H 和 L 链的异源二聚体形成 IgM 同型的完整抗体，此抗体新形成的未成熟 B 细胞的表面进行表达。[17]

除了上述的组合多样性，由 V、D 和 J 基因片段的重排也可能发生，剪接变体也促进了这种多样性，它在 V-D、D-J 和 V-J 剪接点产生模板不依赖的核苷酸插入和缺失。[18] 库的大小也在 B 细胞受体中进一步增加，通过初次遇到抗原后亲和力成熟过程中 B 细胞受体基因的体细胞超突变（SHM）。

这一重排机制有望在人体中产生超过 1018 个独特的 T 细胞受体以及更多样的 B 细胞库。[19,20] 据估计，人的整个 VDJ 区域的长度在 300-400 个核苷酸，这让高通量测序的读长成为关键参数。[21,22,26]

互补决定区（CDR）是抗体或 T 细胞受体中与抗原性状互补的区域。在 3 个互补决定区中，CDR3 区变化最大，也是最关键的抗原特异性决定因素。[23-26] 大多数重排的功能性 TCR β 和免疫球蛋白重链中 CDR3 区域的长度在 66[21,27] 至 90[22] bp。因此，1 x 109 的测序深度成功鉴定出整个 B 细胞和 T 细胞库。

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免疫组库测序能够应用于鉴定造血干细胞移植后 B 细胞和 T 细胞库的重构，追踪恶性血液病中的淋巴细胞，评估疫苗效力，鉴定与自身免疫性疾病相关的淋巴细胞库变异，以及鉴定癌症（如结肠直肠癌）中的淋巴细胞受体变异 [29,30]。

综述

Georgiou G., Ippolito G. C., Beausang J., Busse C. E., Wardemann H., et al. (2014) The promise and challenge of high-throughput sequencing of the antibody repertoire. Nat Biotechnol 32: 158-168

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Benichou J., Ben-Hamo R., Louzoun Y. and Efroni S. (2012) Rep-Seq: uncovering the immunological repertoire through next-generation sequencing. Immunology 135: 183-191

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作者鉴定出重排的 T 细胞受体基因中可变的 CDR3 区域的序列特征，这些特征可将 CD4+ 与 CD8+ T 细胞区分开，包括所选取的可变基因和 CDR3 区域的长度。他们预计，至少需要 1000 条 T 细胞受体序列，才能准确估计 CD4+ 和 CD8+ T 细胞的比例。

Illumina 的技术：HiSeq 2000

Putintseva E. V., Britanova O. V., Staroverov D. B., Merzlyak E. M., Turchaninova M. A., et al. (2013) Mother and child T cell receptor repertoires: deep profiling study. Front Immunol 4: 463
作者对 3 位母亲和 6 位孩子的 TCR 库开展比较分析。在有或没有亲缘关系的配对中，胸腺选择决定了 TCR 重组机制的初始产出，而遗传差异的影响很小。以 TCR β CDR3 变异作为克隆标识符的 TCR 分析也表明，成熟的 T 细胞，在怀孕期间通过胎盘转移，可在它们新宿主中作为功能性的微嵌合克隆而扩增和维持。

Illumina 的技术：HiSeq 2000

Meier J., Roberts C., Avent K., Hazlett A., Berrie J., et al. (2013) Fractal organization of the human T cell repertoire in health and after stem cell transplantation. Biol Blood Marrow Transplant 19: 366-377

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实验设计的注意事项

CDR3 测序的主要挑战在于 PCR 错误、测序错误和比值偏好性的积累。这些因素可能导致虚假的 TCR 多样性（人工多样性），以及无法准确解释序列信息。例如，产生更多的测序 reads 可能导致带一个、两个或更多错配的错误序列变异的扩增。这些扩增的错误可能被解释为序列多样性的证据。[31,32]

为了解决人工多样性，之前的研究建议撤出低丰度的 CDR3 变异，它们与高丰度的变异只有单个核苷酸错配，或消去低丰度的序列变异，它们在所有的测序 reads 中占 4%。研究表明，这种方法会导致高达 50% 的测序 reads 损失，而在非 Illumina 平台损失更多。[33]

为了避免 PCR 和测序错误，文献中提出了下列建议。[34]

- 将每条序列与 IMGT/GENE-DB 数据库中的基因组 VDJ 片段比对，提取出每个测序 read 的 CDR3。VDJ 片段中低质量的核苷酸被视为可允许的错配。
- 定位低质量的 reads。CDR3 中每个核苷酸位置的高质量序列形成“核心克隆型”。这些与低质量核苷酸≤ 3 的低质量序列 reads 合并。
- 校正 PCR 错误。考虑到 TCR 不经历体细胞超变异，CDR3 中 VD 或 J 片段的核苷酸错配只能来源于 PCR 和测序错误。低丰度的核心克隆型与较高丰度（丰度至少高 5 倍）的核心克隆型合并，它们之间相差不超过 3 个碱基。

mRNA 是 TCR 分析中理想的起始材料。[35]

- T 细胞包含多个拷贝的 RNA 分子，它们编码 β 和 α 链。这些拷贝打破了采样 T 细胞与最终 TCR 扩增子之间的瓶颈。
- 鉴于基因组 DNA 需要扩增整个样本才能计算 TCR 库，这在技术上颇具挑战性，特别是在研究相当大的 T 细胞群体时，这需要非常大的量。

31. Warren R. L., Freeman J. D., Zeng T., Choe G., Munro S., et al. (2011) Exhaustive T-cell repertoire sequencing of human peripheral blood samples reveals signatures of antigen selection and a directly measured repertoire size of at least 1 million clonotypes. Genome Res 21: 790-797
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单细胞组库测序

免疫球蛋白可变区和 T 细胞受体库的分析对于我们了解健康和疾病中的适应性免疫很重要。[36] 然而，绝大多数的库研究都来自于免疫受体上两条链中的一条的数据，因而不能提供由单个 B 细胞或 T 细胞所编码的天然受体对特性的信息。[37,38]

噬菌体和酵母展示技术，[39-41] 尽管能有效分离抗原特异的抗体，但依赖随机配对，不能提供链天然配对的信息。那些涉及到淋巴细胞克隆的培养，[42] 或抗原特异 T 细胞 [43] 或 B 细胞 [44] 群体的分选的方法，受限于可鉴定的克隆数量，以及生物样本的复杂度。

解决这一问题的新方法利用了新一代测序的灵敏度，对单个细胞测序，并在单个实验中鉴定多个天然的 TCR 链配对。[45]

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之前研究显示，B 细胞库多样性的 VH:VL 配对在 B 细胞群体的裂解过程中丢失。在此，作者采用单细胞 mRNA 捕获、逆转录和扩增的方法，开展配对的 VH:VL 链 emulsion RT-PCR。这些配对经过测序，以鉴定健康外周血的 IgG+ B 细胞、接种破伤风类毒素后分离的抗原特异的外周浆母细胞以及接种流感疫苗后的记忆性 B 细胞应答中独特的抗体克隆型。

Illumina 的技术：MiSeq 2 x 250 bp

Turchaninova M. A., Britanova O. V., Bolotin D. A., Shugay M., Putintseva E. V., et al. (2013) Pairing of T-cell receptor chains via emulsion PCR. Eur J Immunol 43: 2507-2515

作者提出一种单细胞方法，以鉴定乳滴中 α-β T 细胞受体（TCR）CDR3 链的天然配对，这种方法采用 α 和 β 链的逆转录、PCR 扩增以及随后重叠延伸而融合。这种 PCR 抑制技术解决了基因对的随机重叠延伸，它们有可能造成 emulsion 阶段后的高噪音。作者提出，这种方法可用于鉴定可变的抗体重 - 轻链的天然配对。

Illumina 的技术：MiSeq 2 x 150 bp

Han A., Newell E. W., Glanville J., Fernandez-Becker N., Khosla C., et al. (2013) Dietary gluten triggers concomitant activation of CD4+ and CD8+ alphabeta T cells and gammadelta T cells in celiac disease. Proc Natl Acad Sci U S A 110: 13073-13078

乳糜泻是一种由食物中的麸质和麸质特异的 CD4+ T 细胞反应而引起的肠道自身免疫性疾病。麸质暴露也诱导外周血中出现激活、肠道归巢的 CD8+ αβ 和 γδ T 细胞。单细胞的 T 细胞受体序列分析表明，这两种细胞群体都有着高度集中的 T 细胞受体库。这种集中的库通常表明诱导是由抗原驱动的。

Illumina 的技术：MiSeq 双端测序

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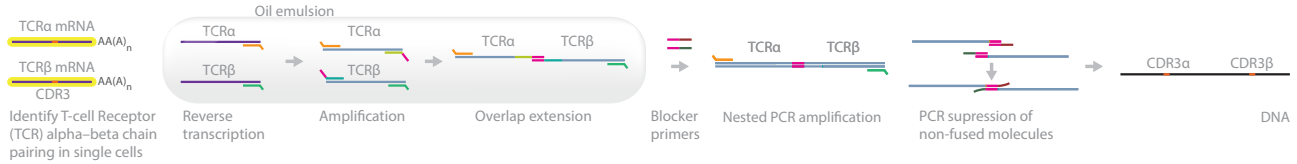
46. Turchaninova M. A., Britanova O. V., Bolotin D. A., Shugay M., Putintseva E. V., et al. (2013) Pairing of T-cell receptor chains via emulsion PCR. Eur J Immunol 43: 2507-2515

TCR Chain Paring



基于细胞的 emulsion RT-PCR 技术用于鉴定 TCR α-β 链配对。释放的 TCR α 和 β mRNA 在每个液滴内经过逆转录、扩增和重叠延伸。从 emulsion 和融合分子中提取出的产物经过选择性扩增。未融合的分子被阻断引物所抑制。[46]

淋巴细胞发育

T 细胞发育

多潜能或淋巴偏向的前体细胞进入 T 细胞发育通路，应答来自胸腺微环境的信号。[47] 研究表明，通常与胚胎细胞发育相关的 Notch 是 T 细胞谱系决定中重要的引发器。胸腺中的 Notch 信号导致造血前体细胞并决定 T 细胞的命运，调动 T 细胞的基因表达程序，让细胞为 T 细胞抗原受体（TCR）做准备，基于 TCR 的库选择，并最终为免疫效应分子的功能作用做准备。[48]

关于这一决定的分子机制，目前还有许多问题。例如，进入胸腺的前体细胞显示或表达或诱导的调控基因，然而一旦决定，这些基因不仅被抑制，还被不可逆地沉默。[49]

其他问题涉及到 T 细胞成功发育过程中的多个调控需求。例如，需要阐明更多转录因子的功能作用，包括 E2A 和 HEB、TCF-1 和 LEF-1、GATA-3、Myb、Runx1、Ikaros 和 Gfi1。[50]

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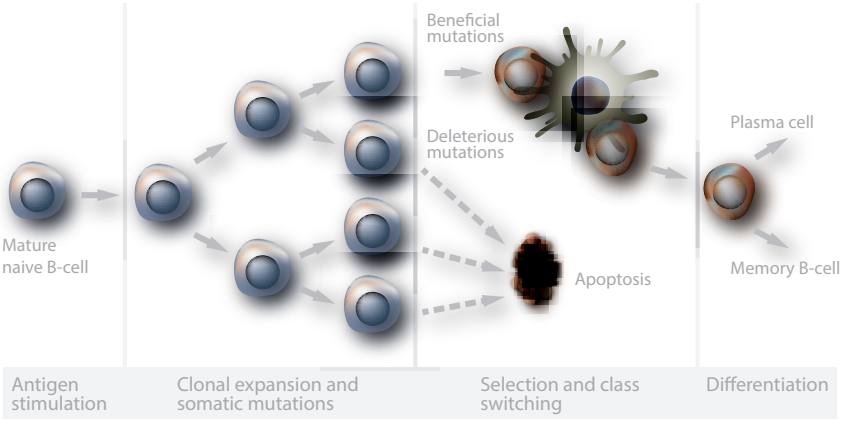

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Vigano M. A., Ivanek R., Balwierz P., Berninger P., van Nimwegen E., et al. (2013) An epigenetic profile of early T-cell development from multipotent progenitors to committed T-cell descendants. Eur J Immunol

在这项研究中，作者分析和比较了不同发育阶段的 T 细胞的基因表达谱和全基因组的组蛋白修饰标记 H3K4me3（H3 赖氨酸 4 三甲基化）和 H3K27me3（H3 赖氨酸 27 三甲基化）。他们观察到基因表达的整体变化以及启动子区 H3K4me3 和 H3K27me3 的表观遗传图谱。

Illumina 的技术：Genome Analyzer 用于 ChIP-Seq 分析

Vahedi G., Takahashi H., Nakayamada S., Sun H. W., Sartorelli V., et al. (2012) STATs Shape the Active Enhancer Landscape of T Cell Populations. Cell 151: 981-993

作者利用辅助性 T 细胞 Th1 和 Th2 中的高 H3K4me1 和高 p300 区域来定位增强子的活性，以研究活性的增强子库。他们利用辅助性 T 细胞的 RNA-Seq 转录组图谱分析，来鉴定每个亚群中前 100 个差异表达的基因，并开展野生型和 STAT 缺陷型细胞的比较分析，以评估正调控基因的 STAT 依赖性。他们还利用 ChIP-Seq 来证明 STAT 缺陷型细胞不能完全恢复 STAT 依赖的增强子染色体特征。总的来说，这些研究结果表明，STAT 蛋白在塑造专门的增强子结构中发挥了直接和间接的作用。

Illumina 的技术：Genome Analyzer$_{IIx}$ 用于 ChIP-Seq，HiSeq 2000 用于 RNA-Seq，100 个循环（单端）。RNA-Seq 的文库是利用 TruSeq 样本制备试剂盒制备的

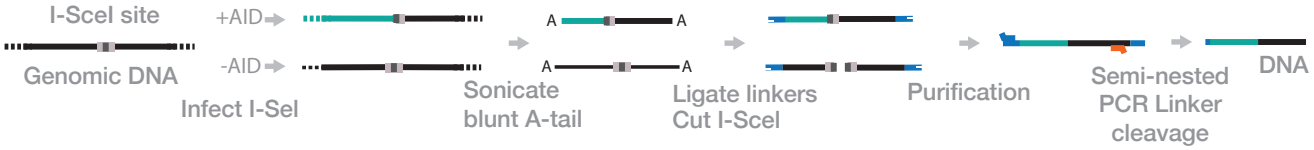
Zhang J. A., Mortazavi A., Williams B. A., Wold B. J. and Rothenberg E. V. (2012) Dynamic Transformations of Genome-wide Epigenetic Marking and Transcriptional Control Establish T Cell Identity. Cell 149: 467-482

Notch 通路信号促进造血前体细胞并决定 T 细胞的命运，并让细胞准备好 TCR 的表达和基于 TCR 的库选择。作者采用 RNA-Seq 和 ChIP-Seq 来鉴定转录和表观遗传标记的动态变换，这些标记发生在 T 细胞分化的五个阶段，跨越谱系定型（FLDN1、FLDN2a、FLDN2b、ThyDN3 和 ThyDP 细胞）。他们报道称，导致 T 细胞谱系的主要全基因组转录变化发生在向 DN2b 或 DN3 的转化时期；因而，在决定和 β- 选择阶段。作者还利用 ChIP-Seq 来富集与三种 H3 修饰（H3K(9,14)Ac、H3K4me2 和 H3K27me3）相关的 DNA。他们利用潜在的顺式调控元件上组蛋白标记模式在体内追踪 GATA-3 和 PU.1 的数据，这些转录因子，在早期 T 细胞发育中有互补作用，并表明潜在位点上这些转录因子对不同细胞亚群的功能具有相关性。

Illumina 的技术：Genome Analyzer 用于 RNA-Seq 和 ChIP-Seq

Malinge S., Thiollier C., Chlon T. M., Doré L. C., Diebold L., et al. (2013) Ikaros inhibits megakaryopoiesis through functional interaction with GATA-1 and NOTCH signaling. Blood 121: 2440-2451

Genolet R., Stevenson B. J., Farinelli L., Osteras M. and Luescher I. F. (2012) Highly diverse TCRalpha chain repertoire of pre-immune CD8(+) T cells reveals new insights in gene recombination. EMBO J 31: 1666-1678



易位捕获测序（TC-Seq）是一种为研究染色体重排和易位而开发的方法。在这种方法中，细胞被表达 I-SceI 位点的逆转录病毒感染，这些细胞带或不带活化诱导胞苷脱氨酶（AICDA 或 AID）蛋白。细胞的基因组 DNA 经过超声处理、接头连接、纯化，并通过半巢式 LM-PCR 扩增。随后切割接头，对 DNA 进行测序。任何 AID 依赖的染色体重排都将通过 LM-PCR 扩增，而 AID 不依赖的易位将被丢弃。

B 细胞发育

当成熟的 B 细胞遇到抗原时，它们经历了一个程序化的 DNA 重排过程，称为类别转换重组（CSR），这改变了抗体分子的效应子功能。在类别转换中，通过引入双链断裂（DSB）及随后插入序列的删除，一个恒定区基因（通常是 Cμ）被另一个（Cγ3、Cγ1、Cγ2b、Cγ2a、Cε 或 Cα 中的任一个）所取代。[51-53]

在 B 淋巴细胞中，V(D)J 重排、类别转换重组（CSR）和体细胞超变（SHM）产生单链和双链 DNA 断裂中间体，可称为易位底物。[54,55] 这些重排可能引发癌症。[56] 支持这一观点的是那些在 V(D)J 重排（RAGs）或 CSR 和 SHM（AID）期间创建 DNA 损伤的酶的基因消融，这对 B 细胞转化有着明显的保护作用。[50,57]

核构造是染色体易位发生的另一潜在贡献者。[59] 基因组的空间结构被划分成染色体领域以及转录活性和沉默的亚核环境。[60-63] 这些区域被认为会影响不同染色体的基因相互作用和重组的频率。[64]

综述

Robbiani D. F. and Nussenzweig M. C. (2013) Chromosome translocation, B cell lymphoma, and activation-induced cytidine deaminase. Annu Rev Pathol 8: 79-103

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Holwerda S. J., van de Werken H. J., Ribeiro de Almeida C., Bergen I. M., de Bruijn M. J., et al. (2013) Allelic exclusion of the immunoglobulin heavy chain locus is independent of its nuclear localization in mature B cells. Nucleic Acids Res 41: 6905-6916

染色质构象是调控基因表达的多个机制之一。在发育的 B 细胞中，免疫球蛋白重链（IgH）位点经历 V、D 和 J 基因片段的既定基因组重排。在这项研究中，作者采用等位基因特异的染色体构象捕获测序技术（4C-Seq），来追踪成熟 B 细胞中的单个 IgH 等位基因。作者发现，IgH 拥有淋巴特异的核位置，而在成熟的 B 细胞中，IgH 等位基因位置远端的 VH 区域远离活性染色质。

Illumina 的技术：Genome Analyzer*IIx*，HiSeq 2000

Hakim O., Resch W., Yamane A., Klein I., Kieffer-Kwon K. R., et al. (2012) DNA damage defines sites of recurrent chromosomal translocations in B lymphocytes. Nature 484: 69-74

作者开展了染色体构象捕获实验和深度测序（4C-Seq），以鉴定在空间上与 Igh 和 Myc 接近的基因组区域，这些区域转录活跃并被 AID 靶定。通过染色体构象捕获芯片（4C-Seq）图谱与全基因组的表观遗传、转录和 TC-Seq 数据集比较，作者得出结论，在 AID 缺乏的外周 B 细胞中，Igh 和 Myc 位点与表观遗传上可接近的基因组位点关联更为紧密。他们还采用了一种新的 ChIP-Seq 形式，称为 RPA-S，来测定活化 B 细胞中复制蛋白 A（RPA）的获得。他们利用 RPA 作为 AID 介导的 DNA 损伤替代过程，表明 DNA 损伤的频率直接解释了易位的比率。

Illumina 的技术：Genome Analyzer*IIx* 用于双端 4C-Seq 和 ChIP-Seq

Rocha P. P., Micsinai M., Kim J. R., Hewitt S. L., Souza P. P., et al. (2012) Close proximity to Igh is a contributing factor to AID-mediated translocations. Mol Cell 47: 873-885

大约 95% 的淋巴瘤是来源于 B 细胞，其中许多都被认为是异常重排所致，这些重排是由活化诱导胞苷脱氨酶（AID）介导的 Igh 位点外断裂而产生的。作者利用染色体构象捕获芯片及大规模并行测序（4C-Seq）来证明与 Igh 有着显著相互作用的位点，同时富集了 RNA Pol II、Spt5、H3K4me3 和 AID。他们采用以结

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构域为中心的方法来分析 4C-Seq 数据，发现以高频率接触 Igh 的染色体区域包含绝大多数（90%）被鉴定为 AID 热点靶基因的已知位点。这项研究有助于深入了解核结构在 AID 靶定和维持基因组稳定性中的作用。

Illumina 的技术：Genome Analyzer$_{IIx}$ 用于 4C-Seq 单端 72 个循环的运行，HiSeq 2000 用于重测序 Cγ1 库

综述

Chaumeil J., Micsinai M., Ntziachristos P., Roth D. B., Aifantis I., et al. (2013) The RAG2 C-terminus and ATM protect genome integrity by controlling antigen receptor gene cleavage. Nat Commun 4: 2231

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Medvedovic J., Ebert A., Tagoh H., Tamir I. M., Schwickert T. A., et al. (2013) Flexible long-range loops in the VH gene region of the Igh locus facilitate the generation of a diverse antibody repertoire. Immunity 39: 229-244

Yamane A., Robbiani D. F., Resch W., Bothmer A., Nakahashi H., et al. (2013) RPA Accumulation during Class Switch Recombination Represents 5'-3' DNA-End Resection during the S-G2/M Phase of the Cell Cycle. Cell Rep 3: 138-147

Hakim O., Resch W., Yamane A., Klein I., Kieffer-Kwon K. R., et al. (2012) DNA damage defines sites of recurrent chromosomal translocations in B lymphocytes. Nature 484: 69-74

Kovalchuk A. L., Ansarah-Sobrinho C., Hakim O., Resch W., Tolarova H., et al. (2012) Mouse model of endemic Burkitt translocations reveals the long-range boundaries of Ig-mediated oncogene deregulation. Proc Natl Acad Sci U S A 109: 10972-10977

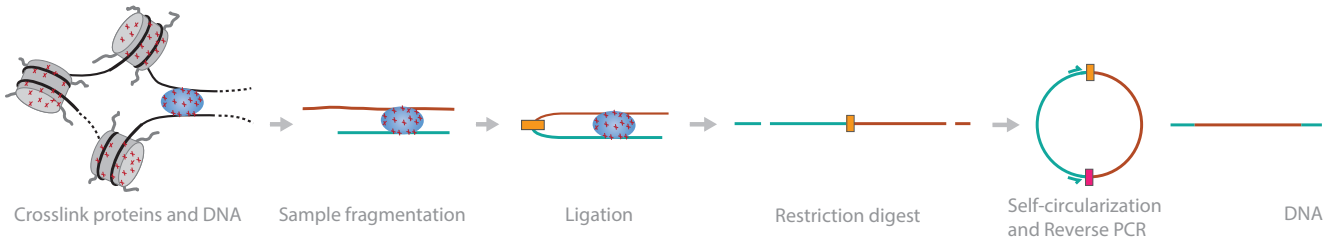
Rocha P. P., Micsinai M., Kim J. R., Hewitt S. L., Souza P. P., et al. (2012) Close proximity to Igh is a contributing factor to AID-mediated translocations. Mol Cell 47: 873-885

实验设计的注意事项

在分析单个基因组位点的 DNA 接触图谱时，4C-Seq 是首选的染色体构象捕获技术。这种分析在研究特定基因与远距离调控元件的关联时特别有用。[65,66]

（更多详情，请看染色质结构与重排）。

4C 目前仅限于评估与染色体其他位置（顺式）或其他染色体（反式）的较大区域的远距离接触。例如，基因与其增强子之间的局部相互作用（距离不到 50kb）就不大容易检测到。大多数 4C 策略使用限制性内切酶和 6- 核苷酸识别序列，每隔几 kb 切割一次。这产生了比一般调控序列要大得多的片段，而后者通常不超过几百 bp。分辨率的增加可能取决于使用更具选择性的限制性内切酶，它们产生更短的片段，这实现了 *de novo* 局部调控相互作用的检测。



环形染色质构象捕获（4C）[67]，实现了与感兴趣的特定区域存在相互作用的所有基因组区域的无偏向检测。[68] 在这种方法中，利用甲醛交联 DNA- 蛋白质复合物。样本被片段化，而 DNA 被连接和消化。所产生的 DNA 片段自身环化，接着进行反向 PCR 和测序。深度测序带来了连接片段的单碱基分辨率。

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先天性免疫

先天性免疫是宿主防御的前线。它引发针对病原体的快速而局部的反应，对于宿主及其微生物群之间的共生关系也很重要。先天性免疫和适应性免疫组成了免疫应答的二元分类。从历史上看，这两个免疫分支之间的区别存在一种共识，即先天性免疫是非特异的，缺乏记忆，而适应性免疫的特点是识别特定抗原和随后的记忆应答。然而，表明 B 细胞和 T 细胞的先天性免疫和自然杀伤（NK）细胞的适应性免疫的新证据正在模糊这种传统的二元分类。[69]

先天性免疫涉及到受体家族的协调行动，被称为模式识别受体（PRRs），或微生物传感器，它们通过检测保守的微生物模式或分子而响应广泛的微生物。[70-73] 这种先天的免疫反应是由专门的一组受体激活的，这些受体存在于巨噬细胞、肥大细胞、树突状细胞、自然杀伤细胞和多形核白细胞中。它们包括膜结合的 Toll 样受体（TLRs）和 C 型凝集素受体（CLRs），胞质的 RIG-1 样受体（TLRs）、NOD 样受体（NLRs）及其他 DNA 传感器。[74-78] 此外，循环蛋白是补充识别分子，它们构成了先天性免疫的体液（血清和体液）装备。[79] 在配体结合后，受体诱导不同信号通路的激活，它们涉及到效应分子，如干扰素（IFNs）或抗菌肽（AMPs），这都是消灭病原体或危险信号所必需的。

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作者采用单细胞 RNA 测序来研究小鼠骨髓来源的树突状细胞（BMDCs）对脂多糖反应的异质性。BMDCs 的成熟可作为对来自病原体的配体（如脂多糖）的反应，这导致防御细胞因子的共表达。在此，作者鉴定了 137 个高度变化但共同调节的抗病毒反应基因。100 个基因在单细胞中以两种模式表达，但在群体水平高表达。作者刺激并分析了干扰素受体敲除（Ifnr -/-）小鼠的 BMDCs，发现这些细胞中 Stat2 和 Irf7 以及其他基因的表达下降。作者得出结论，干扰素信号是诱导 Stat2 和 Irf7 所必需的，这随后诱导可变的抗病毒基因簇。

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癌症和免疫反应

从正常的造血细胞向癌细胞的发展涉及到克隆进化的多步骤过程，这由一系列体细胞突变所驱动。这些突变逐渐将细胞从正常生长转化到癌前状态及最终的癌状态，其中旨在调控细胞生长的所有检查点被打破。

恶性转化的诱导似乎涉及到至少两个不同的阶段：起始（initiation）和促进（promotion）。起始涉及到基因组的变化，但它本身不导致恶性转化。恶性转化需要第二个步骤，称为促进。在起始阶段后的侵袭性细胞分裂过程中，因新的 DNA 改变不断积累，促进可能发生，通常影响原癌基因、肿瘤抑制基因或凋亡基因，导致不受调控的细胞生长。

新一代测序通过深度测序检测稀有克隆类型或细胞中的突变的能力，使其能够研究免疫效应子在恶性血液病发病中的作用。一个明显的例子是大量报道认为克隆干细胞疾病的发病牵涉到自身反应性 T 细胞克隆，例如骨髓增生异常综合征（MDS）和再生障碍性贫血（AA）。[80] 这些研究已经得到广泛统一的认识，即抗肿瘤免疫力的破坏，这在生理上是由 T 细胞介导的，可能容易诱发恶性血液病的发展。总之，这些 T 细胞库研究以及将免疫球蛋白重链的重排牵连到急性淋巴细胞白血病的克隆进化的新报道已迅速成为血液学中最令人兴奋的研究领域之一。[81-83]

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更多信息，请参见：癌症和免疫反应

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微生物群和免疫系统

微生物群是指与哺乳动物免疫系统有着共同进化关系的特大且多样的微生物库。这些复杂的微生物群落栖息在几乎所有脊椎动物的身体表面。免疫系统在维持常住微生物群落的稳态上起了至关重要的作用，以确保宿主 - 微生物关系的互惠关系得以维持。因此，保护宿主免受病原体和培养复杂的微生物群落以发挥其保护和代谢优势的需求，进而推动了脊椎动物免疫系统的协同进化。考虑到宿主 - 微生物群稳态的改变与病毒感染、[84,85] 自身免疫性疾病、[86] 癌症、代谢性疾病和心血管疾病相关，这对研究人员来说是一个研究微生物群与宿主免疫反应之间相互作用的令人兴奋的机会。

新一代测序技术已经让研究人员能够通过在操作上定义细菌基因的多态性来定义这些微生物群的结构；特别是那些编码 16S 核糖体 RNA 序列的基因。测序人类微生物组让研究人员能够研究微生物群落与宿主免疫之间的相互作用，进而 , 揭示了免疫系统在调节这个稳态关系上扮演的重要角色。

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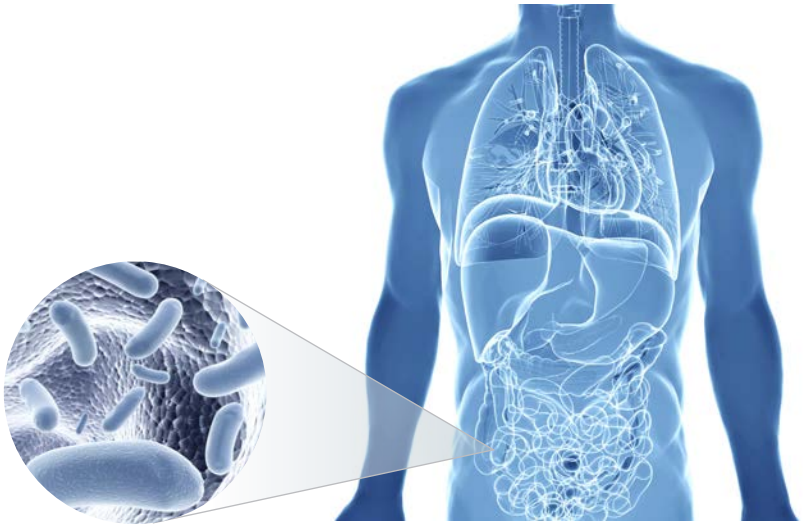
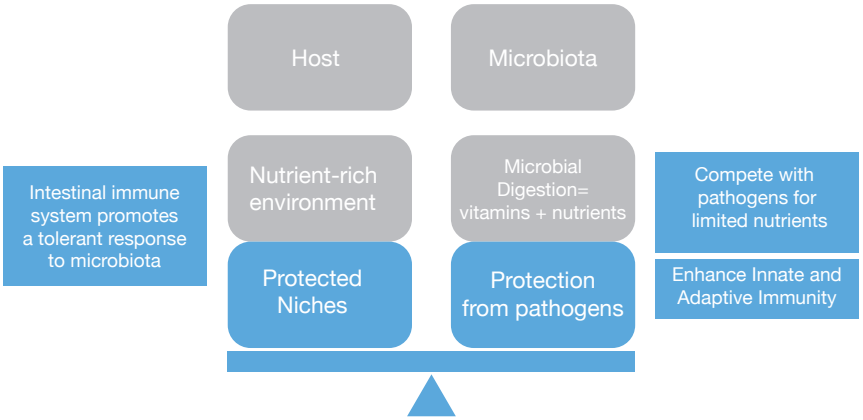
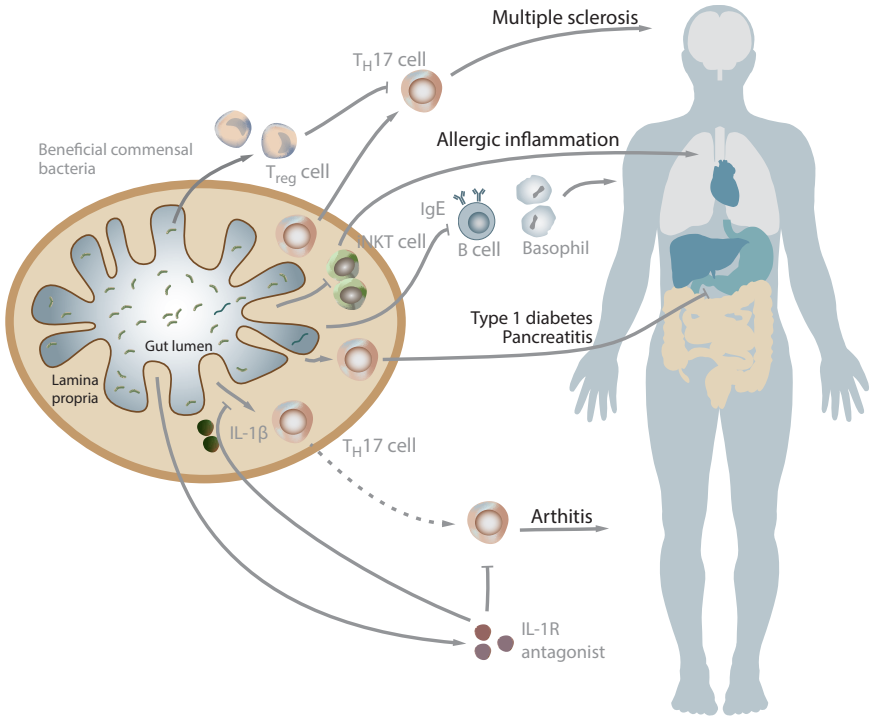


人类肠道含有超过 1 x 1014 个微生物，它们代表了大约 500 个不同种类的细菌。



宿主和微生物群共同进化出互利的结果，而免疫系统在保持稳态上发挥了关键的作用。宿主为微生物群提供了富含营养及保护的环境。而微生物群则为宿主提供了维生素和营养物质，作为微生物消化的副产物，并保护宿主免受病原体。微生物群增强了先天和适应性免疫应答。相反，宿主需要一种宽容的免疫反应，让微生物群栖息在肠道环境中。



这一网络阐明了肠道微生物群在肠道外自身免疫性疾病中的各种作用。[87]

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Castelino M., Eyre S., Upton M., Ho P. and Barton A. (2013) The bacterial skin microbiome in psoriatic arthritis, an unexplored link in pathogenesis: challenges and opportunities offered by recent technological advances. Rheumatology (Oxford)

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细菌分类群的改变可能与炎症性肠病的发病相关。作者对细菌 16S rRNA 的可变区 4（V4）开展深度测序分析，以研究活检样本中的粘膜微生物群落，这些 pinch 活检样本来自一些溃疡性结肠炎（UC）患者。这个深度测序研究结合流式细胞数据，证明了 UC 患者炎症活动期间 Th22 细胞（一类产生 IL-22 的 CD4+ 辅助性 T 细胞）的耗竭与 Clostridiales 群体的减少和 Proteobacteria 群体的增多相关联，而粘膜微生物群还有着其他特定的改变。

Illumina 的技术：MiSeq 用于 16S rRNA 的测序

Markle J. G., Frank D. N., Mortin-Toth S., Robertson C. E., Feazel L. M., et al. (2013) Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science 339: 1084-1088

微生物因素，特别是肠道微生物群，被认为影响了 I 型糖尿病易感性。在 I 型糖尿病的非肥胖糖尿病（NOD）小鼠模型中，雌性小鼠明显比雄性更易患上疾病。这种差异在无菌条件下并不明显，表明了微生物在 I 型糖尿病易感性中的作用。作者对从盲肠内容物中制备获得的细菌 16S rRNA 文库进行测序，以鉴定性别之间的微生物组分差异。在发病之前将雄性 NOD 小鼠盲肠的内容物转移到雌性 NOD 小鼠，避免了胰岛炎，减少了自身抗体的产生，防止了糖尿病的发生，并与雌性小鼠的睾酮升高相关。当睾酮受体被阻断时，M → F 微生物组转移所赋予的保护被减弱。这项研究表明，微生物群可能对性激素有调控作用，并可能影响遗传风险更高的个体的自身免疫性疾病的命运。

Illumina 的技术：MiSeq 用于 16S rRNA 的双端测序

Wang X., Lin Z., Gao L., Wang A., Wan Z., et al. (2013) Exome sequencing reveals a signal transducer and activator of transcription 1 (STAT1) mutation in a child with recalcitrant cutaneous fusariosis. J Allergy Clin Immunol 131: 1242-1243

镰刀菌可能在免疫功能低下和免疫功能正常的患者中引起 papopustular 病变及脓肿、溃疡甚至坏死。作者报告了一名患有难治性皮肤镰刀菌病的 7 岁女孩的案例研究。他们采用外显子组测序，在信号传导与转录激活子 1（STAT1）基因中鉴定出单个杂合错义突变，这是最有可能引起此患者镰刀菌病的遗传缺陷。

Illumina 的技术：HiSeq 2000 外显子组测序

综述

Schwab C., Berry D., Rauch I., Rennisch I., Ramesmayer J., et al. (2014) Longitudinal study of murine microbiota activity and interactions with the host during acute inflammation and recovery. ISME J

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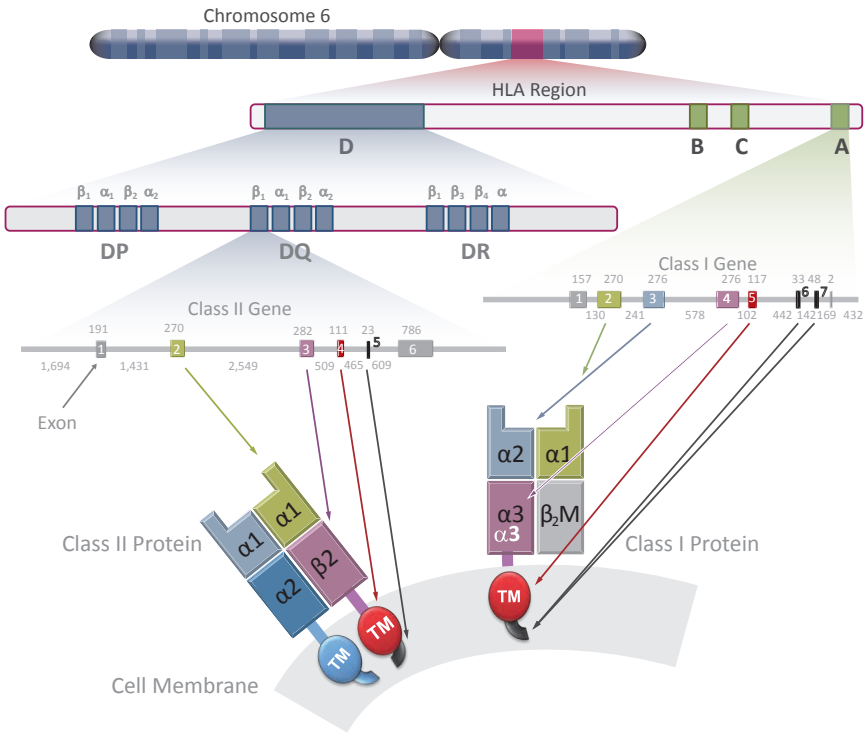
Caporaso J. G., Lauber C. L., Walters W. A., Berg-Lyons D., Huntley J., et al. (2012) Ultra-high-throughput microbial community analysis on the Illumina HiSeq and MiSeq platforms. ISME J 6: 1621-1624

Maslanik T., Tannura K., Mahaffey L., Loughridge A. B., Benninson L., et al. (2012) Commensal bacteria and MAMPs are necessary for stress-induced increases in IL-1beta and IL-18 but not IL-6, IL-10 or MCP-1. PLoS ONE 7: e50636

主要组织相容性复合物

尽管 T 细胞和 B 细胞都利用表面受体来识别抗原，但它们是以两种不同的方式来实现的。与抗体或 B 细胞受体直接识别抗原不同，T 细胞受体只识别抗原呈递细胞（如树突状细胞和巨噬细胞）表面所呈递的抗原。这些抗原肽段位于细胞表面蛋白的凹槽中，这些蛋白被称为主要组织相容性复合物（MHC）分子。

在人体中，MHC 位点指的是人类白细胞抗原（HLA），它编码 6 号染色体短臂上一段 4 Mb 连续区域内的一组基因。[88] 此外，扩展 MHC，称为（xMHC），跨越一段更大的 7.6 Mb 区域，其中包含 400 多个注释基因和假基因。[89]



这是一张人类 MHC 位点的图谱。MHC I 类基因是红色的，MHC II 类基因是蓝色的，而 MHC III 类基因是绿色的。所列出的 6 个位点编码了 I 类和 II 类 MHC 分子的肽段结合位点。在造血细胞和实体器官移植时，需要例行评估这些位点，以配对捐献者和接受者。

HLA 基因中的 6 个（HLA-A、-B、-C、-DQA1、-DQB1 和 –DRB1）特别多态，构成了一组重要的标记，在实体器官移植 [90] 和造血干细胞移植 [91,92] 时常用于患者和捐赠者配对。HLA 基因还在传染病（HIV、Hep C 和 CMV）、自身免疫性疾病（糖尿病、类风湿性关节炎和乳糜泻）以及药物过敏中发挥重要作用。[93]

通过传统的技术，只有编码肽段结合位点的多态性高的区域（即 HLA I 类的外显子 2 和 3 及 II 类的外显子 2）在临床背景下评估。新一代测序为临床研究人员提供了对整个基因测序的能力，实现了分辨相位、无偏向的 HLA 分型。临床研究已表明，配对 6 个主要 HLA 位点区域提供了最佳的临床结果，且实体器官和造血干细胞移

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植中排斥反应和移植物抗宿主病（GVHD）的发生率降低。不过，即使这些区域都匹配，大约 30% 的接受者在 5 年内还是会出现不良反应。[94]

这些不完全匹配的来源不明，但有几种可能性。不良反应可能反映在目前分析区域以外的区域不匹配。鉴于高度的多态性，HLA 分型中可能出现不明确的等位基因组合。这些可能源于顺式 / 反式的歧义，或由于通常所分析区域内的特定等位基因组合是相同的。例如，在传统的测序中，杂合的等位基因被同时扩增和测序。当两个或更多等位基因在目标外显子中享有相同的序列，但在未测序的外显子中表现出差异时，组合歧义会发生。[95] 新一代测序提供了相位信息，这可能明显改善 HLA 队列的分析（更多详情，请看 Phase-Defined HLA 测序）。

95. Wang C., Krishnakumar S., Wilhelmy J., Babrzadeh F., Stepanyan L., et al. (2012) High-throughput, high-fidelity HLA genotyping with deep sequencing. Proc Natl Acad Sci U S A 109: 8676-8681

综述

de Bakker P. I. and Raychaudhuri S. (2012) Interrogating the major histocompatibility complex with high-throughput genomics. Hum Mol Genet 21: R29-36

Erlich H. (2012) HLA DNA typing: past, present, and future. Tissue Antigens 80: 1-11

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Wang C., Krishnakumar S., Wilhelmy J., Babrzadeh F., Stepanyan L., et al. (2012) High-throughput, highfidelity HLA genotyping with deep sequencing. Proc Natl Acad Sci U S A 109: 8676-8681

作者提出了高通量的 HLA 基因分型方法，它采用单个长距离 PCR 来扩增基因 DNA，这些 DNA 跨越四个多态性 HLA 基因（HLA-A、-B、-C 和 -DRB1）的大部分编码区域。这种广泛覆盖方法提高了等位基因分辨率，从而减少了来自相位、杂合序列的组合歧义。它们在非多态性区域上的覆盖增加了鉴定之前未描述的等位基因以及错配、插入和缺失的机会。

Illumina 的技术：MiSeq 和 HiSeq 2000 用于 150 bp 和 100 bp 双端测序。利用 Genome Analyzer$_{IIx}$ 从两端测序 150 个碱基。

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Zheng X., Shen J., Cox C., Wakefield J. C., Ehm M. G., et al. (2014) HIBAG-HLA genotype imputation with attribute bagging. Pharmacogenomics J 14: 192-200

Hosomichi K., Jinam T. A., Mitsunaga S., Nakaoka H. and Inoue I. (2013) Phasedefined complete sequencing of the HLA genes by next-generation sequencing. BMC Genomics 14: 355

Kim Y. J., Kim H. Y., Lee J. H., Yu S. J., Yoon J. H., et al. (2013) A genomewide association study identified new variants associated with the risk of chronic hepatitis B. Hum Mol Genet 22: 4233-4238

Lam T. H., Shen M., Chia J. M., Chan S. H. and Ren E. C. (2013) Populationspecific recombination sites within the human MHC region. Heredity (Edinb) 111: 131-138

Levin A. M., Iannuzzi M. C., Montgomery C. G., Trudeau S., Datta I., et al. (2013) Association of ANXA11 genetic variation with sarcoidosis in African Americans and European Americans. Genes Immun 14: 13-18

Riolobos L., Hirata R. K., Turtle C. J., Wang P. R., Gornalusse G. G., et al. (2013) HLA Engineering of Human Pluripotent Stem Cells. Mol Ther 21: 1232-1241

定相 HLA 测序

定相测序表明特定等位基因是来源于两条亲本染色体中的哪一条。双端测序本身提供了定相信息。当一个 read 包括两个或更多的杂合基因型时，杂合基因型的相位被确定，因为一个 read 或一对 reads 来源的每个片段是在单个等位基因中获得的。因此，如果读长足够长，大量的相位信息可获得。[96] 这对于很多应用都有极大意义，包括了解遗传变异与疾病的相互作用，[97] 填充未分型的遗传变异，[98-100] 检出序列数据中的基因型，[101-104] 检测基因型错误，[105] 推断人类群体历史，[106] 推断重组点，[107] 检测频发突变，[107] 特征选择，[108] 以及基因表达顺式调控的建模。

当一个未定相的共有序列产生时，组合歧义会发生。当单个共有序列产生时，这掩盖了变异来自哪条亲本染色体。定相分析让研究人员能够产生两条可鉴别的序列，它们分别对应两条亲本染色体。这解决了组合歧义，让研究人员能鉴定变异来自哪条亲本染色体。

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尽管新一代测序在 HLA 基因分型中迅速崛起，但全面分析会忽略非编码的 HLA 区域和 mRNA 剪接数据，[109-111] 它们可能对基因调控有影响。[112,113] 此外，等位基因确定在传统上是基于序列与 IMGT/HLA 数据库中 HLA 序列参考库的比对，[114] 这阻碍了新的定相 HLA 基因单体型的鉴定。

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Browning S. R. and Browning B. L. (2011) Haplotype phasing: existing methods and new developments. Nat Rev Genet 12: 703-714

Tewhey R., Bansal V., Torkamani A., Topol E. J. and Schork N. J. (2011) The importance of phase information for human genomics. Nat Rev Genet 12: 215-223

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Hosomichi K., Jinam T. A., Mitsunaga S., Nakaoka H. and Inoue I. (2013) Phase-defined complete sequencing of the HLA genes by next-generation sequencing. BMC Genomics 14: 355

这是首个报告 HLA 区域的完整序列的研究。在此，作者能够确定定相的 HLA 基因序列，而无论等位基因是稀有的，还是未报道过的。他们测序了 HLA 基因的长距离 PCR 产物，从启动子到 3'-UTR，并采用了基因标记的方法，以定相 SNV 为基础产生两个 HLA 基因单体型序列。2 x 250 bp 的双端 reads 让他们能够证明并确定 33 个 HLA 纯合样本、11 个 HLA 杂合样本和 3 个亲子家庭的定相等位基因。

Illumina 的技术：MiSeq 2 x 250 bp 和 Nextera DNA Sample Prep Kit 用于文库构建

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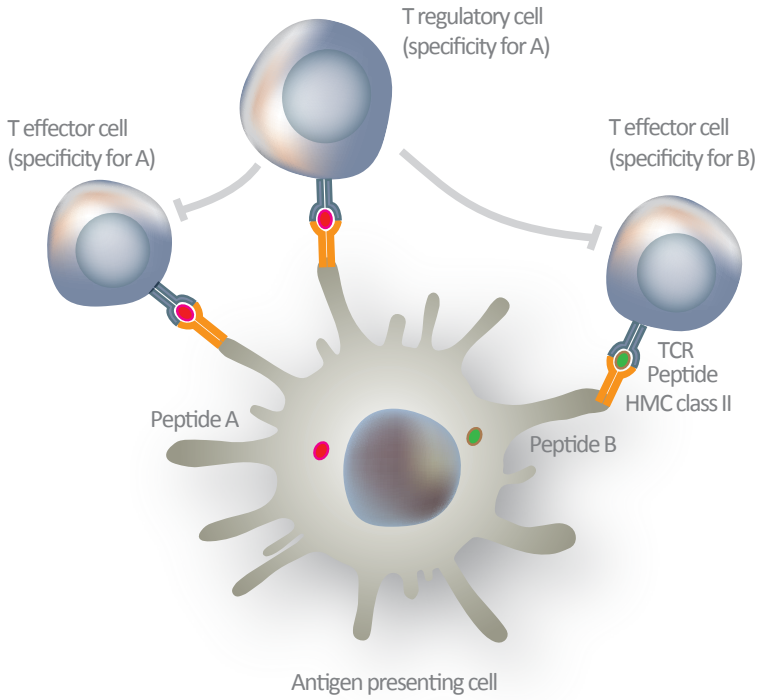
自体和非自体抗原区分

耐受

耐受指的是免疫系统施加的许多层保护，以防止其细胞和抗体对宿主成分的反应。耐受的一个重要形式是自我耐受，这指的是免疫系统缺乏对自身抗原的反应。

最近的研究报道了免疫细胞在对自身抗原的选择性抑制中有着更为积极的作用。例如，调节性 T 细胞（TREG）的研究，它实际上识别自身蛋白，已经彻底改变了耐受和自身免疫领域，更不用说移植。



连锁抑制代表了调节性 T 细胞（TREG）支持自身耐受的一种方式。TREG 细胞抑制抗原呈递细胞（APCs）呈递它们的关联抗原。它们也通过可溶的抑制因子，抑制相同或不同抗原特异性的旁观 T 细胞。

中枢耐受发生在初级淋巴器官中：B 细胞的骨髓和 T 细胞的胸腺。在此过程的第一步，以高亲和力识别自身抗原的 T 或 B 细胞克隆阻止其成熟。外周耐受是二级预防措施，如果一些自身反应性的淋巴细胞确实以自己的方式进入外周和二级淋巴组织。外周耐受将使二级淋巴组织中的一些自身反应性淋巴细胞失活，并产生能积极抑制自身免疫反应的细胞。此外，诱导性细胞死亡，或凋亡，通过限制活化淋巴细胞的寿命，带来进一步的保护措施。

T 细胞无反应性已被鉴定为一种低相应状态，或对抗原刺激无应答，这在缺乏共刺激下由 TCR 参与而诱导。[115,116] 相反，当同一抗原由适当的共刺激分子呈递时，它可能成为有效的免疫原，引发免疫反应。间接的证据表明，肿瘤微环境中 T 细胞功能障碍和移植耐受的建立部分源于 T 细胞无反应性。[117] 尽管 T 细胞无响应的鉴定有了进展，但我们对无响应表型的知识基础还有缺口。这是因为缺乏表面标记，它们可能在鉴定无响应 T 细胞中有用。此外，目前还不清楚那些处于无响应诱导条件下的 T 细胞为什么不从库中删除，以便排除特异性不理想的 T 细胞。

115. Steinert E. M., Schwartz R. H. and Singh N. J. (2012) At low precursor frequencies, the T-cell response to chronic self-antigen results in anergy without deletion. Eur J Immunol 42: 2875-2880
116. Chappert P. and Schwartz R. H. (2010) Induction of T cell anergy: integration of environmental cues and infectious tolerance. Curr Opin Immunol 22: 552-559
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Nishikawa H. and Sakaguchi S. (2014) Regulatory T cells in cancer immunotherapy. Curr Opin Immunol 27C: 1-7

Wherry E. J. (2011) T cell exhaustion. Nat Immunol 12: 492-499

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Zheng Y., Zha Y., Spaapen R. M., Mathew R., Barr K., et al. (2013) Egr2-dependent gene expression profiling and ChIP-Seq reveal novel biologic targets in T cell anergy. Mol Immunol 55: 283-291
T 细胞无反应性促进了外周耐受，并在肿瘤生长和促进同种异体移植接受上起了作用。Egr2 是 T 细胞无反应性的关键转录调节子。为了鉴定 Egr2 的直接转录靶点，作者开展了抗 Egr2 Ab 免疫沉淀核提取物的 ChIP-Seq 分析，这些提取物来自未处理和无反应的 Th1 T 细胞。将这一数据与基因表达谱分析合并，作者发现 Egr2 直接调控的 49 个靶点。他们意外地鉴定出细胞表面分子和分泌因子，包括淋巴细胞活化基因 3（Lag3）、I 类 MHC 限制的 T 细胞关联分子（Crtam）、脑信号蛋白 7A（Sema7A）和趋化因子 CCL1。这些结果表明，无反应性状态可能通过与其他免疫分子的相互作用而发挥功能性作用。

Illumina 的技术：Genome Analyzer*IIx* 对 200-400 bp 的 DNA 片段进行 ChIP-Seq

Roychoudhuri R., Hirahara K., Mousavi K., Clever D., Klebanoff C. A., et al. (2013) BACH2 represses effector programs to stabilize T(reg)-mediated immune homeostasis. Nature 498: 506-510
编码转录因子 BACH2 的单个位点中的遗传多态性与许多种自身免疫和过敏疾病相关。作者使用了 BACH2 基因干扰小鼠。他们发现，BACH2 是免疫激活的调控因子。

Illumina 的技术：HiSeq 用于 miRNA 测序和 ChIP-Seq

综述

Ferraro A., D'Alise A. M., Raj T., Asinovski N., Phillips R., et al. (2014) Interindividual variation in human T regulatory cells. Proc Natl Acad Sci U S A 111: E1111-1120

自身免疫

自身免疫是因耐受失败而引起的，耐受是为了保护宿主免受自身反应性的 T 或 B 细胞克隆。这些疾病的发病表现为其本身的蛋白质、细胞和器官被自身反应性的淋巴细胞所破坏。自身免疫的发生和发病取决于 T 和 B 细胞的内在因素，如生殖系或体细胞突变，[118-120] 以及环境因素，如微生物群或感染，[121] 细胞因子环境，以及微环境中其他免疫细胞的存在。[122]

对于大部分慢性的自身免疫和炎性疾病，患者群体是异质的，不能一致响应特定疗法。因此，大多数自身免疫和炎性疾病的治疗决策主要基于试错观察。“可行动的生物标志物”的开发有望改善临床试验的设计，并告知治疗决策。[123] 例如，高通量 DNA 测序有助于追踪自身免疫疾病中 T 细胞和 B 细胞的疾病相关克隆。此外，这些细胞群体的改变能与患者对疗法的响应相关联。[124]

治疗这些疾病的最大希望在于更深入地了解遗传和表观遗传变异在自身免疫疾病中的功能作用。[125] 全外显子组和全基因组的新一代测序已成为一种重要的工具，能够鉴定大量自身免疫疾病患者中的稀有遗传变异。此外，测序表观遗传标记的最新进展也增添了更多信息，有助于阐明表观遗传修饰、遗传因素和环境信号的微妙作用，这些因素使个体易患自身免疫疾病。

综述

Chan A. C. and Behrens T. W. (2013) Personalizing medicine for autoimmune and inflammatory diseases. Nat Immunol 14: 106-109

Graham D. B. and Xavier R. J. (2013) From genetics of inflammatory bowel disease towards mechanistic insights. Trends Immunol 34: 371-378

Knoechel B. and Lohr J. G. (2013) Genomics of lymphoid malignancies reveal major activation pathways in lymphocytes. J Autoimmun 45: 15-23

Orrù V., Steri M., Sole G., Sidore C., Virdis F., et al. (2013) Genetic variants regulating immune cell levels in health and disease. Cell 155: 242-256

Viatte S., Plant D. and Raychaudhuri S. (2013) Genetics and epigenetics of rheumatoid arthritis. Nat Rev Rheumatol 9: 141-153

Maecker H. T., Lindstrom T. M., Robinson W. H., Utz P. J., Hale M., et al. (2012) New tools for classification and monitoring of autoimmune diseases. Nat Rev Rheumatol 8: 317-328

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Joseph C. G., Darrah E., Shah A. A., Skora A. D., Casciola-Rosen L. A., et al. (2014) Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 343: 152-157

硬皮病是一种结缔组织的自身免疫性疾病，其中患者对有限的一组自身抗原产生抗体。硬皮病以及带有 RPC1 抗体的患者的癌症风险增加。作者对 16 名患者的 POLR3A、TOP1 和 CENPB 基因的肿瘤和正常编码序列进行了测序。结果表明，POLR3A 突变引发了细胞免疫和交叉反应性的体液免疫应答。

Illumina 的技术：Genome Analyzer*IIx*

Christodoulou K., Wiskin A. E., Gibson J., Tapper W., Willis C., et al. (2013) Next generation exome sequencing of paediatric inflammatory bowel disease patients identifies rare and novel variants in candidate genes. Gut 62: 977-984

作者利用外显子组测序分子来鉴定已知的炎症性肠病（IBD）易感基因中的稀有和新发现变异。在 169 个已知 IBD 易感基因的分析中，他们从 8 名儿科 IBD 患者中鉴定出大约 300 个非同义、截短和移码突变。在排除 HLA 变异后，他们发现了 39 个基因中的 58 个变异，其中 17 个是之前没有报道的。在队列中，2 名严重溃疡性结肠炎（UC）患者表现出不同的图谱；他们都携带了 B 细胞调控基因 BACH2 和 IL10 基因的潜在有害变异，这在其他 IBD 患者中未发现。溃疡性结肠炎的 GWAS 分析未报道 BACH2 的变异。

Illumina 的技术：HiSeq 2000 用于外显子组测序

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121. Yurkovetskiy L., Burrows M., Khan A. A., Graham L., Volchkov P., et al. (2013) Gender bias in autoimmunity is influenced by microbiota. Immunity 39: 400-412
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123. Chan A. C. and Behrens T. W. (2013) Personalizing medicine for autoimmune and inflammatory diseases. Nat Immunol 14: 106-109
124. Maecker H. T., Lindstrom T. M., Robinson W. H., Utz P. J., Hale M., et al. (2012) New tools for classification and monitoring of autoimmune diseases. Nat Rev Rheumatol 8: 317-328
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Coit P., Jeffries M., Altorok N., Dozmorov M. G., Koelsch K. A., et al. (2013) Genome-wide DNA methylation study suggests epigenetic accessibility and transcriptional poising of interferon-regulated genes in naive CD4+ T cells from lupus patients. J Autoimmun 43: 78-84

DNA 甲基化的改变与系统性红斑狼疮患者的 T 细胞分化有关联。作者对红斑狼疮患者及对照的初始 CD4+ T 细胞开展了全基因组的 DNA 甲基化研究和基因表达谱分析。在红斑狼疮患者初始 CD4+ T 细胞的 86 个差异甲基化的位点中，作者发现 35 个低甲基化基因中的 21 个是由 1 型干扰素调控的，包括 IFIT1、IFIT3、MX1、STAT1、IFI44L、USP18、TRIM22 和 BST2。这些结果表明，异常的 DNA 甲基化存在于激活和分化前的狼疮 T 细胞中，也为狼疮 T 细胞对 1 型干扰素的高反应性提供了表观遗传的解释。

Illumina 的技术：Infinium Human-Methylation450 BeadChip 芯片用于 DNA 甲基化研究，HumanHT-12 v4 Expression BeadChip 用于基因表达研究。DNA 甲基化分析是用 GenomeStudio 甲基化分析包开展的

Han A., Newell E. W., Glanville J., Fernandez-Becker N., Khosla C., et al. (2013) Dietary gluten triggers concomitant activation of CD4+ and CD8+ alphabeta T cells and gammadelta T cells in celiac disease. Proc Natl Acad Sci U S A 110: 13073-13078

乳糜泻是一种由食物中的麸质和麸质特异的 CD4+ T 细胞反应而引起的肠道自身免疫性疾病。麸质暴露也诱导外周血中出现激活、肠道归巢的 CD8+ αβ 和 γδ T 细胞。单细胞的 T 细胞受体序列分析表明，这两种细胞群体都有着高度集中的 T 细胞受体库。这种集中的库通常表明诱导是由抗原驱动的。

Illumina 的技术：MiSeq 双端测序

Roychoudhuri R., Hirahara K., Mousavi K., Clever D., Klebanoff C. A., et al. (2013) BACH2 represses effector programs to stabilize T(reg)-mediated immune homeostasis. Nature 498: 506-510

BACH2 在 B 细胞中表达，在那里它作为 Blimp-1 及其他类别转换重组基因的转录抑制子。编码转录因子 BACH2 的单个位点上的多态性与许多自身免疫和过敏性疾病相关联。通过研究 BACh2 基因被破坏的小鼠，作者发现，BACH2 是 CD4+ T 细胞分化的关键调节因子，通过控制耐受和免疫之间的平衡来防止炎性疾病。他们刺激 BACH2 敲除小鼠的初始 CD4+ T 细胞，随后开展大规模并行 RNA 测序，以表明大多数差异表达的基因在 BACH2 缺陷型细胞中不受调控。作者通过染色质免疫沉淀和大规模并行测序，测定了 iTreg 细胞中全基因组范围的 BACH2 结合。他们确定 BACH2 结合了 43.6% 的去阻遏基因，包括 408 个去阻遏效应谱系关联的基因。

Illumina 的技术：HiSeq 2000，使用 TruSeq Sample Prep Kit 来制备 RNA-Seq 文库

Lessard C. J., Li H., Adrianto I., Ice J. A., Rasmussen A., et al. (2013) Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome. Nat Genet 45: 1284-1292

干燥综合征（Sjögren's syndrome）是一种常见的自身免疫性疾病，典型表现为角膜炎（keratoconjunctivitis sicca）和口干综合征（xerostomia）。在这篇文献中，作者利用 Illumina 的 Omni1 Quad 芯片、Illumina ImmunoChip 开展全基因组关联研究，并在 Illumina 的 Human WG-6 v.3.0 BeadChip 芯片上开展基因表达谱分析。利用生物信息学工具，全基因组显著性阈值和暗示相关变异的组合为直接和间接的蛋白之间相互作用提供证据，也富集了参与免疫信号传导过程的基因，包括 TNFAIP3、PTTG1、PRDM1、DGKQ、FCGR2A、IRAK1BP1、ITSN2 和 PHIP。

Illumina 的技术：HumanOmni1 Quad、Human ImmunoChip

Martin J. E., Assassi S., Diaz-Gallo L. M., Broen J. C., Simeon C. P., et al. (2013) A systemic sclerosis and systemic lupus erythematosus pan-meta-GWAS reveals new shared susceptibility loci. Hum Mol Genet 22: 4021-4029
在这个两项全基因组关联研究（GWAS）的 Meta 分析中，作者搜索了系统性硬化症（SSc）和红斑狼疮（SLE）的常见遗传易感位点。这两种疾病都是典型的自身免疫性疾病，而之前的研究已表明，一些自身免疫性疾病有着共同的遗传基础。在这个总共有 ~21,000 个样本的研究中，一个新的关联位点被确定，而两个之前描述的 SLE 位点也被发现与 SSc 共享。

Illumina 的技术：HumanCNV370-Duo、HumanHap550、Human610-Quad、Human Gene Expression – BeadArray

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Bhanusali D. G., Sachdev A., Olson M. A., Gerlach J. A. and Sinha A. A. (2014) PTPN22 profile indicates a novel risk group in Alopecia areata. Hum Immunol 75: 81-87

Leung J. M., Davenport M., Wolff M. J., Wiens K. E., Abidi W. M., et al. (2014) IL- 22-producing CD4+ cells are depleted in actively inflamed colitis tissue. Mucosal Immunol 7: 124-133

Furukawa H., Oka S., Matsui T., Hashimoto A., Arinuma Y., et al. (2013) Genome, epigenome and transcriptome analyses of a pair of monozygotic twins discordant for systemic lupus erythematosus. Hum Immunol 74: 170-175

Guo X., Brenner M., Zhang X., Laragione T., Tai S., et al. (2013) Wholegenome sequences of da and f344 rats with different susceptibilities to arthritis, autoimmunity, inflammation and cancer. Genetics 194: 1017-1028

Koelsch K. A., Webb R., Jeffries M., Dozmorov M. G., Frank M. B., et al. (2013) Functional characterization of the MECP2/IRAK1 lupus risk haplotype in human T cells and a human MECP2 transgenic mouse. J Autoimmun 41: 168-174

Nakano K., Whitaker J. W., Boyle D. L., Wang W. and Firestein G. S. (2013) DNA methylome signature in rheumatoid arthritis. Ann Rheum Dis 72: 110-117

Wang C., Ahlford A., Laxman N., Nordmark G., Eloranta M. L., et al. (2013) Contribution of IKBKE and IFIH1 gene variants to SLE susceptibility. Genes Immun 14: 217-222

Ahn J., Gutman D., Saijo S. and Barber G. N. (2012) STING manifests self DNAdependent inflammatory disease. Proc Natl Acad Sci U S A 109: 19386-19391

Cottrell T. R., Hall J. C., Rosen A. and Casciola-Rosen L. (2012) Identification of novel autoantigens by a triangulation approach. J Immunol Methods 385: 35-44

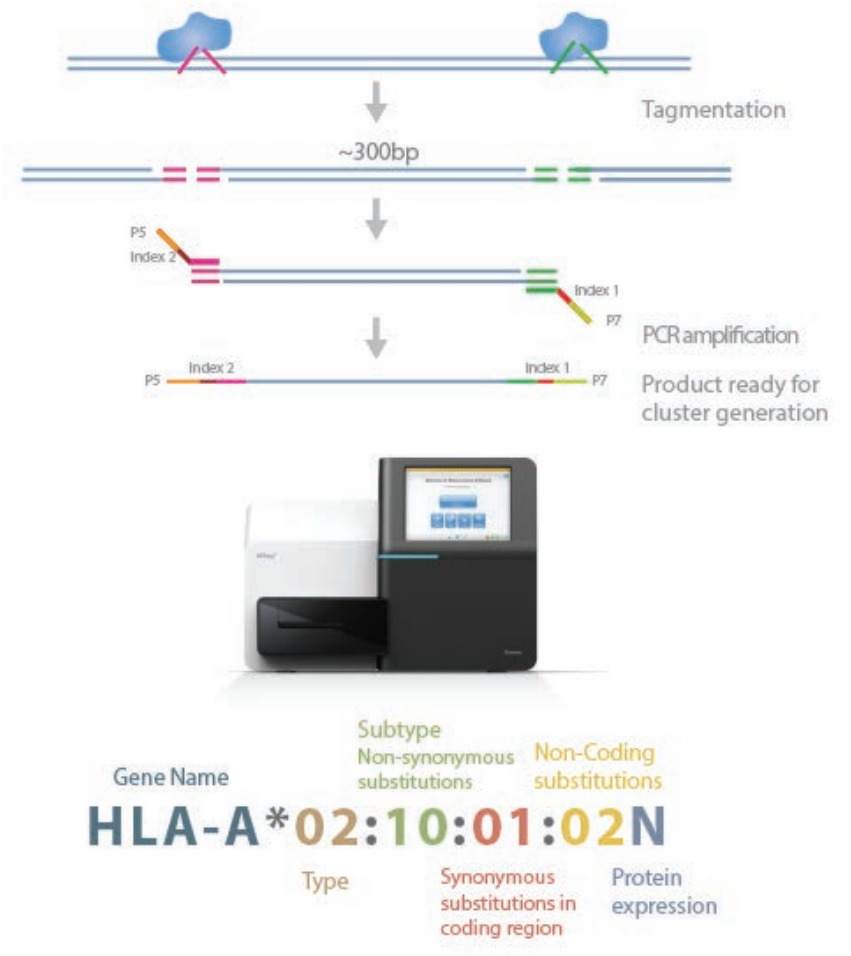
Labbe C., Boucher G., Foisy S., Alikashani A., Nkwimi H., et al. (2012) Genomewide expression profiling implicates a MAST3-regulated gene set in colonic mucosal inflammation of ulcerative colitis patients. Inflamm Bowel Dis 18: 1072-1080

实体器官移植

实体器官移植中的移植体排斥反应被归因于组织不相容的组织。一种类型的移植组织是同种异体移植物（allograft），它是在相同物种但遗传上不同的成员之间转移。由于同种异体移植物在遗传上与宿主不同，因此表达独特的抗原，这些往往不被识别成自身抗原，而导致移植体的排斥。

享有足够的抗原相似性的组织，让转移无免疫排斥，被认为是组织相容的，同卵双胞胎之间的转移就属于这种情况。大多数移植都是在 ABO 血型匹配且 HLA 匹配的个体之间进行的。然而，即使 MHC 抗原相同，移植的组织也可能排斥，这是因为其他多个位点的差异，包括次要组织相容性位点。

目前，对于心脏移植接受者，心内膜心肌活检（EMB）已成为排斥监测的“金标准”。然而，心内膜心肌活检是一种昂贵且侵入性检测，受限于采样误差、观察者之间的分级差异、排斥的晚期发现和发病风险。[126,127] 因此，目前有相当一部分工作在开发非侵入性的技术，它们可能取代或减少 EMB 的需求，将更多重点放在监控接受者的免疫反应上，以检测排斥的发生。



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Gabriel C., Furst D., Fae I., Wenda S., Zollikofer C., et al. (2014) HLA typing by next-generation sequencing - getting closer to reality. Tissue Antigens 83: 65-75

Boyd S. D. (2013) Diagnostic applications of high-throughput DNA sequencing. Annu Rev Pathol 8: 381-410

De Santis D., Dinauer D., Duke J., Erlich H. A., Holcomb C. L., et al. (2013) 16(th) IHIW : review of HLA typing by NGS. Int J Immunogenet 40: 72-76

Starzl R., Brandacher G., Lee W. P., Carbonell J., Zhang W., et al. (2013) Review of the early diagnoses and assessment of rejection in vascularized composite allotransplantation. Clin Dev Immunol 2013: 402980

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Chen Y., Zhang H., Xiao X., Jia Y., Wu W., et al. (2013) Peripheral blood transcriptome sequencing reveals rejection-relevant genes in long-term heart transplantation. Int J Cardiol 168: 2726-2733
作者对 6 位静态和 6 位严重排斥的心脏移植接受者的外周血单核细胞（PBMC）进行了转录组测序。通过数字基因表达谱（DGE）分析，基于相同或类似序列的 reads 数量的表达测定，他们鉴定出 10 个基因的 PBMC 特征，能够区分发生急性心脏同种异体移植物排斥反应的患者。根据蛋白间相互作用网络的分析，作者表明，CXCR4 和 HLA-A 是最具信息量的基因，更高度控制信息流向协作网络中的其他 10 个基因。

Illumina 的技术：Genome Analyzer*IIx*，用于 85 bp reads RNA-Seq

Hosomichi K., Jinam T. A., Mitsunaga S., Nakaoka H. and Inoue I. (2013) Phase-defined complete sequencing of the HLA genes by next-generation sequencing. BMC Genomics 14: 355
人类白细胞抗原（HLA）区域，人类基因组 6p21 上 3.8 Mb 的片段，已经与 100 多种不同的疾病相关联，其中大部分是自身免疫性疾病。由于 HLA 基因的复杂性质，通过传统测序方法阐明整个 HLA 基因的序列，特别是 HLA 基因单体型结构还很困难。这项研究介绍了一种新方法，在 Illumina MiSeq 上利用带索引的多重样本对 HLA 基因进行经济高效的定相测序。此方法在 53 个样本上验证过，表现出高分辨率的 HLA 分型。

Illumina 的技术：MiSeq、Nextera DNA Sample Prep

Snyder T. M., Khush K. K., Valantine H. A. and Quake S. R. (2011) Universal noninvasive detection of solid organ transplant rejection. Proceedings of the National Academy of Sciences of the United States of America 108: 6229-6234
由于移植体排斥期间器官中的细胞死亡增加，预计这段时间血液中存在更多的供体分子。在此，作者对供体和受体进行基因分型，以建立一个独特的供体“遗传指纹”，这随后可通过对心脏移植受体外周血中的游离 DNA 进行高通量测序而检测。他们鉴定了供体和受体的 SNP 检出 reads，以确定供体 DNA 的百分比。这项研究将低于 1% 的平均值作为供体来源游离 DNA 的健康正常水平。相反，在器官排斥期间，供体 DNA 信号的水平上升至总的游离 DNA 的平均 3-4%。

Illumina 的技术：Genome Analyzer*IIx* 和 Omni-Quad BeadChip

传染病和疫苗

T 细胞分离和 T 受体测序上新的技术进展让我们更好地了解免疫 T 细胞库的基本结构，个体内部和之间的反应多样性，库的时间性变化以及对传染病的反应。

综述

Vladimer G. I., Marty-Roix R., Ghosh S., Weng D. and Lien E. (2013) Inflammasomes and host defenses against bacterial infections. Curr Opin Microbiol 16: 23-31

病毒感染

诸如 HIV（一种逆转录病毒）的病毒感染能够通过几种机制破坏和改变基因表达。研究已利用新一代测序分析了 HIV 感染后细胞 miRNA 和一些 sncRNA 的表达。[128-130] 新兴的研究集中在基因表达调控的新机制，围绕最近发现的 HIV 和免疫系统之间的角色。例如，人类白细胞抗原（HLA）蛋白家族在逆转录病毒的进程中发挥重要作用，因为它是免疫应答的关键调节剂。

最终，了解免疫细胞（如病毒特异的初始 CD8+ T 细胞）如何影响病毒感染后所产生的免疫应答，这对利用 CD8+ T 细胞介导强化疗法和疫苗接种策略的开发很关键。

综述

Bauersachs S. and Wolf E. (2013) Immune aspects of embryo-maternal cross-talk in the bovine uterus. J Reprod Immunol 97: 20-26

Vladimer G. I., Marty-Roix R., Ghosh S., Weng D. and Lien E. (2013) Inflammasomes and host defenses against bacterial infections. Curr Opin Microbiol 16: 23-31

Celsi F., Catamo E., Kleiner G., Tricarico P. M., Vuch J., et al. (2013) HLA-G/C, miRNAs, and their role in HIV infection and replication. Biomed Res Int 2013: 693643

La Gruta N. L. and Thomas P. G. (2013) Interrogating the relationship between naive and immune antiviral T cell repertoires. Curr Opin Virol 3: 447-451

Lipkin W. I. and Firth C. (2013) Viral surveillance and discovery. Curr Opin Virol 3: 199-204

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Dillon S. M., Lee E. J., Kotter C. V., Austin G. L., Dong Z., et al. (2014) An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia. Mucosal Immunol

在这篇文章中，作者研究了 HIV-1 感染对肠道微生物组的影响及其与粘膜 T 细胞和树突状细胞（DC）频率和激活的关联，以及研究全身性 T 细胞激活、炎症和微生物移位的水平。作者发现，HIV-1 相关的微生物组变化与增强的粘膜细胞免疫激活、微生物移位和血液 T 细胞激活相关联。

Illumina 的技术：MiSeq 及 250 bp paired-end kit

128. Duskova K., Nagilla P., Le H. S., Iyer P., Thalamuthu A., et al. (2013) MicroRNA regulation and its effects on cellular transcriptome in human immunodeficiency virus-1 (HIV-1) infected individuals with distinct viral load and CD4 cell counts. BMC Infect Dis 13: 250
129. Whisnant A. W., Bogerd H. P., Flores O., Ho P., Powers J. G., et al. (2013) In-depth analysis of the interaction of HIV-1 with cellular microRNA biogenesis and effector mechanisms. MBio 4: e000193
130. Chang S. T., Thomas M. J., Sova P., Green R. R., Palermo R. E., et al. (2013) Next-generation sequencing of small RNAs from HIV-infected cells identifies phased microrna expression patterns and candidate novel microRNAs differentially expressed upon infection. MBio 4: e00549-00512

O'Connor K. S., Parnell G., Patrick E., Ahlenstiel G., Suppiah V., et al. (2014) Hepatic metallothionein expression in chronic hepatitis C virus infection is IFNL3 genotype-dependent. Genes Immun 15: 88-94

IFNL3 基因型预示着丙型肝炎病毒（HCV）的清除，自发或通过干扰素治疗。作者鉴定 ISGs 簇、金属硫蛋白（MTs）和 IFNL3 基因型之间的关联。他们发现，在 HCV 感染的 IFNL3 基因型 rs8099917 应答者的肝脏活检中，金属硫蛋白（MTs）明显上调（相对于大多数其他的 ISGs）。

Illumina 的技术：HiSeq 2000 TruSeq RNA 样本制备和 Human HT-12_V3

Wang X., Wang H. K., Li Y., Hafner M., Banerjee N. S., et al. (2014) microRNAs are biomarkers of oncogenic human papillomavirus infections. Proc Natl Acad Sci U S A 111: 4262-4267

作者研究了 158 个宫颈标本中的 miRNA 表达，包括 38 个正常，52 个宫颈上皮内瘤变（CIN）和 68 个宫颈癌（CC）组织。他们发现，在 HPV 感染的组织中随着病变发展 miR-25、miR-92a 和 miR-378 表达增加，但 miR-22、miR-29a 和 miR-100 没有明显变化。miR-25/92a 组相对于 miR-22/29a 组的表达率≥ 1.5 可作为临界值，以区分正常宫颈和 CIN 以及区分 CIN 和 CC。

Illumina 的技术：HiSeq 2000

Chang S. T., Thomas M. J., Sova P., Green R. R., Palermo R. E., et al. (2013) Next-generation sequencing of small RNAs from HIV-infected cells identifies phased microrna expression patterns and candidate novel microRNAs differentially expressed upon infection. MBio 4: e00549-00512

作者在 HIV 感染后 5、12 和 24 小时（hpi），研究 HIV 感染对 CD4+ T 类淋巴母细胞中小 RNA 表达的影响。作者在单个被感染细胞类型的水平关注宿主反应，并分析了此系统随时间的变化，以检测 microRNA 的表达模式。Small RNA-Seq 确定了 5 和 12 hpi 时 14 个差异表达的 microRNA；其中许多表现出初始的表达抑制，而在 24 hpi 后反弹。他们还鉴定出一个新发现的 microRNA，EPB41L2 基因第一内含子中编码的 18 聚体，它在未感染的细胞中高表达，而在 24 hpi 时下调 90%。

Illumina 的技术：Genome Analyzer*IIx*，用于 54 bp reads 的 RNA-Seq。小 RNA 文库是用小 RNA 1.5 版本样本制备试剂盒制备的

Whisnant A. W., Bogerd H. P., Flores O., Ho P., Powers J. G., et al. (2013) In-depth analysis of the interaction of HIV-1 with cellular microRNA biogenesis and effector mechanisms. MBio 4: e00019

HIV-1 如何与细胞内 microRNA（miRNA）的生物合成和效应机制相关联，这一直是个极具争议的问题。在这篇文章中，作者利用 Illumina 的 HiSeq 2000 对两个不同的感染细胞系和两种类型的原代人类细胞中的小 RNA 进行深度测序，明确表明 HIV-1 不编码任何病毒 miRNA。

Illumina 的技术：HiSeq 2000 及 TruSeq RNA kit 用于小 RNA 和 PAR-CLIP 的深度测序，以找到 HIV-1 基因组中的 miRNA 结合位点

Genolet R., Leignadier J., Osteras M., Farinelli L., Stevenson B. J., et al. (2014) Duality of the murine CD8 compartment. Proc Natl Acad Sci U S A 111: E1007- 1015

Schoggins J. W., MacDuff D. A., Imanaka N., Gainey M. D., Shrestha B., et al. (2014) Pan-viral specificity of IFN-induced genes reveals new roles for cGAS in innate immunity. Nature 505: 691-695

Paquette S. G., Banner D., Chi l., Le?n A. J., Xu L., et al. (2014) Pandemic H1N1 influenza A directly induces a robust and acute inflammatory gene signature in primary human bronchial epithelial cells downstream of membrane fusion. Virology 448: 91-103

Bolen C. R., Robek M. D., Brodsky L., Schulz V., Lim J. K., et al. (2013) The blood transcriptional signature of chronic hepatitis C virus is consistent with an ongoing interferon-mediated antiviral response. J Interferon Cytokine Res 33: 15-23

Duskova K., Nagilla P., Le H. S., Iyer P., Thalamuthu A., et al. (2013) MicroRNA regulation and its effects on cellular transcriptome in human immunodeficiency virus-1 (HIV-1) infected individuals with distinct viral load and CD4 cell counts. BMC Infect Dis 13: 250

Grainger J. R., Wohlfert E. A., Fuss I. J., Bouladoux N., Askenase M. H., et al. (2013) Inflammatory monocytes regulate pathologic responses to commensals during acute gastrointestinal infection. Nat Med 19: 713-721

Haralambieva I. H., Oberg A. L., Ovsyannikova I. G., Kennedy R. B., Grill D. E., et al. (2013) Genome-wide characterization of transcriptional patterns in high and low antibody responders to rubella vaccination. PLoS One 8: e62149

Pociask D. A., Scheller E. V., Mandalapu S., McHugh K. J., Enelow R. I., et al. (2013) IL-22 Is Essential for Lung Epithelial Repair following Influenza Infection. Am J Pathol 182: 1286-1296

macrophages induce the expression of novel microRNAs which may mediate anti-viral properties. Biochem Biophys Res Commun 434: 228-234

Archer J., Weber J., Henry K., Winner D., Gibson R., et al. (2012) Use of Four Next-Generation Sequencing Platforms to Determine HIV-1 Coreceptor Tropism. PLoS ONE 7: e49602

疫苗开发

新一代的测序技术在系统生物学 [131] 和疫苗组学 [132-136] 领域有着广阔的前景，有望更深入了解宿主对疫苗和病毒感染的反应。

那些报告疫苗高反应者和低反应者之间差异基因表达模式的研究有助于了解他们之间不同的免疫调节过程。这些基因座的进一步研究可能带来有关免疫应答的遗传控制的重要发现，这将为新的候选疫苗的改造带来有价值的信息。[132,136]

人类单克隆抗体很有望成为潜在的治疗工具。直到最近，能中和各种不断变化的病毒（如流感病毒或 HIV）的单个抗体还被认为是极其罕见且几乎不可能分离的。通过采用新一代测序技术，精心筛选和仔细选择感染者，研究人员如今能够分离并鉴定这些广泛中和的抗体。[137,138] 现在人们正努力优先靶定这些抗体的表位。

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Wilson P. C. and Andrews S. F. (2012) Tools to therapeutically harness the human antibody response. Nat Rev Immunol 12: 709-719

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预先存在的抗体与差的接种反应之间存在已知的关联，这归因于预先存在的流感特异的记忆 CD4+ T 细胞，它们抑制树突状细胞的抗原呈递，随后抑制 B 细胞应答。作者利用全基因组 DNA 芯片来评估免疫指标的基线水平，这与流感疫苗接种的血球凝集素抑制滴度反应相关。作者报告了 109 个基因模块，即相同一组转录因子结合的共表达基因的组合。九个变量可预测抗体应答，准确性达 84%。这是第一项报告记忆细胞的凋亡与对疫苗的抗体应答之间关联的研究。

Illumina 的技术：HumanHT-12v3 Expression BeadChip 和 GenomeStudio 软件

Kennedy R. B., Oberg A. L., Ovsyannikova I. G., Haralambieva I. H., Grill D., et al. (2013) Transcriptomic profiles of high and low antibody responders to smallpox vaccine. Genes Immun 14: 277-285

牛痘病毒（VACV）是一种免疫上交叉保护性的病毒，用在天花疫苗中。作者利用 mRNA-Seq 转录组分析来鉴定天花疫苗接种者在 VACV 刺激后的外周血单核细胞（PBMC）的宿主和病毒基因表达模式。在 1200 多个表现出差异表达的基因中，他们鉴定出多个趋化因子、细胞因子、干扰素及巨噬细胞相关基因，在这些基因在感染牛痘后明显下调。相反，他们发现一些编码组蛋白、IFNβ、IFNγ 和热击蛋白的基因表达上调。基因组合分析表明，那些表达值最低的基因在病毒生命周期的“晚期”表达，而那些被归为“早期”的基因则以更高的水平表达。作者确定了牛痘特异的高和低应答者的患者队列实现了强体液免疫和弱体液免疫应答之间差异基因调控模式 。

Illumina 的技术：Genome Analyzer$_{IIx}$ 以及 Single Read Cluster Generation Kit (v2) 和 50 cycle Sequencing Kit (v3)。cDNA 文库是利用 mRNA-Seq 8 sample prep kit 构建的

Fulton R. W., d'Offay J. M. and Eberle R. (2013) Bovine herpesvirus-1: Comparison and differentiation of vaccine and field strains based on genomic sequence variation. Vaccine 31: 1471-1479

Larimore K., McCormick M. W., Robins H. S. and Greenberg P. D. (2012) Shaping of human germline IgH repertoires revealed by deep sequencing. J Immunol 189: 3221-3230

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技术

miRNA 和非编码 RNA

只有很小一部分的转录组被翻译，而大部分的转录产出为 ncRNA，它被分为两大类：小的和长的 RNA。microRNA（miRNA）是小的非编码 RNA（ncRNA）家族中的一类，它们作为内源性表达的小分子，调控其 mRNA 靶点所编码的蛋白质的表达。miRNA 与生长、发育和体内的免疫反应相关联。[139-141] 它们主要是通过与 RNA 诱导沉默复合物（RISC）靠近，在转录后水平靶定基因表达，[142,143] RISC 靶定互补 mRNA 的 3'- 非翻译区（3'-UTR），导致转录本被抑制或降解。[144,145]

最近的研究表明，先天和适应性免疫系统、CNS 和癌症的细胞中有着独特的 miRNA 表达谱。[146-149] 此外，新证据显示 HIV 靶细胞中 miRNA 改变 mRNA 表达以响应病毒复制的核心作用。[150] 高通量测序技术的改进，特别是深度和灵敏度，让研究人员能够分析已知和新发现的 miRNA，并鉴定它们确切的序列和长度，这有助于了解 RNA 编辑过程和突变事件。[151] 这让研究人员能够解码适应性和先天免疫系统发育及其功能反应中的非编码 RNA 调控网络。

> "Wherever the requirement for miRNAs has been tested in the immune system, essential roles have been found"
> Ansel et al. 2013

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ChIRP-Seq

通过 RNA 纯化的染色质分离（ChIRP-Seq）是一种检测基因组中非编码 RNA（ncRNA）（如长链非编码 RNA，lncRNA）所在位置及其结合蛋白的操作。[152] 在这种方法中，样本首先被交联和超声处理。之后让生物素化的探针与感兴趣的 RNA 杂交，再利用链霉亲和素磁珠捕获这个复合物。经 RNase H 处理后，DNA 被提取出来并测序。通过深度测序，lncRNA/ 蛋白质相互作用位点可以以单碱基分辨率得以确定。[153]

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哺乳动物基因组的非蛋白编码部分编码了数千个大的基因间非编码 RNA（lincRNA）。为了鉴定与先天免疫反应激活相关的 lincRNA，这项研究应用定制芯片和 Illumina RNA 测序来分析 THP1 巨噬细胞。作者发现，先天激活后 159 个 lincRNA 差异表达。RNA-Seq 数据的进一步分析表明，linc1992 是许多免疫应答基因表达所必需的，包括细胞因子和 TNF-α 表达的调控因子。

Illumina 的技术：HiSeq 2000

Kirigin F. F., Lindstedt K., Sellars M., Ciofani M., Low S. L., et al. (2012) Dynamic microRNA gene transcription and processing during T cell development. J Immunol 188: 3257-3267

作者利用新一代测序来构建 T 细胞发育 miRNA 图谱，这反映了从鼠类造血干细胞到成熟的 CD4 和 CD8 胸腺细胞的发育过程中 miRNA 基因转录和加工的动态特性。他们发现，许多在骨髓祖细胞群中高表达的 miRNA 在胸腺群体中下调了 2-3 个数量级。他们也利用 ChIP-Seq 和 polyA RNA 富集（RNA-Seq）来定位 CD4 T 细胞中表达的 miRNA 基因的结构。

Illumina 的技术：Genome Analyzer$_{IIx}$，RNA-Seq 和 ChIP-Seq

Wang P., Gu Y., Zhang Q., Han Y., Hou J., et al. (2012) Identification of resting and type I IFN-activated human NK cell miRNomes reveals microRNA-378 and microRNA-30e as negative regulators of NK cell cytotoxicity. J Immunol 189: 211-221

作者利用新一代测序，对细胞因子激活过程中的人 CD56+ CD3- 自然杀伤（NK）细胞开展 smRNA 表达谱分析。在鉴定出的 200 多个新 miRNA 中，作者报告两个高丰度的 miRNA，miRNA-378 和 miRNA-30e，在 IFN-α 激活的 NK 细胞中下调。他们还发现，这两个 miRNA 分别靶定粒酶 B 和穿孔素，这表明 miRNA-378 和 miR-30e 在 NK 细胞激活过程中抑制人 NK 细胞的毒性。

Illumina 的技术：smRNA-Seq，18-30 bp 之间

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Bryniarski K., Ptak W., Jayakumar A., Pullmann K., Caplan M. J., et al. (2013) Antigen-specific, antibody-coated, exosome-like nanovesicles deliver suppressor T-cell microRNA-150 to effector T cells to inhibit contact sensitivity. J Allergy Clin Immunol 132: 170-181

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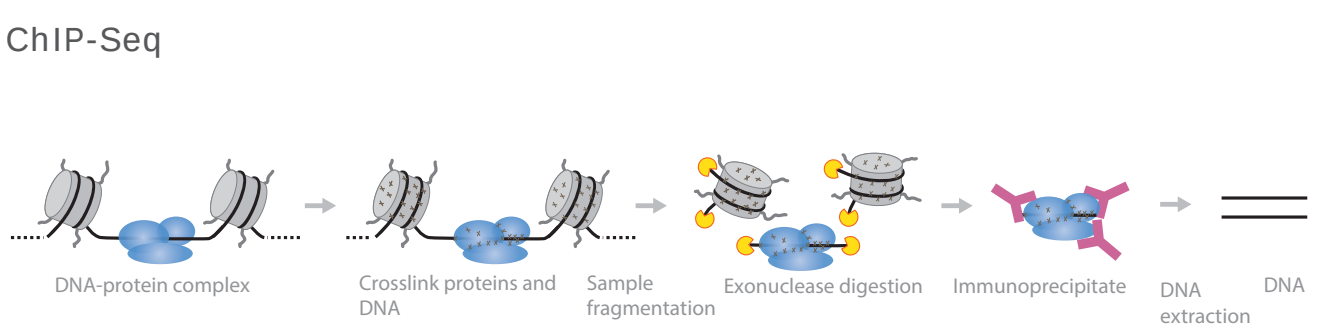
Nolte-'t Hoen E. N., Buermans H. P., Waasdorp M., Stoorvogel W., Wauben M. H., et al. (2012) Deep sequencing of RNA from immune cell-derived vesicles uncovers the selective incorporation of small non-coding RNA biotypes with potential regulatory functions. Nucleic Acids Res 40: 9272-9285

Yang G., Yang L., Zhao Z., Wang J. and Zhang X. (2012) Signature miRNAs Involved in the Innate Immunity of Invertebrates. PLoS ONE 7: e39015

ChIP-Seq

许多转录因子和染色质修饰酶都与先天和适应性免疫相关联。[154-157] 将染色质免疫沉淀技术应用于新一代测序分析中（ChIP-Seq），加速了全基因组范围内转录因子和染色体修饰酶的位置以及组蛋白修饰状态的鉴定。这种方法采用针对靶蛋白的抗体来分离 DNA- 蛋白复合物。从免疫沉淀的 DNA- 蛋白复合物中获得纯的 DNA，随后与测序接头连接，通过 PCR 扩增并在新一代测序平台上测序。[158] 最终，了解免疫系统的整体转录调控的需求让 ChIP-Seq 成为一项强大的应用，它会加深我们对干细胞分化、免疫记忆形成、疾病发展以及对环境刺激应答的动态过程的了解。[158,159]



ChIP-Seq 的流程。染色质免疫沉淀测序（ChIP-Seq）是一种定位特异的蛋白结合位点且相对成熟的方法。在这种方法中，DNA- 蛋白复合物在体内交联。样本随后被破碎并用核酸外切酶处理，以剪切未结合的寡核苷酸。使用蛋白特异的抗体对 DNA- 蛋白复合物进行免疫沉淀。DNA 被提取和测序，进而获得蛋白结合位点的高分辨率序列。

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Pub. No. 470-2014-003 Current as of 24July 2014

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