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尼安德特人、丹尼索瓦人基因组的发现及其对现代人类的影响

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摘要 2022年度诺贝尔生理学或医学奖授予瑞典生物学家、进化遗传学权威斯万特·帕博(Svante Pääbo), 以表彰他“在已灭绝古人类基因组和人类进化方面的发现”所作出的突出贡献. 人类之所以为“人”是科学家们一直以来感兴趣的研究方向, Svante Pääbo针对尼安德特人和丹尼索瓦人的研究有助于进一步加深对人类演化进程的理解, 意义重大. 他发现基因交流存在于早期的不同古人类之间, 现代人类的基因组中含有已灭绝古人类的基因序列, 比例不大, 却在生理和病理方面影响着当今人类. 本文简要总结了Svante Pääbo的研究发现, 并介绍遗传自尼安德特人和丹尼索瓦人的基因在新型冠状病毒肺炎(COVID-19)、免疫功能和低氧适应等方面是如何影响当今人类的.

关键词 尼安德特人, 丹尼索瓦人, 现代人类, 基因交流

北京时间10月3日下午, 备受瞩目的2022年度诺贝尔生理学或医学奖正式公布, 获奖者是瑞典科学家Svante Pääbo. 人类从何而来? 又将去往何处? 人类为什么独一无二? 诸如此类的问题长久以来深深地萦绕在科学家的脑海中. Svante Pääbo对已灭绝古人类的研究贡献以及他创造性建立的学科——古基因组学的发展应用为回答上述难题提供了基础, 距离最终答案更进一步.

尼安德特人和丹尼索瓦人遗传给现代人类的基因序列并不多, 但是对机体的生理和病理产生了不容小觑的影响, 备受研究者瞩目. 譬如, 尼安德特人的基因促进现代人类免疫系统的进一步完善, 可更好地抵御病原体的侵犯[1]. 丹尼索瓦人的基因提高了现代人类面对极端环境时的适应能力, 有利于生存繁衍[2]. 再者, COVID-19肆虐以来, 不同地区人群之间COVID-19的发病率和死亡率差异显著, 研究表明尼安德特人的基因与COVID-19病程进展有关, 可加剧罹患重症的风险, 而其他某些基因能够阻止病情恶化[3,4]. 本文对Svante Pääbo的研究进行简要概述, 着重阐述遗传自尼安德特人和丹尼索瓦人的基因序列对COVID-19、机体免疫功能和低氧适应等方面的影响.

1 Svante Pääbo的研究概述

1.1 尼安德特人

尼安德特人的命名与其被发现时所在的地理位置有关, 该地点位于德国的尼安德山谷. 1856年, 工人在野外工作中无意间发现了一堆化石骨骼, 后经解剖学家研究, 认为这些化石骨骼代表着一个全新的古人类物种[5]. 20世纪90年代初, Svante Pääbo团队针对上述化石骨骼中的一块肱骨展开研究, 从中提取了部分线粒体DNA, 1997年将该研究成果发表在*Cell*上[6]. 当时

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的观点认为，现代人类的体内不存在尼安德特人的遗传信息，但随着研究的不断深入，这一观点被推翻. 2008年, Svante Pääbo团队确定了尼安德特人的完整线粒体DNA，为后续研究尼安德特人的基因组序列奠定了基础[7]. 2010年，Svante Pääbo团队公布了首个尼安德特人的基因组序列草案, 尽管并不完整, 但证明了尼安德特人与现代人类存在基因交流，欧亚大陆的现代人类体内约1.5%~2.1%的基因组来自尼安德特人. 此外, 研究还表明, 基因交流发生地点不是先前推测的欧洲地区, 而是中东地区[8]. 2014年, 在尼安德特人基因组序列草案的基础上, Svante Pääbo团队公布了完整的尼安德特人基因组序列，更为有力地证实了现代人类体内含有遗传自尼安德特人的基因，还发现基因交流同样存在于尼安德特人和丹尼索瓦人之间，丹尼索瓦人基因组中至少有0.5%是由尼安德特人贡献[9].

1.2 丹尼索瓦人

丹尼索瓦人的命名同样与其被发现时所在的地理位置有关，该地点位于俄罗斯西伯利亚的丹尼索瓦山洞. 尼安德特人的发现是通过形态学研究, 而丹尼索瓦人的发现与之不同，凭借的是古基因组学相关研究. 2010年初，Svante Pääbo团队在*Nature*报道了一个完整的线粒体DNA序列，来自于丹尼索瓦山洞的一块化石骨骼, 经研究对比, 认为该序列代表一个未知的古老人种[10]. 同年, 该团队后续正式将这个未知的古老人种命名为丹尼索瓦人，并测序完成了丹尼索瓦人的基因组序列草案. 当时的研究仅表明丹尼索瓦人对大洋洲的现代人类基因组做出了贡献，占比约为3%~6%，并不清楚丹尼索瓦人是否与欧亚大陆的现代人类之间存在基因交流[11]. 直到2012年，Svante Pääbo团队才公布了完整的尼索瓦人的基因组序列[12]. 2014年, 综合一系列的相关研究成果, Svante Pääbo团队最终确定亚洲大陆的现代人类体内含有遗传自丹尼索瓦人的基因序列, 表明2个种群发生过基因交流. 丹尼索瓦人对亚洲大陆的现代人类的基因组贡献极低, 占比约为0.2% [9].

诺贝尔奖委员会对Svante Pääbo颁奖词中提到: 他凭借开创性的研究完成了看似无法完成的工作——对已灭绝的人类近亲尼安德特人的基因组进行测序；发现了以前未知的古人类丹尼索瓦人；证实了已灭绝的古人类的基因渗入到现代人类身上，这些基因仍在生理学上影响着现代人类. 同时，基于Svante Pääbo开创性的研究, 一门新的学科应运而生——古基因组学. 通过揭示、区分现存人类和已灭绝的古人类的基因差异, 他的发现为探索人类之所以为“人”的独特之处奠定了基础.

2 尼安德特人的基因与COVID-19

2.1 加剧COVID-19病程恶化的风险

COVID-19的发病率和死亡率很大程度取决于患者年龄和自身健康状况等关键因素，但遗传危险因素理应受到高度重视[13]. 相关研究发现，重症COVID-19 (sCOVID-19)患者的3号染色体上存在一个基因簇的突变, 鉴于该突变是高度连锁的, 表明与遗传因素关系密切[14]. 研究表明，该基因簇是从尼安德特人遗传而来, 携带者感染COVID-19后进展为sCOVID-19的风险显著升高[4]. 有趣的是，携带该基因簇的现代人群的分布是不均匀的, 多见于南亚和部分中东地区, 而在东亚和非洲地区非常少见. 考虑到现代人类基因组中的大部分尼安德特人的基因源于大约5万~5.5万年前发生在中东地区的杂交, 有观点认为, 导致不均匀分布的原因可能与尼安德特人的地理分布位置有关[4,15]. 一项研究有力地支持了上述观点，通过比较伊朗和蒙古国COVID-19死亡率，发现两国流行的SARS-CoV-2突变株是相同的, 尽管伊朗的人口数量约是蒙古国的26倍, 但伊朗的COVID-19死亡率显著高于蒙古国[16].

为什么3号染色体上的基因簇与sCOVID-19相关联? 可能与基因簇中包含的基因，如*CCR9*、*CXCR6*、*XCR1*、*LZTFL1*、*SLC6A20*以及*FYCO1*等有关[17]. *CCR9*、*CXCR6*和*XCR1*基因编码的蛋白都属于趋化因子受体家族，在免疫应答和炎症反应等方面起重要作用[18,19]. CCR9在病原体感染期间调节免疫细胞募集, 诱导炎症反应，现已证实COVID-19患者外周血中单核细胞CCR9表达显著降低[19,20]. 常驻记忆T细胞是抵御呼吸道病原体感染的第一道防线，研究表明CXCR6与其配体CXCL16参与调节感染部位常驻记忆T细胞的迁移和募集[21]. XCR1主要与树突状细胞介导的细胞毒性免疫反应有关，而最近的研究发现XCR1可能与血管紧张素转换酶2(ACE2)相互作用[22,23]，推测上述3种受体可能参与机体感染新型冠状病毒(SARS-CoV-2)引起的免疫反应, 影响病程的进展和转归. *LZTFL1*基因编码的亮氨酸拉链转录因子样1在抗原呈递细胞与淋巴细胞相互作用中发挥作用，与免疫突触的形成有关[24]. *SLC6A20*编码亚氨基酸钠(脯氨酸)转运体1(SIT1), 在功

能上与SARS-CoV-2的功能受体——ACE2相互作用[25,26]. 双膜囊泡是冠状病毒的主要复制位点, 并且可以把新合成的病毒RNA释放到细胞质, 而FYCO1蛋白被认为与双膜囊泡的转运有关[27,28]. 综合来讲, 上述基因与机体免疫反应以及SARS-CoV-2感染宿主细胞关系密切, 不过目前的数据仍不能准确地阐述遗传自尼安德特人的基因是如何增加罹患sCOVID-19风险的, 亟需未来深入研究探讨.

2.2 降低COVID-19病程恶化的风险

COVID-19全球范围内大流行的背景下, 伊始的研究成果仿佛表明遗传自尼安德特人的基因只会造成悲剧性的后果. 其实不然, 同样是遗传自尼安德特人的某些基因在抵御sCOVID-19中起到重要作用. 一段位于12号染色体上的基因区域被证实能够降低约22%感染COVID-19后发展为sCOVID-19的风险[3,29]. 经研究确认, 在不到10万年前现代人类与尼安德特人相遇, 通过基因交流获得上述基因区域. 现代人群中该基因区域的主要分布除非洲和澳洲以外的欧亚大陆以及美洲. 值得注意的是, 在撒哈拉以南的非洲人群几乎完全不携带该基因区域, 但分布于美洲的非洲血统人群是携带的, 可能的原因是不同血统人群之间的基因交流[29,30].

深入的研究部分揭示了位于12号染色体上特定的基因区域是如何降低sCOVID-19风险的. 寡苷酸合成酶基因(*OAS1*)就定位于此区域, 其编码的蛋白质OAS1具有抗病毒功能. 病毒感染细胞后, OAS1识别病毒的RNA被激活, 催化形成寡聚腺苷酸2-5A, 2-5A进一步激活核酸内切酶RNaseL, 被激活的RNaseL可以降解病毒的RNA, 抑制病毒蛋白合成, 促进感染病毒的细胞发生凋亡, 最终有效地阻止病毒感染[31,32]. 关于免疫系统疾病的研究显示, OAS1在体内的变化水平可用于辅助诊断疾病以及判断病程进展. 同样, 研究证实OAS1蛋白表达量的多少以及酶活性的高低能够影响COVID-19的易感性和严重性, 提示OAS1可能是用于评估COVID-19易感性和判断病程发展转归的临床应用指标[33]. 与新型冠状病毒(SARS-CoV-2)相同家族的其他类型的冠状病毒尽管能够产生降解2-5A以及降低RNase-L酶活性的病毒蛋白, 但仍能逃避宿主的免疫系统. 然而, 现有的实验数据认为SARS-CoV-2感染细胞后无法运用上述的免疫逃逸机制拮抗OAS1-RNaseL介导的抗病毒效应. 体外实验表明, SARS-CoV-2对OAS1-RNaseL介导的抗病毒效应敏感[34~36]. 因此, 遗传自尼安德特人的基因编码的抗病毒蛋白OAS1是潜在的抗COVID-19新型药物靶标, 为人类能够成功战胜COVID-19带来了一丝曙光. 但是, 围绕OAS1的抗病毒药物研发工作需要多学科之间的精诚协作, 任重而道远.

同样是遗传自尼安德特人的基因片段, 一个起助燃的作用, 加剧COVID-19的进程; 另一个则阻断病程的恶化, 起保护作用. 既然两者互为对立面, 那么所涉及的多个免疫相关基因之间存在怎样的关联? 确切的调控机制是什么? 诚然, 综合现今的研究并不能清晰地解答上述问题, 相信细致深入的研究已然展开, 问题的答案终将公布于众.

3 尼安德特人的基因与免疫系统

尼安德特人在欧亚大陆生存了几十万年, 可能已经很好地适应了当地环境以及各种病原体[37,38]. 现代人类走出非洲踏入欧亚大陆与其相遇, 尼安德特人的基因渗入到现代人类, 促进了现代人类免疫系统的进一步构建和完善[39].

针对遗传自尼安德特人的基因数据, 利用生物信息分析等相关技术从中鉴定出多个与免疫反应有关的基因, 其中大多数基因所涉及的研究数量较少, 扩大探索显得尤为重要[40,41]. 目前, 对于*OAS1*、*TLR1*、*TLR6*和*TLR10*几个基因的研究相对较多, 而*OAS1*基因已在本文的2.2中对其进行了详细的阐述. *TLR1*、*TLR6*、*TLR10*基因以基因簇的形式定位于人体的4号染色体上, 其编码的蛋白质分别为TLR1、TLR6和TLR10, 均属于Toll样受体(TLRs)家族. 三者发挥作用需要与TLR2结合形成异二聚体, 能够识别多种病原体, 引发炎症反应和介导先天免疫[42~44]. 遗传自尼安德特人的*TLR1*、*TLR6*、*TLR10*基因单倍型在欧洲和亚洲人的基因组中有较高的表达频率[45~47]. 研究发现, 上述基因单倍型上调淋巴细胞中TLR1、TLR6和TLR10蛋白的表达量, 意味着机体对病原体识别的能力大幅提高[45]. 研究证实*TLR1*、*TLR6*、*TLR10*基因单倍型与幽门螺杆菌血清抗体阳性相关, 能够降低感染幽门螺杆菌的风险[48,49]. 另有研究报道称携带*TLR1*、*TLR6*、*TLR10*基因单倍型的人群暴露于过敏原时更容易诱发过敏性哮喘和鼻炎[50,51], 说明遗传自尼安德特的基因提高机体先天免疫的同时, 过高的免疫应答会引发超敏反应, 机体对过敏原更加敏感, 导致过敏性疾病的发生和发展. 现代人类基因组约1.5%~2.1%来源于尼安德特人, 占比虽小, 却对现代人类的免疫系统产生了深远的影响. 当

前的研究仅揭示了遗传自尼安德特人的基因与现代人类免疫系统之间复杂关系的冰山一角，系统全面地了解两者复杂的关系需要今后不断地探索.

4 丹尼索瓦人的基因与低氧适应

类似于尼安德特人，丹尼索瓦人的基因同样在环境适应方面影响着现代人类，尤其是极端恶劣的生存环境.

在我国，藏族人群长期居住在平均海拔超过4000 m、氧含量比海平面低40%左右的青藏高原地区，具备极强的低氧适应能力[52]. 研究证实, 藏族人群的低氧适应能力与*EPAS1*基因关系密切. *EPAS1*基因编码的蛋白质是低氧诱导因子HIF-2α，转录调控与红细胞生成、血管生长和铁代谢等方面有关的靶基因[53,54]. 研究对藏族人群的*EPAS1*基因进行测序, 发现多个单核苷酸多态性(SNPs)的存在频率远高于低海拔地区人群. 而针对丹尼索瓦人的研究观察到了几乎完全吻合的基因测序结果，表明藏族人群的*EPAS1*基因遗传自丹尼索瓦人[2,55,56]. 藏族人群*EPAS1*基因的SNPs下调HIF-2α表达, 引起血细胞和血红蛋白浓度的降低，血液黏滞度下降, 有利于血液流动，机体更能适应低氧环境. 此外, *EPAS1*基因的遗传变异降低了藏族人群罹患红细胞增多症的风险, 抑制肺动脉高压的形成, 利于人群在低氧环境中生存[57,58]. 再者, 喜马拉雅山脉南麓的尼泊尔人长期暴露在恶劣的高海拔低氧环境中, 适应力极强. 研究同样表明尼泊尔人*EPAS1*基因的多个SNPs是其抵抗缺氧的多个原因之一. 现已被证实上述*EPAS1*基因的SNPs遗传自丹尼索瓦人[59,60]. 携带者形成了不同于低海拔地区人群的氧气摄取、运输和交换能力，在应对高原低氧的生存环境中优势显著[61]. 遗传自丹尼索瓦人的基因给居住于极端环境的藏族人群以及尼泊尔人带来了一定的优势，对其如何调节低氧适应的认识仍不够全面, 需要扩大研究. 另外, 低氧适应很可能是多个基因共同参与调控的，梳理清楚*EPAS1*与其他基因之间复杂的互作机制需要国内外学者不懈地研究和探索.

5 总结与展望

Svante Pääbo凭借在已灭绝古人类基因组和人类进化方面的发现摘得2022年诺贝尔生理学或医学奖的桂冠，其开创性的研究成果为探索人类之所以为“人”奠定了坚实基础. 诚然, 尼安德特人和丹尼索瓦人已经灭绝，但是遗传自它们的基因序列仍在sCOVID-19、免疫功能和低氧适应等方面深深影响着现代人类. 伴随古基因组学的发展和科学家们积极的探索，一扇全新的大门正在缓缓打开，对未来全面阐述已灭绝的古人类是如何在生理和病理方面影响现代人类的意义重大. 同时, 研究遥远陌生的古人类加深了现今对各种疾病的理解, 为开发更好的治疗方案提供新思路, 终将造福全人类.

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Summary for “尼安德特人、丹尼索瓦人基因组的发现及其对现代人类的影响”

Discovery of genomes of Neanderthal, Denisova and its impact on modern human

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The 2022 Nobel Prize in Physiology or Medicine was surprisingly awarded to Svante Pääbo for his establishment of a novel discipline, paleogenomics. Paleogenomics offers a potent means of understanding the course of modern human evolution. Pääbo’s research lays a solid foundation for answering the question of what makes us, Homo sapiens, different from other hominins. This year’s Nobel laureate has observed genetic admixture in different groups of archaic humans, and found that parts of the genetic code of these extinct branches of the human evolutionary tree are present in the genomes of modern humans, influencing us both physiologically and pathologically. In this paper, Pääbo’s research findings are first summarized to deepen, consolidate, and broaden the understanding of extinct hominins and paleogenomics. Pääbo’s team was responsible for the first draft sequence of the Neanderthal genome, showing that between 1.5% and 2.1% of modern Eurasian genomes are derived from Neanderthals. They followed this with the complete Neanderthal genome sequence. Similarly, Pääbo and colleagues published both the first draft and the complete sequence of the Denisovan genome. They found evidence of genetic admixture between the Denisovans and modern humans, showing that the genomes of people in Oceania are between 3% and 6% Denisovan while the figure for people in Asia is about 0.2%. Furthermore, at least 0.5% of the Denisovan genome was derived from the Neanderthals. The COVID-19 pandemic provided evidence of the good and bad qualities of the Neanderthal inheritance, particularly in relation to the immune systems of modern humans. A gene cluster on chromosome 3 that was inherited from Neanderthals was found to be associated with severe COVID-19. This gene cluster is mainly found in modern humans from the Middle East and southern Asia. Several genes included in this cluster have been demonstrated to play a role in immune functions and may be involved in the infection process of SARS-CoV-2. Interestingly, a gene segment on chromosome 12 which was also inherited from Neanderthals is protective against severe COVID-19. This gene segment is mainly distributed in inhabitants of Europe, Asia, and the Americas, but not of Africa and Oceania. This segment contains the OAS1 gene which encodes proteins that activate enzymes that are important during RNA-viral infections. This is part of the reason why carrying this gene segment can reduce the risk of developing severe COVID-19. The Neanderthals have contributed many immune-related genes to modern humans, including the well-documented cluster containing the TLR1, TLR6, and TLR10 genes. TLR1, TLR6, and TLR10 gene haplotypes inherited from Neanderthals show high expression frequencies in the genomes of Europeans and Asians. These three genes play important roles in the innate immune system that is the first line of defense against pathogens and can trigger adaptive immunity. The TLR1, TLR6, and TLR10 haplotypes increase the expression of their encoded proteins, which not only enhances innate immunity but can also induce hypersensitivity resulting in allergy. Lastly, the way in which Denisovan genes affect Tibetan and Nepalese people to adapt to the extreme conditions of the Qinghai-Tibet Plateau and the Himalayas, respectively, are discussed. The EPAS1 gene in Tibetans and Nepalese is inherited from the Denisovans and encodes the hypoxia-inducible factor HIF-2α, a transcription factor involved in the body’s response to low-oxygen conditions. That is to say, both Tibetan and Nepalese people are well adapted to hypoxic and cold conditions thanks to a gene inherited from the Denisovans. This paper intends to inspire more research into extinct hominins and paleogenomics, which can enhance our knowledge of certain diseases, allowing the development of new beneficial therapeutic targets. Thus, surprising results in a new field will eventually reap great benefits.

Neanderthal, Denisova, modern human, genetic admixture

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