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终结结核病

·专题报道·

宿主基因与结核病易感性研究概览

胡文娟,徐凯进

浙江大学医学院附属第一医院 传染病诊治国家重点实验室 国家感染性疾病临床医学研究中心 国家传染病医学中心 感染性疾病诊治协同创新中心,浙江 杭州 310003

[摘 要] “吕贝克灾难”、双胞胎研究及收养研究等流行病学观察性研究结果都充分表明,宿主基因是决定机体对结核分枝杆菌是否易感和感染后是否发病的重要因素。从连锁分析到全基因组关联研究已发现,人白细胞抗原(HLA)类基因和非HLA类基因(*SLC11A1*、*VDR*、*ASAP1*、细胞因子类基因及模式识别受体类基因)与结核病易感性相关。本文对近年涉及结核病易感性基因的研究进行回顾,重点叙述HLA类基因和非HLA类基因与结核病发病的关联,并对文中涉及的基因进行富集分析,结果提示大部分基因参与免疫炎症调控,并与自身免疫性疾病关系密切,可为后续结核感染风险预测和结核病诊治提供参考。

[关键词] 结核病;宿主基因;易感性;富集分析;风险预测;综述
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Research progress on genetic control of host susceptibility to tuberculosis

HU Wenjuan, XU Kaijin (*The First Affiliated Hospital, Zhejiang University School of Medicine, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou 310003, China*)
Corresponding author: XU Kaijin, E-mail: zdyxyxkj@zju.edu.cn, https://orcid.org/0000-0001-8126-5008

[**Abstract**] The “Lübeck disaster”, twins studies, adoptees studies, and other epidemiological observational studies have shown that host genetic factors play a significant role in determining the host susceptibility to *Mycobacterium tuberculosis* infection and pathogenesis of tuberculosis. From linkage analyses to genome-wide

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第一作者:胡文娟,硕士研究生,主要从事结核分枝杆菌及非结核分枝杆菌治疗的临床与基础研究;E-mail:wenjuanhu@zju.edu.cn;https://orcid.org/0000-0001-9726-9660
通信作者:徐凯进,主任医师,教授,博士生导师,主要从事结核病等重大、新突发传染病防治研究;E-mail:zdyxyxkj@zju.edu.cn;https://orcid.org/0000-0001-8126-5008

association studies, it has been discovered that human leucocyte antigen (HLA) genes as well as non-HLA genes (such as *SLC11A1*, *VDR*, *ASAP1* as well as genes encoding cytokines and pattern recognition receptors) are associated with tuberculosis susceptibility. To provide ideas for subsequent studies about risk prediction of MTB infection and the diagnosis and treatment of tuberculosis, we review the research progress on tuberculosis susceptibility related genes in recent years, focusing on the correlation of HLA genes and non-HLA genes with the pathogenesis of tuberculosis. We also report the results of an enrichment analysis of the genes mentioned in the article. Most of these genes appear to be involved in the regulation of immune system and inflammation, and are also closely related to autoimmune diseases.

[**Key words**] Tuberculosis; Host gene; Susceptibility; Enrichment analysis; Risk prediction; Review

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[**缩略语**] 人白细胞抗原(human leucocyte antigen,HLA);孟德尔遗传易感分枝杆菌病(mendelian susceptibility to mycobacterial disease,MSMD);全基因组关联分析(genome wide association study,GWAS);单核苷酸多态性(single nucleotide polymorphism,SNP);白介素(interleukin,IL);溶质载体家族11成员1(solute carrier family 11 member 1,SLC11A1);维生素D受体(vitamin D receptor,VDR);二磷酸腺苷核糖化因子鸟苷酸激酶1(Arf GAP with SH3 domain,ankyrin repeat and PH domain 1,ASAP1);模式识别受体(pattern recognition receptor,PRR);肿瘤坏死因子(tumor necrosis factor,TNF);Toll样受体(Toll-like receptor,TLR)

结核病是结核分枝杆菌引起的感染性疾病。2021年全球有1060万人罹患结核病[1]。全世界约1/4人口感染过结核分枝杆菌,但仅5%~10%感染人群会在其一生中发展为结核病[1],其余感染者则为结核潜伏感染。还有研究发现,尽管持续高水平暴露于结核分枝杆菌,但10%~20%“抵抗者”不会受到感染[2-5]。宿主遗传因素会导致结核感染的个体差异。从流行病学观察性研究、连锁分析到全基因组关联研究都发现宿主遗传背景与结核病易感性相关,并发现许多基因位点与结核病关系密切,包括HLA类基因和非HLA类基因[6]。本文综述了结核易感基因研究发展过程及已知相关基因,探讨结核病与宿主基因易感性关系,以期为结核病精准防控提供依据,助力结核病疫情早日得到控制。

1 结核病易感性研究发展过程

20世纪30年代,“吕贝克灾难”、双胞胎研究和收养研究等流行病学观察性研究是较早聚焦宿主基因与结核病易感性相关的研究。之后的连锁分析、候选基因关联研究及全基因组关联研究相继发现许多基因位点与结核病关系密切,其中MSMD基因突变位点的发现是结核基因易感性的有力例证。

1.1 流行病学观察性研究提示宿主基因与结核病易感性相关

1929年,德国吕贝克总医院251名新生儿接种了被不明剂量活结核分枝杆菌污染的卡介苗,致使228名婴儿罹患结核病,其中72名婴儿在接种1年内死于结核病,这就是“吕贝克灾难”。而后Fox等[7]对该事故进行回顾性分析,发现部分新生儿对结核分枝杆菌感染具有明显抵抗力,但部分暴露于低剂量结核分枝杆菌即发病的新生儿可能具有先天易感性。双胞胎研究及收养研究结果也表明,人类遗传背景与结核病易感性相关。1943年,Kallmann等[8]一项涉及2534份样本的双胞胎研究表明,发展为活动性结核病的概率与指示病例的血缘关系成正比,最高概率为同卵双胞

胎,达87.3%;且当同卵双胞胎中一个在明确接触结核病患者后并不发病时,另一个死于结核病的概率接近零。1988年,Sørensen等[9]一项关于基因和环境因素对成年被收养者早逝影响的研究指出,早逝尤其因感染(包含结核病)而早逝的成年人具有很强的遗传背景。以上研究提示,宿主对结核分枝杆菌的易感程度受遗传背景影响,这开启了结核病宿主基因易感性研究的序幕。

1.2 关联研究等方法引入结核病易感性研究

疾病遗传易感性研究方法主要有基于家系的连锁分析、基于群体基因频率分析的候选基因关联研究和全基因组关联研究。每种研究方法都有其优势和局限性,一般来说,连锁分析特别适用于有高外显率,符合经典孟德尔单基因性状遗传规律的相关罕见基因定位;而对于复杂性状而言,运用关联研究则更具优势,但关联研究亦不能识别复杂性状的所有遗传决定因素。关联研究可分为候选基因关联研究和GWAS,其中前者由于候选基因是主观设定的,研究结果重复性差,结果可靠性有待提升,正逐渐被GWAS取代。GWAS指在全基因组层面上筛选出疾病相关SNP位点。2010年,第一个识别结核基因易感性位点的GWAS来源于加纳和冈比亚人群样本分析,结果表明位于染色体18q11.2上基因贫乏区的rs4331426与结核病易感性相关[10]。GWAS在遗传力缺失、责任位点识别及疾病预测方面具有一定局限性[11],因此需要进一步联合全基因组测序和基因型填充的方法,可为破译整个基因组提供可能,有利于发现罕见变异与疾病的关联。值得注意的是,对关联研究所得出的结论须客观、谨慎解释,因为统计学上的关联并不代表实际因果关联,得出的变异序列很有可能只是与真正的致病序列存在连锁不平衡关系[12]。

1.3 MSMD是宿主基因与结核病易感性相关的确切证据

通过连锁分析及关联研究发现了MSMD基因突变的许多位点,这是宿主基因与结核病易感性的有力证据。MSMD是一组以对微弱毒力的分枝杆菌(如卡介苗、环境分枝杆菌)和沙门菌易感为特点的原发性免疫缺陷病。从1996年明确第一个MSMD突变位点以来,截至目前已发现17个基因突变,分别为*IFNGR1*、*IFNGR2*、*IL12B*、*IL12RB1*、*STAT1*、*NEMO*、*CYBB*、*TYK2*、*IRF8*、*ISG15*、*SPPL2A*、*JAK1*、*RORC*、*IL12RB2*、*IL23R*、*IFNG*、*TBX21*。这些突变基因与γ干扰素/IL-12/23通路相关,该通路对结核分枝杆菌感染清除至关重要,通路障碍会导致γ干扰素分泌或免疫应答缺陷,从而使得个体对结核分枝杆菌易感[13]。Alangari等[14]指出,对于γ干扰素产生受损而发生播散性结核病的年轻患者,重组γ干扰素的补充治疗是有效的。临床上对于儿童反复发生严重的分枝杆菌感染,应警惕MSMD的可能。

2 结核病易感性相关基因概述

与结核病易感性相关的基因大致可以分为HLA类基因和非HLA类基因两大类。当前涉及非HLA类基因研究较多。

2.1 与结核病易感性相关HLA类基因

HLA复合体位于第6号染色体短臂上,是迄今已知的人体最复杂的基因系统。整个复合体基因分为HLA-Ⅰ类、HLA-Ⅱ类和HLA-Ⅲ类基因。HLA-Ⅰ类和HLA-Ⅱ类基因分别编码结合及提呈抗原的HLA-Ⅰ类和HLA-Ⅱ类分子,其中HLA-Ⅰ类分子将抗原提呈给$CD8^+$T细胞,HLA-Ⅱ类分子则将抗原提呈给$CD4^+$T细胞,均与适应性免疫应答调节相关。大部分HLA-Ⅲ类基因的功能不明,少数HLA-Ⅲ类分子可以通过补体途径进行免疫调节。2019年中国香港的一项研究结果提示,HLA-DQA1*03位点(rs9272785)在全年龄分析时与结核病易感性无关,但进行年龄亚组分析时,发病年龄为20~40岁的患者该位点与结核病易感性相关,因此提出临床结核病在不同年龄组有不同的发病机制,而遗传因素可能只在早发性结核病中起重要作用[15]。早在2010年,Alcaïs等[16]指出遗传效应在传染病早发患者中比晚发患者更明显。这提示在结核病基因易感性研究中,不能只单纯考虑结核感染状态,也需要注重年龄对研究结果的影响,年龄亦是发病机制中不可忽略的因素。近年HLA类基因与结核病易感性关系研究详见表1。

2.2 与结核病易感性相关非HLA类基因

目前关于非HLA类基因与结核病易感性的研究较多,大致分为*SLC11A1*基因、*VDR*基因、*ASAP1*基因、细胞因子类基因和PRR基因。

2.2.1 *SLC11A1*基因 *SLC11A1*基因也称为*NRAMP1*,位于染色体2q35区域,是第一个被识别的结核病易感性相关基因,1998年被证明与西非

表 1 与结核病易感性有关的HLA类基因研究汇总
Table 1 Summary of relationship between HLA genes and tuberculosis susceptibility

HLA类型	样本来源	HLA等位基因	与结核病关系	参考文献
HLA-Ⅰ	加拿大	A*03	易感	[17]
	南非	A*30:01、B*41:01、B*42:02、C*05:01、C*06:02、C*17:01	易感	[18]
		A*01:01、A*34:02、B*07:02、C*04:01、C*07:02	抵抗	[18]
HLA-Ⅱ	巴西	DRB1*04:11:01	易感	[19]
		DRB1*04:07:01	抵抗	[19]
	加拿大	DRB1*05:03	易感	[17]
	泰国	DRB1*09:01、DQB1*03:03	易感	[20]
	中国汉族	rs9272461	抵抗	[21]
	南非	DRB1*11:01	抵抗	[18]
		DRB1*04:01、DRB1*15:01	易感	[18]
	中国香港	DQA1*03	易感	[15]
	南印度	DPB1*0101/0201、DQB1*050301/0601	易感	[22]
		DPB1*1501、DQB1*0303	抵抗	[22]
	中国新疆	*DQB2*:rs7453920 G>A:GA	易感	[23]
HLA-Ⅲ	莫桑比克	rs1800629(*TNF-α*)	易感	[24]
	中国藏族和伊朗	rs1800629(*TNF-α*)	抵抗	[25-26]
	墨西哥	rs361525:A(*TNF-α*)	易感	[27]
	中国	rs1799724(*TNF-α*)	易感	[28]
	北印度	rs1041981(*TNF-β*)	易感	[29]

HLA:人白细胞抗原;TNF:肿瘤坏死因子.

地区人群的结核病易感性显著相关[30]。*SLC11A1*是一种控制细胞内病原体(沙门菌、分枝杆菌及利什曼虫)的宿主抗性因子,在调节铁稳态、吞噬小体成熟、固有淋巴细胞激活、一氧化氮和活性氧及脂质运载蛋白2的生成方面具有重要作用[31]。*SLC11A1*作为被广泛研究的宿主基因之一,许多学者发现其与患者结核病易感性相关;*SLC11A1*基因3′非翻译区与中国和印度安得拉邦肺结核风险增加相关,通过对研究对象进行性别和年龄亚组分析,发现中国女性和年龄不超过65岁者该位点与肺结核风险增加相关[32-33]。2022年一项研究提示,rs17235409(D543N)位点与增加脊柱结核发病风险相关[34]。除此之外,*SLC11A1*还与耐多药结核病、较长的痰培养转化时间及空洞形成相关[35]。SLA11A1蛋白主要分布于巨噬细胞吞噬溶酶体膜上,与巨噬细胞清除结核分枝杆菌密切相关,其作为结核病防治生物标志物具有较大前景,值得进一步深入研究。

2.2.2 *VDR*基因 研究表明,1,25-二羟维生素D3可以抑制结核分枝杆菌生长[36],而缺乏25-羟维生素D3与结核病易感风险增加相关[37]。与结核病易感性关联密切的*VDR*基因多态性位点有APaI、Bsm、TaqI和FokI。一项荟萃分析结果显示,*VDR* FokI:f vs.F会增加东亚及东南亚人群结核病患病风险[38]。在中国、韩国、巴西、印度和伊朗等国的研究均发现,*VDR*基因与结核病易感性有关[25,39-42],其中中国和印度的*VDR* FokI:f与增加结核病患病风险相关,*VDR* FokI:F则与抵抗结核病患病风险相关[39,42]。摩洛哥的一项研究则指出,*VDR* f-b-a-T单倍型基因与当地肺结核抵抗显著相关[43]。当前,*VDR*基因在结核病易感性方面有较大争议,未能达成共识,若开展人体结核病测定血维生素D浓度的前瞻性临床试验,可为确定*VDR*基因与结核病易感性提供依据,为临床补充维生素D防治结核病提供可能。

2.2.3 *ASAP1*基因 *ASAP1*基因位于染色体8q24位置,编码腺苷二磷酸核糖基化因子鸟苷三磷酸酶活化蛋白(Arf GAP)。2015年,Curtis等[44]对来自俄罗斯标本的760万个基因突变位点进行研究,发现*ASAP1*基因的rs4733781位点和rs10956514位点与肺结核抵抗显著相关。由遗传决定的*ASAP1*表达的过度减少会引起被结核分枝杆菌感染的树突状细胞的迁移受损,这可能是结核病的发病机制之一。而后发现rs4733781等位基因A是中国汉族人群结核病的保护因素[45]。中国香港的一项研究结果表明,*ASAP1*基因的rs4733775、rs10089819及rs17210536位点与结核病易感性关系均无统计学意义[15]。作为新发现的基因,*ASAP1*在不同研究中不一致甚至相互矛盾的结果,还需更多的研究明确其意义。

2.2.4 细胞因子类基因 细胞因子对免疫细胞的发育分化、免疫应答及免疫调节至关重要,其参与了抗感染免疫应答的全过程。细菌可刺激感染部位的巨噬细胞释放IL-1、TNF-α、IL-6、IL-8和IL-12等细胞因子,引起局部和全身炎症反应,促进对病原体的清除。目前已发现很多编码细胞因

子、细胞因子受体的基因与结核病易感性相关，见表2。细胞因子类基因位点突变会影响机体对病原体的固有免疫及适应性免疫应答，从而对疾病易感。将包含*TNF*在内的26个细胞因子类基因在Metascape(www.metascape.org/gp/index.html)进行富集分析可发现，其中15个基因参与IL-10信号通路(多重检验调整后$P=10^{-32.57}$)，提示IL-10信号通路在结核病易感性中可能起重要作用，可以作为

表 2 与结核易感性有关的编码细胞因子类基因
Table 2 Summary of genes encoding cytokines and their receptors related to susceptibility to tuberculosis

基 因	基因多态性位点	样本来源	与结核病关系	参考文献	基 因	基因多态性位点	样本来源	与结核病关系	参考文献
IFNG	rs1861494	北印度、中国	易感	[29,46]	*IL-1B*	rs1143634	巴西	易感	[65]
	rs1861494	阿根廷	抵抗	[47]		rs16944	中国藏族	抵抗	[26]
	rs2069718	中国	抵抗	[48]	*IL-1R1*	rs10490571、rs956730、rs3917225	中国	易感	[66]
	rs1861493	北印度	易感	[29]	*IL-1RA*	rs4252019	北印度	易感	[29]
IFNAR1	rs72552343	中国	抵抗	[49]	*IL-1R2*	rs4851527	中国	抵抗	[66]
IFNGR1	rs1327474	中国新疆南部	抵抗	[50]	*IL-2*	–330T/G:TG	印度	易感	[54]
	rs11914、rs7749390	伊朗	抵抗	[51]	*IL-4*	rs2070874	北印度	易感	[29]
TNFRSF1B	rs3397	非洲	抵抗	[52]		–589C/T:CC	印度	易感	[54]
	rs1061624	中国	易感	[53]	*IL-6*	rs1800795	巴西南部	抵抗	[67]
TGF-β1	+869T/C:TC	印度	易感	[54]		rs2069837	中国汉族	抵抗	[26]
	rs2317130、rs4803457、rs4803455、rs11466313、rs11466334	中国	易感	[55]	*IL-10*	rs1800872	苏丹、巴西	易感	[41,63]
EREG	rs2367707、rs6446993	中国	易感	[56]	*IL-12B*	rs3212220、rs2853694	北印度	易感	[29]
	rs7675690	越南	易感	[57]		rs3212227	墨西哥、乌干达	易感	[27,68]
CCR2	rs1799864	印度	抵抗	[58]	*IL-17A*	rs2275913	巴西南部	抵抗	[67]
CCR5	rs2734648、rs1799987	中国	易感	[59]		rs8193036	中国	易感	[69]
CCL2	rs1024611	北印度、泰国、中国	易感	[60-62]		–152A/G	伊朗	易感	[70]
	rs2857656:CC	北印度	易感	[60]	*IL-17F*	rs763780	阿根廷	易感	[71]
	rs2857656:GC、rs1024611:AG	北印度	抵抗	[60]	*IL-18*	rs1946518、rs187238:C、rs2430561:AA	埃及	抵抗	[72]
CCL5	rs2280788	苏丹	抵抗	[63]		rs187238:GC+GG、rs2430561:A	埃及	易感	[72]
	rs2280789	摩尔多瓦	易感	[64]	*IL-22*	rs2227473:G	中国	易感	[73]
	rs2107538	印度	易感	[58]	*IL-27*	rs17855750	中国	抵抗	[74]
IL-8	rs2227307	墨西哥	易感	[27]		–964A/G	韩国	抵抗	[75]
IL-1A	rs1800587	巴西	易感	[65]					

IFN:干扰素;TNF:肿瘤坏死因子;TGF:转化生长因子;EREG:上皮调节蛋白;CCR:C-C-基元趋化因子受体;CCL:C-C-基元趋化因子配体;IL:白介素.

下一步重点研究的方向。

2.2.5 PRR基因 PRR是一类能够直接识别病原体相关分子模式以及在受损宿主细胞上表达损伤相关分子模式的受体。固有免疫细胞通过PRR识别病原体相关分子模式和损伤相关分子模式，介导非特异性抗感染、抗肿瘤、免疫调节以及适应性免疫应答过程。目前已发现许多结核病易感性相关基因可编码PRR，见表3。*TLR8*基因位于性染色体Xp22.2位置，许多研究结论都呈现出性别分层现象，如rs3764879和rs3764880等位基因G是南非女性结核病的易感因素，但在南非男性群体中却是结核病的保护因素[76]；rs3764880位点等位基因A与中国汉族女性人群结核病患病风险增加相关，但在中国汉族男性人群中与结核病抵抗相关[77]。男性X染色体数较女性少1条，*TLR8*等X染色体上基因效应可能对男性影响更大。《2022年全球结核病报告》指出，结核病最高负担来源于成年男性，占2021年全部结核病病例的56.5%，

表3 与结核易感性有关的编码模式识别受体类基因

Table 3 Summary of the relationship between genes encoding pattern recognition receptors and tuberculosis susceptibility

基 因	样本来源	基因多态性位点	与结核病关系	参考文献	基 因	样本来源	基因多态性位点	与结核病关系	参考文献
TLR1	中国藏族	rs5743604	易感	[78]			rs3764880:A(男)	抵抗	[77]
		rs5743557、rs5743596	抵抗	[78]		土耳其	rs3764880:A/(-)(男)	易感	[90]
	中国汉族儿童	rs5743618:G	易感	[79]	*TLR9*	中国汉族	rs187084:G/GA(肺结核)	易感	[77]
	加纳	rs3923647	抵抗	[80]			rs187084:GA(MTB感染)	抵抗	[77]
	印度	rs4833095	抵抗	[81]		越南	rs352142(显)、rs352143(隐)	易感	[91]
	伊朗	rs5743551、rs5743618	易感	[82]	*TLR10*	中国藏族	rs1146617、rs4129009(隐)	抵抗	[92]
	南非、巴西	rs5743618	易感	[76,83]		克罗地亚	rs11096957:A/A	易感	[93]
TLR2	中国	rs1898830	抵抗	[84]			rs11096957:A/C	抵抗	[93]
	印度	196–174 Ins > del	易感	[85]	*MBL2*	中国汉族	rs930507、rs2099902、rs10824793	易感	[94]
	巴基斯坦	Arg753Gln:AA	易感	[86]	*DC-SIGN*	巴西东北部	rs735240、rs2287886	易感	[95]
TLR4	墨西哥	rs4986790、rs4986791	抵抗	[87]			rs735239、rs4804803	抵抗	[95]
	中国新疆南部	rs4986790	易感	[50]		伊朗东南部	rs4804803	易感	[96]
	中国藏族	rs11536889:GC	抵抗	[84]	*CRP*	中国	rs1130864	易感	[97]
	中国江苏	rs10759932、rs2737190	易感	[88]	*AIM2*	巴西	rs1103577	抵抗	[98]
	印度	Thr399Ile	易感	[85]	*P2X7*	中国藏族	rs208290	易感	[99]
TLR6	中国藏族	rs5743808、rs5743827	易感	[89]		北印度	rs3751143	易感	[100]
TLR8	南非	rs3761624、rs3764879、rs3764880(女)	易感	[76]		中国汉族	rs2393799:C、rs208294	易感	[101]
		rs3764879、rs3764880(男)	抵抗	[76]	*NOD2*	印度	802C>T(隐)、2105G>A(隐)	易感	[102]
TLR8	中国汉族	rs3764880:AA(女)	易感	[77]					

显：显性模型；隐：隐性模型. TLR：Toll样受体；MTB：结核分枝杆菌；MBL：甘露糖结合凝集素；DC-SIGN：树突状细胞特异性细胞间黏附分子-3-结合非整合素；CRP：C反应蛋白；AIM：黑色素瘤缺乏因子；NOD：核苷酸结合寡聚化结构域.

远高于女性和儿童(分别为32.5%和11%)[1]。因此推测,男女结核病患病率呈现差异的原因可能与基因效应的性别偏倚现象有关。

3 结核病易感性相关基因富集分析

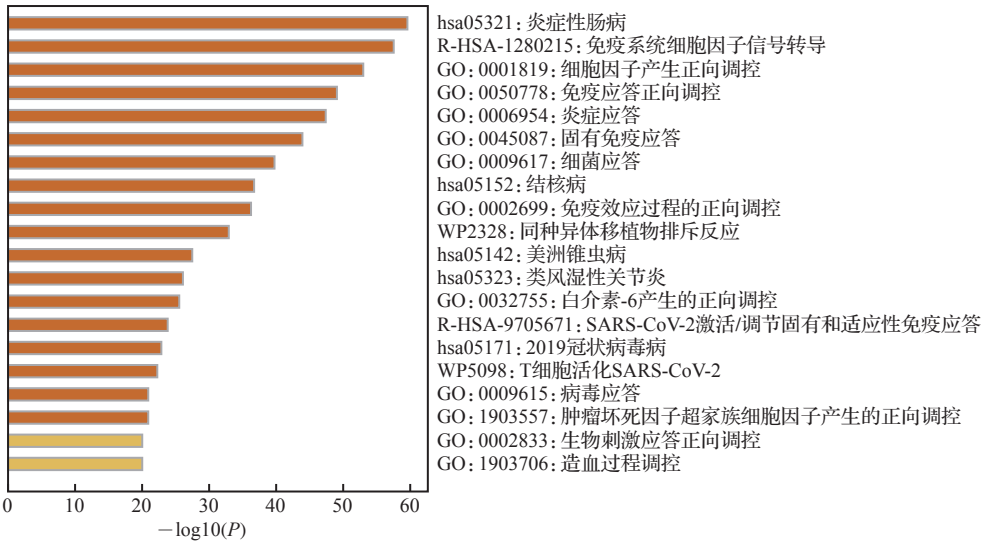
为解读易感基因背后所代表的生物学意义,挖掘其与通路或生物学过程的关联,采用Metascape(www.metascape.org/gp/index.html)对文献涉及的66个结核易感相关基因进行富集分析[103],得出前20个与富集基因相关的生物学过程或通路聚类,其中与免疫系统细胞因子信号转导、细胞因子产生正向调节和炎症性肠病相关的基因分别占70.31%、60.94%和43.75%。炎症性肠病相关基因占比虽不是最高,却与本次富集基因最显著相关(多重检验调整后$P=10^{-55.27}$)。图1为富集分析所得与富集基因相关前二十位生物学过程或通路聚类,推测结核病易感性相关基因绝大部分都参与炎症免疫调控。基于DisGeNET数据库进行富集分析,与富集基因相关前二十位疾病聚类见图2。可见与富集基因关系密切的疾病除结核病以外,还有炎症性肠病[104]、白塞综合征以及川崎病,表明结核与自身免疫性疾病具有共病可能,两者潜在病理机制可能是共通的[105]。

4 结 语

全球有近1/4的人口感染过结核分枝杆菌,绝大多数为潜伏感染,如果能在个体发展为活动性结核病之前将其识别,并且进行预防性治疗,这对结核病诊治及阻止结核病流行大有裨益。目前研究发现,许多基因都与结核病易感性相关,这提示可能有多基因参与致病。从宿主基因角度探究结核发病机制,通过易感基因对结核病发病及病情进展进行风险预测,可为临床预防结核感染及结核病诊疗提供新靶点。

对结核病与宿主基因易感性相互关系的探索需要运用多组学的系统生物学方法,如基因组学、蛋白质组学、转录组学等。目前已发现许多可用来预测结核病病情进展风险的转录组基因生物标志物,以协助诊断不同类型结核病和预测疾病进展。2016年,Zak等[106]在南非进行了一项青少年前瞻性队列研究,用外周血进行转录组分析得出16个全血基因标志物,可用来预测1年内结核病进展,敏感度为66.1%,特异度为80.6%,并在南非和冈比亚独立队列样本中得到验证。2020年巴西的一项研究指出,基因转录组标志物PREDICT29可以预测近期暴露结核病的个体在结核病发病前至少5年的疾病进展或再激活风险,敏感度为74.2%,特异度为84.8%[107]。也许在不久的将来,结核易感基因也可对疾病进展人群进行风险分层,用多基因风险评分预测疾病发病风险。

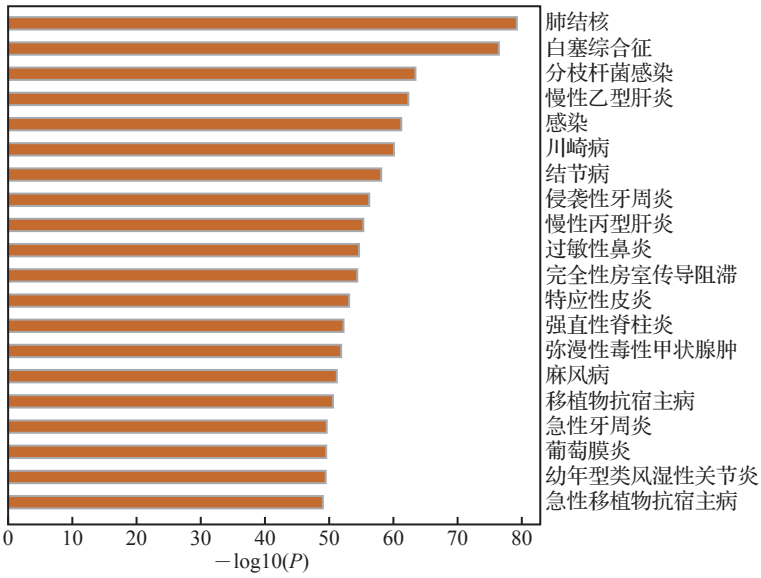
结核基因易感性研究虽多,但尚未得出统一的结论,由于疾病发生发展机制复杂、研究对象缺



条目长短及颜色深浅对应–log10(*P*)值大小,代表富集程度. –log10(*P*)>20,条目框为红色;10<–log10(*P*)≤20,条目框为黄色;–log10(*P*)值越大,则长度越长,与富集所得生物过程或通路相关性越大. SARS-CoV-2:严重急性呼吸综合征冠状病毒2.

图 1 与结核病易感性相关富集基因相关的生物过程或通路聚类图

Figure 1 Biological process and pathway clusters of tuberculosis susceptibility related enriched genes



条目长短对应−log10(*P*)值,代表富集程度,−log10(*P*)值越大,长度越长,与疾病相关性越大.

图 2　与结核病易感性相关富集基因关系密切的疾病富集分析聚类图

Figure 2　Enrichment analysis clusters of diseases closely related to tuberculosis susceptibility related enriched genes in DisGeNET

少种族和地域代表性、结核感染状态不同,都会导致研究结果不一致和不可重复性,研究中需要均衡基因−基因及基因−环境相互作用因素[108]。当前,结核病基因易感性研究所得出的结果只是“冰山一角”,如上所述,GWAS等研究方法在风险判断、疾病预测、位点识别等方面仍存在不足,结果正确性有待提高。期待统计效能更高、定位更精细、成本效益更好的研究方法和大样本量、多中心的研究,以便得出更为可靠的结论,同时也需更多基础研究阐明基因易感性的具体机制。

利益冲突　所有作者均声明不存在利益冲突

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