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生态免疫学研究进展

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摘要: 随着整合生物学思想的发展,生态学与免疫学的相互渗透与交叉,产生了生态免疫学这一崭新的学科,自从其诞生虽然只有短短的十几年时间,但发展迅速。生态免疫学主要从免疫代价的视角来解释生活史权衡、性选择和种群动态变化等生态学问题。动物的免疫功能对其抵抗疾病和最终的生存起至关重要的作用,影响动物免疫的因素具有多样性和复杂性的特点,而研究动物免疫功能变化的原因和结果一直是生态免疫学研究的重要内容。免疫防御是否具有能量或资源代价,这种代价是否昂贵是生态免疫学需要回答的基本问题之一,大量的实验已表明免疫防御的代价是昂贵的。由于能量或资源不是无限的,有限的能量或资源必须在多种经常相互竞争的生理功能间进行分配,这导致了免疫功能与动物的生长、繁殖等生活史组分之间的权衡,很多的研究表明增加一个过程的投资会降低对另一过程的投资。免疫同样在性选择特征进化以及维持雌性偏爱性修饰的雄性中发挥至关重要的作用,免疫功能障碍假说认为睾丸激素负责第二性征的产生并同时具有免疫抑制作用,表达性征的代价是降低了免疫功能,这使得宿主对病原体或寄生物攻击的易感性增加,因此只有高质量的雄性个体才能充分表达性征同时又不遭受大量寄生负荷。综述了生态免疫学的概念、研究内容以及未来研究需要关注的领域。

关键词: 生态免疫学; 免疫防御; 生长; 繁殖; 权衡; 性选择

Advances in ecological immunology

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Abstract: Ecology is the study of the distribution and abundance of organisms and their interactions with their environment, including parasites and pathogens. Immunology is the study of physiological functioning of the immune system in states of health and disease. The two disciplines has unified and led to the new discipline of ecological immunology, or ecoimmunology in integrative perspectives. Ecoimmunology is a rapidly expanding research field. Its prime concern is to understand the ecological questions such as life-history trade-offs, sexual selection, population dynamics and so on in view of the cost of immunity. The immune system, which can protect animals from infection and attack of pathogens in the environment, plays an important role in determining organisms' survival and their fitness. The focus of ecoimmunology has been to examine the causes and consequences of variation in immune function in the context of evolution and of ecology, specifically why and how biotic and abiotic factors contribute to variation in immunity in free-living organisms. Whether immune defense is costly in terms of energy or resources is a basic scientific question in ecoimmunology. Many researchers have demonstrated that immune defense is costly. Resources is not limitless, hence organisms must allocate limited resources among competing, costly physiological functions. Trade-offs occur between immunity and reproduction or growth, in which investing in one particular process, such as reproduction, limits the resources available to other processes, such as somatic growth or fighting a parasitic infection. Parasites were of fundamental importance in the evolution of sexually

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selected characters and in the maintenance of female preferences for ornamented males. The immunocompetence handicap hypothesis states that testosterone is responsible for the production of male secondary sexual traits and is simultaneously immunosuppressive, the cost of being able to express sexual traits is decreased immune function. Immunosuppression should result in greater vulnerability to pathogen or parasite attack; therefore, only high-quality males could afford to display sexual characteristics fully without suffering large parasite loads. In this paper we review the development, the focuses and the prospects of ecoimmunology.

Key Words: ecological immunology or ecoimmunology; immune defense; growth; reproduction; trade-offs; sexual selection

生态学研究有机体的分布和多度及其与环境(包括病原体和寄生物)的相互作用,免疫学是研究在健康和疾病状态下免疫系统的生理功能。很显然,前者把后者包含进去了,只不过把后者当作一个“黑箱”来处理,而后者则没有涉及环境对免疫的影响[1]。近年来随着整合生物学研究思想的发展,免疫学与生态学等学科的相互渗透和结合,产生了许多新学科和新的研究领域,如生态免疫学[2]和进化免疫学[3]等。

1 生态免疫学的概念

Sheldon 和 Verhulst 首先提出了生态免疫学,并认为免疫防御的能量代价是昂贵的,通过观察个体在面临其它耗能生理过程时对寄生物的免疫反应能深入理解生活史权衡、性选择、寄物生介导的选择和种群动态变化的机制[2]。尽管从生态免疫学诞生到现在只有短短 10 多年时间,但它引起了许多学者的关注,并且取得了较大的进展。Rolff 和 Siva-Jothy 认为生态免疫学是快速发展的领域,是在进化和生态学背景下研究免疫功能变化的原因和结果,其终极目的是回答“免疫功能为什么有变化?”的问题[4]。张志强和王德华认为生态免疫学是以野生动物为研究对象,采用免疫学方法,测定动物免疫能力的变化,以解释生活史进化、种群动态和寄主-寄生物之间的相互作用等生态学问题为主要内容的一门新兴交叉学科[5]。影响动物免疫系统的生态因子具有多样性和复杂性的特点,这些生物的和非生物的生态因子决定了动物的免疫功能和免疫系统的进化[1,6-7],生态免疫学试图从免疫的代价和权衡(trade-offs)角度来解释免疫防御变化的原因以及个体间、种群间免疫功能的差异[8-9]。生态免疫学的快速发展为人们理解许多生态学问题提供了独特和有趣的视角[10-11]。

2 生态免疫学的研究内容

2.1 免疫功能的自然变化及其影响因素

维持强有力的免疫功能对抵抗疾病和动物的生存至关重要,然而,动物的免疫功能不是静态的,而是会随环境的变化而发生变化。在低温、食物可利用性降低等恶劣条件的严冬季节,许多动物(包括人)的免疫系统易于遭受“挑战”,冬季免疫能力增强假说认为许多小型哺乳动物已经进化出了一套可利用光周期等季节性变化信号来增加它们的免疫功能,从而提高冬季存活的生活史对策,但同时繁殖功能受到抑制[12-13]。作为对繁殖阶段的反应,许多物种表现出免疫功能的季节性变化,通常情况下,许多爬行类和鸟类在夏季免疫功能受到抑制,这包括淋巴组织(如脾脏、胸腺)重量和抗体浓度的降低[14];一些小型哺乳动物,免疫功能同样表现出季节性变化,例如在冬季(短光照条件),欧䶄(*Clethrionomys glareolus*)的体液免疫、刚毛棉鼠(*Sigmodon hispidus*)细胞介导的免疫、黑线毛足鼠(*Phodopus sungorus*)自然杀伤细胞的溶解细胞活性增强,而拜氏黄鼠(*Spermophilus beldingi*)的体液免疫、黑线毛足鼠的噬菌能力与伤口愈合能力(反映天然免疫功能)降低[15]。张志强和王德华发现长爪沙鼠体液免疫功能在冬季高于夏季,为冬季免疫功能增强假说提供了一个野外例证[16]。尽管不同物种免疫的季节性变化会有所不同,但免疫受到抑制通常发生于非常耗能的繁殖季节,这暗示着在动物的生活史中免疫与繁殖两者之间存在权衡,而能量分配格局不同以及免疫防御和其它高能耗的生理过程之间的权衡可能是导致动物免疫功能季节性差异的原因;许多激素包括褪黑激素、糖皮质激素、雄性激素、瘦素等可调节能量在不同生理功能之间分配,并且它们对免疫系统具有广泛的影响,因此激素可能是免疫功能季节性变化的内分泌介导者[12,15]。免疫功能季节性变化的研究,还需要在更广泛的物种中开展,由于免

疫系统非常复杂,也需要检测多种免疫指标以便从不同角度反映其免疫能力,导致免疫功能变化的生理机制还需要探讨。

除季节因素外,许多非生物因子(光周期、食物等)和生物因子(社群压力等)都会影响动物的免疫功能,这也一直是生态免疫学研究的重要内容[1,17]。室内条件下通过模拟生态因子对免疫影响的研究很多,例如短光照能增强拉布拉多白足鼠(*Peromyscus maniculatus*)细胞介导的免疫功能[18]和金色中仓鼠(*Mesocricetus auratus*)[19]体液免疫功能。食物资源限制通过降低脾脏中产生抗体的 B 细胞数目损害拉布拉多白足鼠免疫记忆[20–21],75%食物限制(喂食自由取食量的75%)降低短光照条件下黑线毛足鼠细胞介导的免疫功能[22],90%限食抑制低温、短光照条件下棕背䶄(*Myodes rufocanus*)体液免疫功能[23],妊娠期雌性大仓鼠(*Cricetulus triton*)经70%限食处理后,其后代雄性个体的体液免疫功能受到抑制[24];种群密度引起的母体应激能降低子代根田鼠(*Microtus oeconomus*)体液免疫功能[25]。有些研究报道了不同的研究结果,例如短光照会抑制黑线毛足鼠的体液免疫[26],热带阿兹台克鹿鼠(*Peromyscus aztecus hylocetes*)的体液免疫功能不受光周期的影响[27];70%限食增加了黑线毛足鼠的体液免疫[28]。研究组以长爪沙鼠和布氏田鼠为对象开展了生态免疫学研究,例如急性食物资源短缺能抑制长爪沙鼠(*Meriones unguiculatus*)细胞介导的免疫功能,其部分原因是由动物血糖浓度降低引起的[29–30],而长期适度的食物资源短缺(80%限食)对长爪沙鼠的体液和细胞介导的免疫功能没有显著影响[31];布氏田鼠(*Lasiopodomys brandtii*)免疫功能受社会等级的影响,社群地位较高的动物体液免疫功能较低[32]。由于大多数室内研究只考虑了单一因素对动物免疫的影响,利用室内可以对多种因素进行操控的优势,开展模拟多种生态因素(如光周期、温度、食物、社群地位等)对动物免疫功能影响的研究是必要的;野外条件下通过控制生态因子探索动物免疫功能变化的研究还很少,将室内与野外实验相结合探索多种生态因素对动物免疫能力及其适合度后果的研究需要加强。

2.2 免疫反应的代价

生态免疫学的一个基本观点是免疫反应是有能量或资源代价的,然而动物维持或激活免疫系统是否具有能量代价?这种代价是否昂贵?这是生态免疫学和进化免疫学需要首先回答的问题之一[2–3]。尽管在20世纪早期,Barr 等已发现在发热状态下,体温每升高1℃,氧消耗就增加7%—13%,这已暗示了免疫反应具有能量代价[33]。然而令人感到吃惊的是,此后很长时间里有关免疫的能量代价问题几乎没被研究过,直到20世纪90年代初,该领域的研究才重新引起关注[34–35]。

免疫与繁殖、生长等适合度组分之间存在权衡的很多研究间接地表明提高免疫反应具有代价,然而首先对免疫反应的能量代价直接进行测定的是 Demas 等,他们在成年(10—12个月)和老龄(22—24个月)小家鼠(*Mus musculus*)中注射匙孔血蓝蛋白(Keyhole limpet haemocyanin, KLH)抗原,发现其氧消耗和代谢产热大约比对照组高20%—30%,在相对温和的 KLH 抗原刺激下,小家鼠在能量代谢上就大幅增加,因此能够激发更强免疫反应的抗原如病毒、细菌及其它病原体将可能导致更为明显的能量代价[34]。Ots 等[36]发现注射绵羊红细胞(Sheep red blood cells, SRBC)的大山雀(*Parus major*)比对照组的基础代谢率高约9%。把植物血球凝集素(Phytohaemagglutinin, PHA)注射到家麻雀(*Passer domesticus*)翅膀中,与注射盐水的对照组相比,PHA 挑战显著提高了家麻雀的静止代谢率(Resting metabolic rate, RMR),经计算这一免疫活动的总代价是4.20 kJ/d(29% RMR),这一代价相当于产半个卵的代价(8.23 kJ/卵)[37]。Hawlena 等[38]采用啮齿动物和跳蚤系统研究了免疫反应的能量代价,即使在没有寄生虫或病原体攻击时,安氏小沙鼠(*Gerbillus andersoni*)也需要消耗能量用于维持其组成性免疫反应,而其近缘种狐尾小沙鼠(*Gerbillus dasyurus*)只有在寄生虫或病原体攻击时,才诱导其启动免疫反应,结果发现安氏小沙鼠比狐尾小沙鼠需要更多的能量来维持免疫反应。Devevey 等[39]发现跳蚤(*Nosopsyllus fasciatus*)寄生的普通田鼠(*Microtus arvalis*)的 RMR 较高,但免疫反应较低。最近,Muehlenbein 等[40]研究了年轻成年男性暴露于自然病原体时 RMR 的变化,发现患者的 RMR 平均增加量高于14%。对于免疫反应能量代价直接测定的上述研究,说明动物免疫活动在代谢上所消耗的能量很大。然而也有一些研究发现免疫反应的代价很小,如注射百日咳-破伤风(diptheria-tetanus, DPT)病毒的青山雀(*Parus* *caeruleus*) RMR 没有显著变化[41]；Verhulst 等[42]报道了斑胸草雀(*Taeniopygia guttata*)中引起体液免疫反应的代谢代价可以忽略。之所以没有检测到免疫反应的代价，原因是很多因素如资源可利用性、非生物因子和生物因子等环境条件可能会掩盖免疫代价，因此在检测免疫代价时，应注意考虑环境条件、动物的种系发生以及所测定的免疫指标等因素[8,43]。由于免疫系统的复杂性，未来还需要针对不同的免疫类型进行定量测定其代价，例如检测不同免疫组分的维持代价和激活代价，从而更深入理解免疫代价的问题。

2.3 免疫防御与适合度组分间的权衡

权衡的观点是进化生物学中的核心概念，它的最基本假设是动物需要相对稳定的能量或资源供应以维持生物学功能，然而能量或资源不是无限制的，有限的能量或资源必须在多种经常相互竞争的生理功能间进行分配[12,15]，而免疫功能与生活史组分之间投资的权衡在决定宿主最佳生活史特征中起重要作用[3,44]，尽管现在权衡的思想得到很大的扩展，但它一直是生态免疫学关注的焦点。

2.3.1 免疫与繁殖间的权衡

繁殖是高度耗能的生理过程，因而经常与免疫功能之间发生权衡，许多在鸟类、哺乳类、爬行类和无脊椎动物中的研究表明，过多的繁殖投资会抑制动物的免疫功能[15,45-47]，例如通过增加窝卵数的方法来增加繁殖努力会降低白领姬鹟(*Ficedula albicollis*)[48]和双色树燕(*Tachycineta bicolor*)[49]的体液免疫功能；妊娠和哺乳能抑制黑线毛足鼠(*Phodopus sungorus*)的体液免疫功能[50]；繁殖活跃的雄性蟋蟀(*Gryllus texensis*)免疫能力也受到抑制[51]。同样，增加免疫防御的投资，也能限制对繁殖的投资，例如免疫挑战能降低布氏田鼠(*Lasiopodomys brandtii*)的睾丸和附睾重量[52]以及白足鼠(*Peromycus leucopus*)睾丸重量[53]；通过实验的方法激活白领姬鹟的免疫防御，能降低其繁殖成功[54-55]。以上这些实验结果表明繁殖和免疫功能间存在能量权衡，即增加一个过程的投资会降低或抑制对另一过程的投资。

能否检测到免疫与繁殖间的权衡，还依赖于动物所处的环境和状态，例如，在卵黄形成的高能量需求的繁殖阶段，野外雌性树蜥蜴(*Urosaurus ornatu*)伤口愈合能力受到抑制，但在实验室饲养条件下则不受抑制，室内饲养使雌性树蜥蜴体重显著增加，暗示着它们有更多可利用的资源投资给卵黄形成和免疫功能；为确定资源可利用性是否是其免疫受抑制的原因，将卵黄形成期的雌性树蜥蜴进行食物限制，结果发现其伤口愈合能力受到抑制，而同样的限食条件则不影响非繁殖雌性树蜥蜴的伤口愈合能力，可见免疫与繁殖间的权衡依赖于环境条件[8,56]。

2.3.2 免疫与生长发育间的权衡

生长发育与免疫之间同样存在权衡，对于生长发育的投资会抑制免疫反应[57]，例如 Saino 等发现具有较高生长率的家燕(*Hirundo rustica*)，T 细胞介导的免疫反应较低[58]；第二性征鸡冠较大的家禽，其体液免疫功能较低，表明性修饰物与免疫功能之间存在权衡[59]。同样，动物的免疫系统被激活后，其生长发育甚至生存也会受到影响。与注射盐水的对照组相比，注射 SRBC 鸡(*Gus gallus*)吃的食物更多但体重增加却更少[60]；喜鹊(*Pica pica*)细胞免疫反应被激活后，表现为生长率降低[61]；免疫系统激活可抑制白领姬鹟性修饰物的发育[62]；对非致病性抗原的免疫反应可损害驯养禽类[63]和鹌鹑(*Coturnix coturnix*)[64]的生长性能；在小型哺乳动物中，也发现免疫挑战会抑制黑线毛足鼠的身体生长[65]。饥饿的工蜂(*Bombus terrestris*)免疫系统激活后，生存受到显著的损害[66]；自由生活的鸟类免疫系统被激活后，其生存也受到损害[67]。此外，有机体在生长和发育过程中，免疫系统不同成分之间也存在权衡，这在无脊椎动物[68]和脊椎动物[69]中均有发现。

2.4 免疫与性选择

Hamilton 和 Zuk[70]在其里程碑式的文章中提出了性选择特征的障碍假说，认为寄生是在性选择特征进化以及维持雌性偏爱性修饰的雄性中发挥至关重要的作用，然而该假说很难被检验。Folstad 和 Karter[71]对该假说进行了生理学扩展，即免疫功能障碍假说，该假说认为睾丸激素负责第二性征的产生并同时具有免疫抑制作用，表达性征的代价是降低了免疫功能，免疫抑制使得宿主对病原体或寄生物攻击的易感性增加，因此只有高质量的雄性个体才能充分表达性征同时又不遭受大量寄生负荷；该假说得到大量实验的支持[72]，例如实

验性地增加睾丸激素能损害家雀抗体的产生[73]。一些研究发现睾丸激素抑制免疫的作用与应激激素(如皮质酮)有关[74],Evans 等[73]对免疫功能障碍假说进行了修改,提出了应激相关的免疫功能障碍假说,认为睾丸激素能通过增加皮质酮的含量而起间接的抑制作用。一些研究表明睾丸激素能增加鸟类血液中的皮质酮水平[75],并且有很好的证据说明皮质酮具有免疫抑制作用[76]。然而,也有一些实验不支持免疫功能障碍假说以及应激相关的免疫功能障碍假说[72,77],因此,还需要在更多物种中的研究来检验这些假说。

主要组织相容性复合体(major histocompatibility complex, MHC)基因广泛分布于脊椎动物中,是免疫系统最重要的成员,通过将源自胞内病毒或胞外病原体、寄生虫的抗原肽递呈给 T 淋巴细胞,发挥重要的免疫防御功能; MHC 基因具有高度的遗传多样性,能影响免疫识别、对感染和自身免疫疾病的易感性、个体气味、交配偏爱、亲属识别等许多重要的生物学特征; MHC 多样性的丧失可能导致适合度成分如生存、繁殖输出、生长率的下降,并且损害对环境长期变化的适应能力[78-79]。MHC 多样性在性选择中也起重要作用,气味可能是基于 MHC 配偶选择中所利用的真正信号,肽/MHC 复合体可被释放到细胞外并可能出现在尿和其它身体分泌物中,被用作个体间通讯,目前已在人类和一些啮齿动物中开展了交配偏爱和 MHC 多样性之间关系的研究工作,研究结果还存在争议[80-81]。将 MHC 基因遗传多样性、免疫功能和性选择结合起来进行研究,可以为理解性选择的分子机制提供重要证据,同时也是一个非常有趣的研究方向。

3　展望

生态免疫学是快速发展的新兴交叉学科,除了前面述及的方面,研究者还需要关注以下方向。免疫系统非常复杂,因此,选择和检测哪些指标能更好地反映动物的免疫功能需要考虑; 鉴于野外工作,继续发展检测免疫功能的简便易操作的方法也是必需的,同时测定多个免疫指标也是困难之一[82]。动物分配给免疫功能的资源是一个有弹性的过程,它依赖于其它过程对资源的需求,因此,未来研究应考虑多个生理系统之间的相互作用,例如繁殖投资能同时影响多个系统,包括免疫功能、生长和细胞维持[8]。将动物免疫功能的变化与适合度后果联系起来的研究需要加强,脊椎动物世代时间很长,大大增加了这方面研究的困难,然而对于这一问题的研究,有助于从进化上回答为什么传染性疾病仍是动物死亡的主要原因,为什么自然选择没有消除弱的免疫系统等问题[83]。

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