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昆虫变态发育的激素和营养调控研究进展与展望*

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摘 要 变态发育是促进昆虫进化和多样性形成的重要因素之一。昆虫变态发育主要受到蜕皮激素和保幼激素的协同调控，通过信号通路诱导下游基因表达，保证蜕皮、组织重塑等生理过程的正确发生。除内在激素外，外在营养物质亦可通过营养信号影响激素信号进而控制变态发育进程。本文主要综述了近十年来我国科研工作者在昆虫变态发育的激素和营养调控机制研究方面所取得的突出成果，并对未来潜在的研究方向进行了展望，以期对我国的害虫防治和益虫利用研究提供理论指导。

关键词 变态发育；激素调控；营养调控

Progress in research on hormonal and nutritional regulation in insect metamorphosis

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Abstract Metamorphosis is one of the key factors underlying insect evolution and biodiversity. Insect metamorphosis is mainly regulated by 20-hydroxyecdysone and juvenile hormone which activate the expression of downstream genes to ensure the occurrence of physiological processes such as molting, tissue remodeling and so on. Except for internal hormones, extrinsic nutrients can also regulate metamorphosis by regulating downstream hormone signaling through IIS/TORC1 signaling. This paper summarizes the outstanding achievements of domestic researchers working on the hormonal and nutritional regulation of insect metamorphosis over the past decade, and also discusses prospects for the future research that will provide theoretical guidance for pest control and the utilization of beneficial insects in China.

Key words metamorphosis; hormonal regulation; nutritional regulation

昆虫是地球上进化非常成功、生物多样性最丰富的生物种群，约 250 万种，几乎是地球上所有物种的三分之一（Mora *et al.*，2011）。昆虫不仅种类繁多、形态各异、分布极为广泛，而且与农林生产、人类健康和生态环境等密切相关（Bradshaw *et al.*，2016）。昆虫变态发育行为的出现是昆虫进化和多样性产生的起始驱动力（Misof *et al.*，2014；Nicholson *et al.*，2014；Rainford *et al.*，2014）。昆虫变态发育是指昆虫从胚胎至成虫过程中表现出不同发育阶段明显差异的结构、生理、形态以及生活习性，如翅和蛹形成等。昆虫翅的形成提供昆虫迁飞觅食能力；蛹的出现则增加了昆虫对抗环境压力的能力；翅和蛹的形成均可提高昆虫生存与适应能力，从而促进昆虫不断进化，是昆虫多样性形成的重要原因之一（Hunter，1998；Mayhew，2007；

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Belles，2017)。化石与分子进化分析显示，昆虫的翅和不完全变态最早出现在泥盆纪早期（约 4 亿年前），蛹和完全变态最早出现在石炭纪（约 3.6 亿年前）(Belles，2011；Misof *et al.*，2014)。

昆虫变态发育由低等至高等分为无变态、不完全变态、完全变态三类。无变态昆虫如衣鱼 *Ctenolepisma longicaudata* 的胚后发育除体型大小外，没有显著的形态变化；半变态昆虫如美洲大蠊 *Periplaneta americana*、臭虫 *Cimex lectularius*、飞蝗 *Locusta migratoria* 的胚后发育包括若虫和成虫两个时期，成虫具有可飞行的翅。完全变态昆虫如赤拟谷盗 *Tribolium castaneum*、家蚕 *Bombyx mori*、黑腹果蝇 *Drosophila melanogaster*、埃及伊蚊 *Aedes aegypti* 的胚后发育包括幼虫、蛹和成虫三个时期，这些昆虫的幼虫体内含有翅原基、而成虫具有可飞行的翅，蛹期不摄食且可耐受恶劣的外界环境，幼体与成虫具有迥异的食物来源和生活环境(Belles，2011)。激素和营养是调控昆虫变态发育的两类关键因子，我国昆虫学研究人员针对变态发育的激素和营养调控机制进行了深入研究，极大提高了我国在该领域的科研水平，不仅为变态发育相关的基础研究提供重要理论参考，也为害虫防治和益虫利用提供重要的应用基础。

1 昆虫变态发育的激素调控研究进展

昆虫变态发育主要由两类关键激素调控：蜕皮激素（20-hydroxyecdysone，20E）和保幼激素（Juvenile hormone，JH)。20E 主导所有昆虫的蜕皮和变态，包括变态过程中幼虫组织的死亡与重建、成虫器官的形成与成熟；JH 在变态昆虫中拮抗 20E 作用而维持幼虫性状，从而阻止变态提前发生。

1.1 20E 调控昆虫变态发育

20E 前体蜕皮酮（ecdysone）由昆虫前胸腺细胞合成，经一系列的细胞色素 P450 酶（也称为 Halloween 基因，如 *Nvd*、*Spok*、*Dib*、*Sad*、*Phm* 等）从胆固醇开始催化合成为最终产物蜕皮酮（Gilbert *et al.*，2002），蜕皮酮被前胸腺分泌然后经血淋巴传递到外周组织（如脂肪体），在外周组织中被另外一种 Halloween 基因 *Shd* 编码的 P450 酶催化转换为具有活性的 20E（Petryk *et al.*，2003)。Hallowen 基因调控蜕皮酮合成的功能在模式动物黑腹果蝇中得到详细研究，我国学者在灰飞虱 *Laodelphax striatellus*、白背飞虱 *Sogatella furcifera*、二化螟 *Chilo suppressalis*、马铃薯甲虫 *Leptinotarsa decemlineata* 和棉铃虫 *Helicoverpa armigera* 等昆虫中，利用 RNA 干扰技术验证了其功能保守性(Jia *et al.*，2013，2015；Kong *et al.*，2014；Wan *et al.*，2014a，2014b，2015；Shahzad *et al.*，2015；Zhu *et al.*，2016；Zheng *et al.*，2017b)。

20E 在靶标组织中激活下游信号传导通路：20E 受体是由 EcR 和 USP 两个核受体蛋白组成异源二聚体，在分子伴侣复合物的协助下，20E 与 EcR-USP 结合、并与 DNA 上的 20E 反应元件（Ecdysone Receptor Response Element，EcRE）结合，然后解除共阻遏因子、募集共激活因子，在 RNA 聚合酶的作用下启动 20E 初级反应基因（如转录因子编码基因 *Br-C*，*E74*，*E75* 和 *E93*）的转录。20E 信号由 20E 初级反应基因编码的转录因子诱导次级应答基因的表达而被级联放大，从而诱导蜕皮和化蛹等生理过程（Riddiford *et al.*，2000；Yamanaka *et al.*，2013)。我国学者研究发现 PKC 介导的 USP Ser35 位点的磷酸化对 20E 信号活力非常重要（Wang *et al.*，2012)。下游靶标基因 *Br-C*、*E75* 等还可以直接作用于蜕皮酮生成组织，反馈调控蜕皮酮合成(Xiang *et al.*，2010；Li *et al.*，2016a)。上述信号通路在黑腹果蝇中得到深入研究，随后我国研究人员在马铃薯甲虫、斜纹夜蛾 *Spodoptera litura*、松墨天牛 *Monochamus alternates*、小菜蛾 *Plutella xylostella*、黄脸油葫芦 *Teleogryllus emma*、绿盲蝽 *Apolygus lucorum*、梨小食心虫 *Grapholita molesta*、麦长管蚜 *Sitobion avenae* 等大量非模式昆虫中克隆得到了 *EcR* 或 *USP* 基因序列（Tang *et al.*，2012；Weng *et al.*，2013；Cao *et al.*，2015；He *et al.*，2015；Huang *et al.*，2015；Tan *et al.*，2015；Yan *et al.*，

2016；Xu *et al.*，2019）。正是由于 20E 信号通路在昆虫变态发育中的重要作用，我国科研人员筛选得到 20E 的激动剂或拮抗剂（Zou *et al.*，2018；Wang and Zhou，2019），同时以其关键基因作为靶标基因来改造昆虫病毒或制造转基因植株，这些策略在害虫防治应用中都效果显著（Zhu *et al.*，2012；Liu *et al.*，2019）。

20E 可控制幼虫器官生长和蜕皮、化蛹和蛹期器官重塑等生理过程（Warren *et al.*，2006）。昆虫蜕皮是变态发育的重要过程，涉及皮肤细胞激活、表皮细胞分离、蜕皮液分泌、新表皮形成和旧表皮脱落等过程。几丁质是表皮、围食膜、肌肉等组织的重要组分，其合成和降解过程与蜕皮密切相关，Yao 等（2010）发现 20E 信号促进甜菜夜蛾 *Spodoptera exigua* 几丁质合成通路中多种基因的表达。褐飞虱 *Nilaparvata lugens* 中，20E 信号激活下游基因 *Br-C* 的表达，从而抑制非编码 RNA miR-8-5p 和 miR-2a-3p 的表达，几丁质合成通路中关键基因 *Tre-2* 和 *PAGM* 作为 miR-8-5p 和 miR-2a-3p 的靶标基因被脱抑制，从而促进几丁质合成（Chen *et al.*，2013）。飞蝗和家蚕都是非常好的研究激素调控蜕皮的模式昆虫，蜕皮前，20E 信号通过激活下游基因 *HR39* 影响表皮几丁质酶基因（*Cht5* 和 *Cht10*）和羧肽酶基因（*Carboxypeptidase A* 和 *Carboxypeptidase M*）的表达，促进飞蝗蜕皮（Li *et al.*，2015；Zhang and Zheng，2017；Zhao *et al.*，2019b）。蜕皮后，20E 压制糖蛋白基因 *Abd-9* 的表达，确保飞蝗内表皮正确形成（Zhao *et al.*，2019a）。20E 诱导家蚕酚氧化酶（Phenol oxidase）和多巴脱羧酶（dopa decarboxylase）基因表达，参与表皮黑化作用（Wang *et al.*，2013a，2013b）。Yang 等（2018）在小圆皮蠹 *Stegobium paniceum* 中发现 20E 促进几丁质去乙酰酶（Chitin deacetylases）基因的表达，促进幼虫蜕皮。

组织重塑是完全变态昆虫幼虫向成虫转变的重要生理过程，包括脂肪体、肠道、附肢等器官的重塑。完全变态昆虫脂肪体和肠道变态过程中经历储存物质分解、自噬、解离、凋亡等生理过程，而半变态昆虫和完全变态昆虫都要经历附肢形态发生等过程，20E 在其中起着至关重要的作用。细胞解离是完全变态昆虫变态过程中部分组织重塑的重要表型。Jia 等（2014，2017）和 Zheng 等（2017a）利用果蝇具有大量转基因品系的优势，深入解析了 20E 信号调控金属蛋白酶 Mmps 和 PVR 从而调控脂肪细胞解离的分子机制。其他完全变态昆虫，如家蚕、棉铃虫、柞蚕 *Antheraea pernyi* 等，20E 可通过激活多种蛋白酶（如组织蛋白酶 L 等）的表达，调节脂肪细胞和中肠细胞解离，参与脂肪体和中肠的重塑（Zhang *et al.*，2013；Yang *et al.*，2017；Guo *et al.*，2018；Sun *et al.*，2018）。除细胞解离外，李胜团队发现 20E 信号促进果蝇和家蚕脂肪细胞中脂类物质分解（Wang *et al.*，2010），抑制家蚕蜕皮和变态时期脂肪细胞的糖酵解（Tian *et al.*，2010b）。20E 信号诱导 Caspase 编码基因（*Dronc* 和 *Drice*）和死亡激活因子（*rpr* 和 *hid*）等蜕皮激素次级应答基因的表达，最终导致脂肪细胞程序化凋亡（Liu *et al.*，2009）。20E 信号还可抑制脂肪体营养信号使 TORC1 失活而启动细胞自噬；还可通过下游靶标 E93 等转录因子激活自噬相关基因 *Atg* 的表达从而诱导细胞自噬发生直至凋亡（Tian *et al.*，2013； Liu *et al.*，2013，2014a；Xu *et al.*，2017）。Yu 等（2012）发现，20E 直接结合在家蚕组织蛋白酶 D 的启动子区域的 EcRE 上调控该基因表达，在脂肪体细胞和肠道细胞的程序化细胞死亡中起重要作用。在棉铃虫中，20E 可以通过多种途径调控细胞程序化死亡。20E 信号可促进中肠细胞表达蛋白磷酸酶 6（PP6），加速中肠细胞程序化死亡（Wang *et al.*，2012），20E 还可以通过调节 ATG12 和 ATG5 的结合调节中肠细胞程序化死亡（Li *et al.*，2018b），也可通过调节钙离子流来转变细胞自噬和细胞凋亡（Li *et al.*，2016b），以及通过 EcRB1、USP1 和 HR3 上调 Hippo 表达或 Yki 的细胞定位引起细胞程序化死亡（Dong *et al.*，2015；Wang *et al.*，2016）。

翅是变态发育中附肢重塑的主要研究对象，Feng 团队以家蚕翅为对象，深入研究发现 20E 信号通过激活下游基因 *Br-C* 从而激活转录因子

POUM2 进而促进其与 Abd-A 蛋白结合，该复合物与另一个转录抑制因子 βFTZ-F1 一起分别结合在 WCP4 和其他表皮蛋白的顺式调控元件上调控这些表皮蛋白的表达，从而影响蛹及翅表皮的形成（Deng *et al.*，2011，2012；He *et al.*，2017a）。飞虱类昆虫翅的形态发生同样需要 20E 信号（Wu *et al.*，2012）；马铃薯甲虫 *E74* 基因缺失影响其化蛹及附肢如触角、腿和翅的生长（Xu *et al.*，2018）；通过 CHIP-seq 分析，Wang 等（2019）发现 E93 直接调控 Dpp 信号相关基因，影响果蝇蛹期翅的发育。除附肢重塑外，20E 还调控家蚕鳞片分泌细胞的 DNA 复制和鳞片生成，以及褐飞虱卵巢发育等（Yuan *et al.*，2017；Li *et al.*，2018a；Mao *et al.*，2019）。

变态发育过程中，20E 调控免疫反应的分子机制同样是国内外科研人员研究的热点。脂肪体不仅是能量新陈代谢的重要组织，也是昆虫调控免疫反应的关键组织（Li *et al.*，2019）。Tian 等（2010a）通过基因芯片分析与分子生物学实验，发现 20E 抑制家蚕蜕皮和变态时期脂肪细胞的先天免疫等生理功能）。血细胞作为重要的免疫细胞，家蚕可特异表达 HDD1 调控免疫反应，该基因表达受到 20E 正调控，在蜕皮和变态时期可保障虫体不受侵害（Zhang *et al.*，2017）。20E 信号还可通过下游基因 *Br-C* 和 *Ets*，激活中肠中抗菌肽 Lebocin 的表达，保护变态发育过程中中肠免受外界侵害（Mai *et al.*，2017）。在半变态昆虫飞蝗中，20E 通过激活脂肪体 *PGRP-SA* 基因表达，调控免疫反应（Han *et al.*，2017）。

20E 除通过受体 EcR/USP 介导的基因组作用机制外，还存在非基因组作用（non-genomic）机制，通过下游一系列磷酸化调控网络，快速激活细胞反应。Zhao 团队在该领域作出了突出贡献，她们以棉铃虫为研究材料，发现 20E 通过膜受体 ErGPCR 激活 PLCG1 来调节钙离子流和 PKC 信号通路，从而引起 EcRB1、CDK10 和 USP1 等蛋白的磷酸化，来调控下游基因表达（Liu *et al.*，2014b，2014c；Chen *et al.*，2017）。或者引起 CaMKII 290 位点氨基酸磷酸化和该蛋白核转运，进而调控 USP1 赖氨酸乙酰化，这有利于 EcRB1-USP1 复合体形成，从而促进 20E 下游基因表达（Jing *et al.*，2015）。20E 非基因作用引起β-arrestin1磷酸化，磷酸化的β-arrestin1移动至细胞质膜上与 ErGPCR1 结合，造成 ErGPCR1 接收 20E 信号不敏感，形成负反馈调控（Zhang *et al.*，2015）。

1.2 JH 调控昆虫变态发育研究进展

JH 是昆虫等节肢动物所特有的由其内分泌器官咽侧体（Corpus allatum，CA）合成并分泌的倍半萜类激素（Goodman and Cusson，2012）。从原始到高等昆虫，至少 10 多个目、100 多个种中都发现了一种或多种 JH。JH 最初是由 Wigglesworth 于 1934 年在研究半变态昆虫吸血蝽 *Rhodnius prolixus* 时发现的，摘除吸血蝽早期幼虫的 CA 可以导致幼虫提前羽化成成虫；而重新移植 CA 则可以恢复正常羽化；进一步研究发现 CA 对于成虫期卵巢成熟也是必需的（Wigglesworth，1936）。

从进化的角度上看，JH 最初始的功能可能是调控昆虫胚胎的发育和成虫的生殖，包括生殖腺的发育和卵黄蛋白原的合成（Riddiford，2012；Zou *et al.*，2013）。当古老的昆虫演化出变态，JH 的功能则衍生到在幼虫蜕皮以及幼虫-蛹的变态过程中通过拮抗 20E 信号传导途径而“维持现状”（status quo）。“保幼激素”就是根据其能够维持幼虫性状这一生理功能而命名（Jindra *et al.*，2013）。在一些高度分化的昆虫种类中，JH 的功能除调控变态发育和生殖之外，还调控社会分工、行为、滞育、非遗传多型性和寿命等等（Richards，1981；Flatt *et al.*，2005；Goodman and Cusson，2012；Li *et al.*，2013）。

JH 受体首先在果蝇中被发现。1986 年，Wilson 和 Fabian（1986）通过 EMS 诱导突变体，筛选到一个对 JH 类似物 Methoprene 或 JH III 耐受力强于野生型果蝇 100 倍的突变体，该突变体对应的基因被命名为 *Met*。Met 属于胞内受体（Jindra *et al.*，2013），是 bHLH-PAS 转录调控因子家族成员。通过对果蝇基因组中 bHLH-PAS 蛋白的搜索，发现基因 *Gce* 编码的蛋白与 Met

在序列上高度保守，进化分析发现 Met 是 Gce 在进化过程中通过基因复制产生的（Baumann *et al.*，2010）。Godlewski 等（2006）还发现，JH 不存在的情况下，Met 自身能形成同源二聚体或者与 Gce 形成异源二聚体，而 JH 存在则抑制这两种二聚体的形成。Li 团队研究发现，同时缺失 Met 和 Gce 可导致果蝇白色预蛹期致死以及细胞凋亡的提早发生，这一结果与 JH 完全缺失的果蝇表型类似（Liu *et al.*，2009；Abdou *et al.*，2011；Wen *et al.*，2015）。虽然 JH 受体首先在在果蝇中被发现，但由于 Gce 的存在一度使 Met 是否为 JH 受体充满质疑。Li 团队利用果蝇相对其他昆虫的科研优势，结合其他昆虫如家蚕等的科研结果，最终证明 Met 确实是 JH 的胞内受体（Abdou *et al.*，2011）。Zhao 等（2014）和 Ma 等（2018）也证明了 Met 在棉铃虫中的功能保守性。

Met 作为 JH 胞内受体所行使的生理功能在昆虫中高度保守（Konopova and Jindra，2007；Konopova *et al.*，2011；Lozano and Belles，2011）。JH 与受体 Met 结合后招募其他蛋白形成转录复合体，如 Tai、βFTZ-F1、Cycle 等（Jindra *et al.*，2015）。Li 团队研究发现，当 JH 与 Met 结合后，分子伴侣 Hsp83 与 Met 结合帮助其运输至细胞核孔，细胞核孔蛋白 Nup358 与 Hsp83 结合进而促进 Met 与运输受体 importin-β 结合，最终帮助 Met 穿过核孔复合体进入核内并定位在 DNA 结合区域（He *et al.*，2014，2017b）。除 Hsp83 外，很多 Hsp 蛋白都参与了 JH 信号调控（Gu *et al.*，2012）。Met 与结合蛋白形成的转录复合体结合在调控基因的 JH 反应元件上，调控基因表达。除此之外，Yang 等（2011）还发现 JH 通过受体 Met 调控棉铃虫 RNA 结合蛋白从细胞核向细胞质转移，可能通过帮助蛋白翻译从而影响 JH 下游基因表达。

在昆虫的变态发育过程中，JH 信号主要通过拮抗果蝇 20E 信号而“维持幼虫性状”（Liu *et al.*，2009）。*Kr-h1* 被证明是昆虫中一个典型的 JH 下游初级反应基因，该转录因子可通过调控其他基因的表达来调控昆虫的变态发育（Minakuchi *et al.*，2008；Zhu *et al.*，2010；Kayukawa *et al.*，2012）。Kr-h1 可直接抑制 20E 信号下游基因 *Br-C*（Abdou *et al.*，2011；Huang *et al.*，2011）和 *E93*（Liu *et al.*，2014a，2015c）等的表达，从而拮抗 20E 诱导的幼虫组织死亡与重建和成虫器官的形成与成熟。Kr-h1 与 E93 的相互抑制决定了褐飞虱的变态发育时间（Li *et al.*，2018a）；Kr-h1 介导 JH 拮抗 20E 调控变态发育的功能在棉铃虫中也具有保守性（Zhang *et al.*，2018b）；JH 还拮抗 20E 对家蚕脂肪体糖酵解的抑制作用（Tian *et al.*，2010b），以及拮抗 20E 诱导 Mmps 对脂肪体细胞解离的调控作用（Jia *et al.*，2017）。除了拮抗 20E 信号靶标基因之外，JH 可影响 20E 前体蜕皮酮的合成来达到影响变态发育的目的。Liu 等（2018）和 Zhang 等（2018a）先后发现 JH 通过 Met/Gce 调控 *Kr-h1* 在果蝇或家蚕前胸腺中的表达，Kr-h1 可直接抑制 *Spok* 等蜕皮酮合成酶的表达或干扰蜕皮酮合成自调控作用，阻碍蜕皮酮的合成，从而降低全身 20E 信号活力，影响变态发育。Meng 等（2018）还发现马铃薯甲虫 JH 通过 Met 抑制脑中 PTTH（蜕皮酮上游激活因子）的表达和释放，从而降低幼虫阶段蜕皮酮的合成。

尽管 Met 作为胞内受体被证明参与了 JH 的多种生理功能，但是一些受 JH 诱导的信号是非常快速的，即被认为是“非基因组”上的生物反应。体外给果蝇幼虫唾液腺滴加 JH 后发现可快速诱导线粒体超微结构的改变，而这一现象是不受转录和翻译调控的。JH 的这种快速反应使科学家们猜想 JH 可能还可以通过与膜受体（如 G 蛋白偶联受体，GPCR）结合，从而刺激下游第二信使传递级联反应，包括 PLC、PKC 和 Na+/K+ ATPase 等，进而达到快速发挥功能的作用。研究人员认为在昆虫中有多种类型的膜受体蛋白可介导 JH 引起的生理过程。在烟芽夜蛾 *Heliothis virescens* 中发现 JH II 和 JH III 刺激的滤泡细胞间隙变化依赖 DAG/IP_3 信号通路，而 JH I 依赖 GPCR 和 cAMP 第二信使通路（Pszczolkowski *et al.*，2005，2008）；在赤拟谷盗中进行 RNAi 筛选发现，Dopamine D2 型 GPCR 可能是 JH 调控滤泡细胞间隙变化的关键受体

（Bai and Palli，2016）；在棉铃虫中，JH 通过 GPCR/PLC/PKC 通路引起 Br-C 的磷酸化来抑制变态发育（Cai *et al.*，2014）；而在埃及伊蚊中，JH 可以迅速激活 PLC 途径和 PKC，产生的 IP_3 促进内质网释放钙离子，随后激活 CaMKII，CaMKII 对 Met 的磷酸化可以增加其与 JHRE 的结合能力，但是抑制 GPCR 对 JH 调控基因表达没有明显影响，而在加入 RTK 的抑制剂 Genistein 后，JH 不再促进钙离子浓度增加，说明 RTK 可能作为 JH 膜受体介导 JH 信号（Liu *et al.*，2015b）。此外，在家蚕的中央神经系统中，JH 处理可以使一个 48-kDa 的蛋白发生磷酸化，这个磷酸化过程可能也是通过膜受体介导的，并可被 Genistein 所抑制（Arif *et al.*，2002）。

2 昆虫变态发育的营养调控机制

变态昆虫最终体型的大小主要取决于幼虫的营养状态，变态一旦起始，成虫体型就被基本固定下来。动物进食营养物质后，通过激活 Insulin/insulin-like growth factor （IIS）/ Target of rapamycin complex 1（TORC1）信号通路调节生长。在昆虫中 IIS/TORC1 信号通路具有高度保守性，但 Insulin-like peptides（ILPs）作为上游激活因子在不同昆虫中的数目差别很大。在黑腹果蝇中，共含有 7 种 ILPs，Fu 等（2016）在马铃薯甲虫中发现了 5 种 ILPs，其中抑制 ILP2 可影响 20E 信号，扰乱其幼虫化蛹。在脂肪体中，ILPs 与受体 InR 结合并激活 InR，随后激活 Chico，起始一条蛋白激酶信号通路，包括 PI3K、PDK 和 Akt（Sarbassov *et al.*，2005）等。当 IIS 信号被激活，Akt 通过抑制转录因子 FoxO 促进细胞生长（Junger *et al.*，2003），还可以促进糖原、脂肪和蛋白质的合成来促进细胞生长、器官发生和个体发育等（Liu *et al.*，2010；Hemmings and Restuccia，2015）。此外，InR 也可以通过下游信号激活 Ras-Raf-MAPK 信号传导途径而促进细胞的生长和分裂（Ma *et al.*，2011；Hemmings and Restuccia，2015）；FoxO 可以转录促进翻译抑制者 4EBP 和 InR（Miron *et al.*，2001）；PTEN 发挥抑制 IIS 信号的功能（Goberdhan *et al.*，1999；Gao *et al.*，2000）；Akt 抑制 TORC1 信号的负面调节者 TSC1/2（Gao and Pan，2001；Gao *et al.*，2002）；Rheb 可直接增强 TORC1 信号（Garami *et al.*，2003）。TORC1 信号可以通过抑制 4EBP 和核糖体蛋白 S6 蛋白激酶（S6K）来增强翻译和核糖体生物合成，进而促进细胞生长（Miron *et al.*，2003；Chauvin *et al.*，2014）；TORC1 信号同样可刺激 rRNA 合成激活 TIF-1A 表达（Hietakangas and Cohen，2007），最终 TORC1 信号促进脂肪细胞等内吞作用并抑制细胞自噬。

20E 信号主导调控昆虫蜕皮和变态，决定昆虫的生长时间；IIS/TORC1 信号则决定昆虫的生长速率（Ding *et al.*，2017），这两种信号的相互协调保证了昆虫变态发育的正确进行。一方面，蜕皮酮及 20E 信号通路受营养影响而调控昆虫个体生长。蜕皮酮上游激活因子 PTTH 主要通过其络氨酸受体激酶 TORSO 和下游的 Raf-MAPK 途径和 PI3K-TORC1 途径促进前胸腺细胞生长和蜕皮酮合成（McBrayer *et al.*，2007；Rewitz *et al.*，2009），营养信号可直接通过 IIS/TORC1 途径促进前胸腺细胞生长和蜕皮酮合成（Hyun，2018）。干扰马铃薯甲虫 *Chico* 或 *PI3K* 造成 20E 信号和 JH 信号受到严重影响而阻碍化蛹（Deng *et al.*，2018）。另一方面，20E 信号和 IIS/TORC1 信号通路在外周组织如脂肪体中存在相互拮抗的关系。在果蝇脂肪体中超表达 EcR^{DN} 或 EcR dsRNA 可下调 20E 信号，脂肪体细胞内 Akt 和 TORC1 活性升高、FOXO 活性降低，表明在脂肪体中 20E 可以直接拮抗 IIS 信号（Rusten *et al.*，2004；Colombani *et al.*，2005），该拮抗部分是通过转录因子 cMyc 来发挥作用的（Delanoue *et al.*，2010）。20E 虽然诱导家蚕脂肪体降解，但阻碍糖酵解；而 IIS/TORC1 信号则阻碍 USP 入核而降低脂肪体对 20E 的敏感性（Tian *et al.*，2010b；Wang *et al.*，2010）。棉铃虫中的大量研究显示，IIS 信号通过调控 *PDK1*、*CKS1*、*Rab4b* 等多种基因表达，协调 IIS 信号和 20E 信号在外周组织中的相互作用，影响变态发育过程中细胞凋亡、生长以及糖原合成等生理过程（Hou *et al.*，2012；Liu *et al.*，2015a；Pan *et al.*，

2018)。*Ras* 是 Raf-MAPK 途径的关键基因，在家蚕后部丝腺中过表达 Ras 会增大细胞体积和促进蛋白合成，通过上调 *bcpi* 来抑制组织蛋白酶活力，从而抑制变态发育过程中后部丝腺的破坏（Ma *et al.*，2011，2013)。FoxO 作为 IIS 信号下游重要的转录因子，参与了 20E 信号与营养信号的相互联系。20E 可以增强 FoxO 转录，从而上调 *Bmm* 和 *acid lipase-1* 来诱导家蚕脂肪体脂类分解（Hossain *et al.*，2013)。FoxO 突变家蚕表现出发育延迟但龄期减少的表型，可以通过注射 20E 挽救（Zeng *et al.*，2017)。20E 也可以上调 PTEN 来抑制 FoxO 磷酸化，从而激活 FoxO 来阻碍 IIS 信号，进而促进棉铃虫脂肪体蛋白质水解（Cai *et al.*，2016)。

3　展望

昆虫作为地球上种群数量最多的动物群体，与我们的生活已经密不可分。围绕变态发育这一核心生物学问题，通过研究其激素和营养调控机制，探索应用于害虫防治和益虫利用的新途径，对疾病防控、农业增收、提高经济产能能多方面有重要影响。近年来，我国科学家以模式昆虫果蝇、多种农业害虫和经济昆虫为研究材料，通过高通量测序技术和生物信息学分析等先进技术手段获得了大量准确的基因信息，从已知的激素和营养信号相关基因入手，探索其保守性与差异性，并深入探究具有靶标潜力的新基因等，不仅为动物激素和营养调控发育基础研究提供大量的理论参考，也为安全有效的害虫防治与益虫利用提供技术支撑。我国科研工作者围绕昆虫变态发育的激素和营养调控领域热点问题开展深入研究，包括表观遗传调控、非编码 RNA 调控、小分子化合物开发等等，相信我国在该领域的科研水平将会大大提高。

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