

昆虫*orthodenticle*基因研究进展*

赵 杨 何正波** 陈 斌 司风玲

(重庆师范大学生命科学学院, 昆虫与分子生物学研究所, 重庆高校生物活性物质工程研究中心, 重庆高校动物生物学重点实验室 重庆 400047)

摘 要 昆虫胚胎发育受一系列基因调控, 这些基因按照时间、空间顺序启动或关闭, 对胚胎细胞的生长和分化进行调节. *orthodenticle* (*otd*) 是间隙基因, 编码含同源结构域的转录因子, 是昆虫胚胎发育的关键基因. 在没有*bicoid*基因的昆虫中, *otd*基因取代了*bicoid*的部分功能, 建立胚胎前后轴的极性. 在昆虫原头体节形成过程中, *otd*等间隙基因直接激活体节极性基因的表达, 而对控基因不起作用. 此外, *otd*还与昆虫中枢神经和光感受器的形成有关. 从进化方面来看, *otd*基因可能是从调控后生动物的光感受、脑发育和昼夜节律的基因中逐渐演变形成, 并随着昆虫的系统发育而演化, 其表达模式和功能既具有保守性又具有变异性. 本文就昆虫*otd*基因的结构、功能和进化等方面的研究进展进行了综述. 图1 参62

关键词 *orthodenticle*基因; 昆虫; 胚胎发育; 模式形成; 头部分节

CLC Q961

Progress in Research of Insect *orthodenticle* Gene*

ZHAO Yang, HE Zhengbo**, CHEN Bin & SI Fengling

(Institute of Entomology and Molecular Biology, Chongqing Engineering Research Center of Bioactive Substances, Chongqing Key Laboratory of Animal Biology, College of Life Sciences, Chongqing Normal University, Chongqing 400047, China)

Abstract The embryogenesis of insect is controlled by a series of genes, which are turned on or off according to a precise time and spatial sequence to regulate the growth and differentiation of embryonic cells. Among these genes, *orthodenticle* (*otd*) is a gap gene which encodes a homeobox transcription factor and plays a key role in embryogenesis of insect. In some insects without *bicoid* gene, *otd* partially substitutes for *bicoid* function and establishes the polarity of anterior-posterior axis in early embryogenesis. In the cephalic segmentation in insects, the pair-rule genes do not play function, but gap genes, like *otd*, directly activate the expression of segment polarity genes. Furthermore, *otd* gene also involves in the process of developments of eyes and nervous system. *otd* possibly originates from those genes that regulate the photoreception, brain development and circadian rhythms in metazoan organisms, and then gradually differentiates with the phylogenetic evolution of insects, so the function of *otd* shows diversities in different insect groups. In this paper, the *otd* gene is reviewed, including its structure, function and evolution. Fig 1, Ref 62

Keywords *orthodenticle* gene; insect; embryonic development; patterning formation; cephalic segmentation

CLC Q961

*orthodenticle*基因是一种古老的基因, 它是在研究黑腹果蝇胚胎发育过程中发现的. 其成员包括两类: (1) 在昆虫中与黑腹果蝇*orthodenticle*同源的基因, 简称*otd*; (2) 在脊椎动物中与黑腹果蝇*otd*同源的基因, 简称*otx* [1-5]. 近年来, 有关*otd/otx*基因在动物胚胎发育方面的研究已有大量报道. 例如: 黑腹果蝇 (*Drosophila melanogaster*) [2]、赤拟谷盗 (*Tribolium castaneum*) [6]、蜜蜂 (*Apis mellifera*) [7]、丽蝇蛹集金小蜂 (*Nasonia vitripennis*) [8]、小鼠 (*Mus musculus*) [3]、智人 (*Homo sapiens*) [9]、大鼠 (*Rattus norvegicus*) [10]、穴兔 (*Oryctolagus cuniculus*)、黑猩猩 (*Pan troglodytes*)、短尾猴 (*Monodelphis domestica*)、鸭嘴兽 (*Ornithorhynchus anatinus*)、马 (*Equus caballus*)、牛 (*Bos taurus*)、家犬 (*Canis lupus familiaris*)、猕猴 (*Macaca mulatta*)、野猪 (*Sus scrofa*)、非洲负子蟾 [*Xenopus (Silurana) tropicalis*]、非洲爪蟾 (*Xenopus lae-*

vis) [11]、斑马鱼 (*Danio rerio*) [12-13]、青鳉鱼 (*Oryzias latipes*)、红原鸡 (*Gallus gallus*) [14-15]、紫色球海胆 (*Strongylocentrotus purpuratus*) [16]等, 共6个纲22种动物, 其中很多动物都只是克隆了*otd/otx*基因. *otd/otx*基因在动物胚胎前后轴形成、体节形成、视觉和神经系统发育等方面起着重要作用 [2, 5, 17]. 本文就昆虫*otd*基因的结构、功能和进化等方面的研究进展进行综述.

1 昆虫*otd*基因的结构

黑腹果蝇*otd*位于X染色体的7F1~8A5区域, 包含有4个外显子和3个内含子, mRNA全长3 809 bp, 开放阅读框 (ORF) 位于645~2 793 bp之间, 编码区域内含有较高CAG/A重复序列; *otd*氨基酸序列有一个由60个氨基酸组成的同源异型结构域 (Homeodomain), 与*paired*、*gsbBSH4*和*gsbBSHg*等基因家族的结构域有37个相同的氨基酸; 同源异型结构域的第50个氨基酸为关键的赖氨酸结合位点 (K50), 第51个氨基酸位点处出现螺旋结构 [2]. 与*otd*一样, *bicoid*基因也编码一个含K50同源异型结构域的转录因子, 因此*otd*和*bicoid*具有相似性的DNA结合特性 [18].

赤拟谷盗*otd*有两个同源基因: *otd1*和*otd2*. *otd1* mRNA

收稿日期: 2009-08-05 接受日期: 2009-10-29

*国家自然科学基金项目 (No. 30700435) 和重庆市自然科学基金项目 (Nos. CSTC2008BA5030, CSTC2009BB1387) 资助 Supported by the National Natural Science Foundation of China (No. 30700435) and the Natural Science Foundation of Chongqing, China (Nos. CSTC2008BA5030, CSTC2009BB1387)

**通讯作者 Corresponding author (E-mail: zhengbohe@yahoo.com.cn)

全长1 959 bp, ORF位于125~1 240 bp之间; *otd2*的mRNA序列全长1 708 bp, ORF位于223~1 128 bp之间; *otd1*与黑腹果蝇 *otd*的同源性较高, *otd2*与脊椎动物的 *otx*同源性较高. 对*otd1*和*otd2*的氨基酸序列分析表明, *otd1*和*otd2*都含有一个由60个氨基酸组成的同源异型结构域, 在*otd1*的第50个位点处也有特殊的赖氨酸结合位点; *otd2*编码的氨基酸序列还含有SSIWSPASI的保守结构域, 与脊椎动物*otx*的保守结构域的序列一致^[6]. 丽蝇蛹集金小蜂*otd*也有两个同源基因: *otd1*和*otd2*. *otd1* mRNA全长1 138 bp, ORF位于1~1 008 bp之间, 与赤拟谷盗的*otd1*基因序列相似度极低(17%), 而丽蝇蛹集金小蜂*otd2*的mRNA序列尚未报道^[8].

2 *otd*基因在昆虫发育中的功能

昆虫从一个受精卵发育成一个多细胞的个体受一系列基因调控, 这些基因在发育过程中, 按照时间、空间顺序启动或关闭, 对胚胎细胞的生长和分化进行调节. *otd*是胚胎发育的关键基因之一, 与昆虫胚胎模式形成、体节形成、眼睛以及神经系统发育等有关.

2.1 *otd*基因与胚胎模式形成的作用

前后轴(Anteroposterior axis, A-P轴)的形成是昆虫胚胎发育过程中的中心环节之一^[19-21]. 黑腹果蝇胚胎前后轴的极性是由少数母性效应基因决定^[22-23], 其中作为形态发生原的同源框基因*bicoid*决定了前部系统极性的形成^[24]. *bicoid* mRNA在滋养细胞中转录, 然后通过胞质间桥转运到卵母细胞的前部区, 受精后*bicoid*开始翻译, 形成由前向后的浓度梯度, 细胞的发育前途决定于其所处位置的Bicoid蛋白的浓度^[25]. *bicoid*的突变导致胚胎缺失头和胸部, 偶尔在前端

有极性倒转的重复腹部体节. 尽管*bicoid*在黑腹果蝇胚胎发育过程中起着重要作用, 但*bicoid*却是在进化过程中新近形成的, 只有高等的果蝇才有, 而其它昆虫没有*bicoid*的同源基因^[26-29]. 那么在没有*bicoid*的昆虫里, 胚胎的早期发育模式是如何形成的呢? 目前遗传学和分子生物学研究证据表明, 在没有*bicoid*的昆虫中, *otd*替代了*bicoid*的部分功能^[29-31]. 在*bicoid*突变的黑腹果蝇中, 高浓度的合子基因*hunchback*能够指导部分胸部体节的形成, 但不能指导头部体节的形成, 说明*hunchback*也有部分*bicoid*的功能^[30, 32-33].

黑腹果蝇*otd*在Bicoid蛋白质的激活下表达, 编码含锌指结构的转录因子. 在胚胎发育早期, 该转录因子主要分布在胚胎前部, 通过扩散作用形成浓度梯度, 不同浓度的*otd*可以调控部分间隙基因和体节极性基因的表达^[34-36]. 随着原肠胚的形成, *otd*表达从原头的原头区逐渐向外扩散, 并开始在胸部以及腹部的中线区域表达^[36-37]. 黑腹果蝇*otd*突变体中, 视节和触角节缺失^[18, 37], 母体和合子*hunchback*基因的突变使颌部、胸部和腹部1~2腹节全部缺失, 腹部A7/A8两个腹节发生融合^[38]. 这表明黑腹果蝇*otd*和*hunchback*基因突变缺失的体节与*bicoid*突变缺失的体节相似(图1-A).

赤拟谷盗*otd1*为母体基因, 母体*otd1*的 mRNA均匀地分布在卵内. 到囊胚期时, 胚胎前部的*otd1*开始表达而后部*otd1*基因的表达被抑制, 形成由前向后的浓度梯度^[6]. Schroder等用parental RNAi (pRNAi) 方法抑制*otd1*基因的表达, 使整个头部丢失(图1-C)^[30], 这与果蝇*bicoid*基因弱突变表型^[24]一致. 同时抑制赤拟谷盗的*otd1*和*hunchback*, 头、胸和部分腹节都不能形成(图1-C), 这种表型与黑腹果蝇*bicoid*完全突变的表型很相似(图1-A)^[24, 39], 说明*otd1*和*hunchback*在赤拟

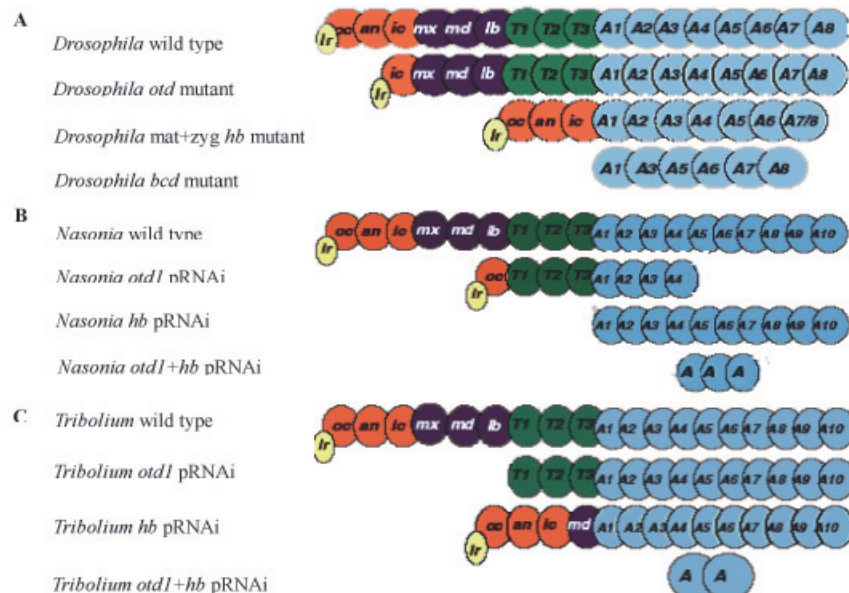


图1 *D. melanogaster*, *N. vitripennis*和*T. castaneum*的*otd*和*hb*基因功能比较

Fig. 1 Comparison of *otd* and *hb* gene functions in *D. melanogaster*, *N. vitripennis* and *T. castaneum*

hb: hunchback; *otd*: orthodenticle; *bcd*: bicoid; Lr: Labral; Oc: Ocular; Ic: Intercalary; Mx: Maxillary; Md: Mandibular; Lb: Labial; T1~T3: Thoracic 1~3; A1~A10: Abdominal segments 1~10.

A: 果蝇*otd*、*hb*和*bicoid*基因突变体模型; B: *Nasonia otd*、*hb*和*otd/hb*基因pRNAi模型; C: *Tribolium otd*、*hb*和*otd/hb*基因pRNAi模型

A: Comparison of *Drosophila otd*, *hb* and *bicoid* gene mutant in phenotypes; B: Comparison of *Nasonia otd* and *hb* pRNAi phenotypes; C: Comparison of *Tribolium otd* and *hb* pRNAi phenotypes

谷盗中代替了*bicoid*基因的功能^[24, 31]。

在丽蝇蛹集金小蜂中, 胚胎发育的前部系统也是通过*otd1*的梯度确定^[8, 40]。与赤拟谷盗不同的是母体*otd1* mRNA分别定位于丽蝇蛹集金小蜂卵的前后两极, 受精后, *otd1*开始表达并通过胚胎的扩散作用分别形成前后两个浓度梯度。前部的Otd蛋白以浓度梯度依赖的方式激活前部靶基因的表达, 如*empty spiracles*、*giant*和*hunchback*等。pRNAi抑制*otd1*的表达, 包括触角在内的头部完全缺失(图1-B), 同时抑制*otd1*和*hunchback*的表达, 头、胸和几个前部的腹节全部丢失, 比单独抑制*otd1*和*hunchback*表型的和还要严重(图1-B), 说明*otd1*和*hunchback*在丽蝇蛹集金小蜂中也代替了*bicoid*的功能^[8, 40]。

2.2 *otd*基因与头部分节

昆虫头部体节由原头和颞节组成, 原头包括头前叶和触角节等, 颞节包括上颞节、下颞节和下唇节。对黑腹果蝇早期胚胎模式形成的研究发现原头与颞节分节的机理不一样, 颞节采用与躯干一样的分节机理^[34, 41-43]。黑腹果蝇躯干的分节是通过母体基因、间隙基因、对控基因、体节极性基因等基因群的级联调控实现的^[2, 17]。母体基因激活间隙基因的表达, 间隙基因沿前后轴将胚胎划分成几个大的区域, 间隙基因再激活下游对控基因的表达, 将胚胎划分成更精细的区域, 这样便建立起了胚胎副体节的模式。这些基因的突变, 直接导致体节的错误形成或缺失, 使胚胎致死。但在原头体节的形成中, 对控基因似乎不起作用, 因此原头分节主要由间隙基因完成^[44, 45]。原头的间隙基因主要包括*otd*、*empty spiracles*、*buttonhead*和*sloppy paired*等, 这些间隙基因是在原头区域最早表达的合子基因, 并直接激活体节极性基因的表达^[44, 46-47]。

黑腹果蝇原头体节的形成主要是在*bicoid*作用下, 通过激活间隙基因的表达, 如: *otd*、*empty spiracles*、*buttonhead*和*sloppy paired*等基因, 从而调控原头体节的形成^[2, 34-44, 46, 48]。Gao等用*otd*转录起始位点上游约7.6 kb的片段作启动子能使*lacZ*标记基因在黑腹果蝇胚胎头部原基中表达, 其中约186 bp片段含有*Bicoid*的结合位点, 证明了*otd*为*bicoid*的靶基因, 与原头体节形成有关^[36, 49-50]。*Bicoid*与靶基因启动子亲和力的强弱决定了靶基因的表达程度^[51-52], 由于*bicoid*在胚胎前部的表达水平高, 因此在头部原基中表达的基因应该含有低*Bicoid*亲和力的启动子^[44]。Gao等证实黑腹果蝇*otd*的激活和前头体节的形成都不需要高浓度的*Bicoid*, 而且*otd*在头部的表达除受*bicoid*基因的调控外, 还受*tailless*和*huckebein*基因的调节^[36]。

黑腹果蝇*otd*突变后, 视节和触角节等原头体节缺失^[37]。采用RNAi方法抑制赤拟谷盗的头部间隔基因*otd1*、*empty spiracles*和*buttonhead*等基因的表达, *buttonhead*被干扰后对头部早期发育影响不大, 而*otd1*被抑制后使整个头部(包括原头和颞部)丢失^[30, 53]。丽蝇蛹集金小蜂的Otd蛋白以浓度梯度依赖的方式激活前部靶基因的表达, 如*empty spiracles*、*giant*和*hunchback*等, pRNAi抑制*otd1*的表达使视节外的头部体节全部缺失^[8, 40]。

*otd*对昆虫头部发育的表达调控是一个复杂的过程, 在不同种类的昆虫中, 其表达和调控机制不一样。目前, 关于

*otd*与昆虫头部体节的形成也仅局限于黑腹果蝇、赤拟谷盗和丽蝇蛹集金小蜂等少数几种昆虫。因此, 进一步比较不同类型、不同进化水平尤其是较为低等昆虫*otd*的表达模式和功能, 对于昆虫头部体节的形成及其演化具有重要意义。

2.3 *otd*基因与昆虫神经发育

昆虫的中枢神经系统(CNS)是由脑和腹神经索组成, 它是由一系列早期胚胎外胚层细胞中成神经细胞发育而来^[49, 54]; *otd*对昆虫早期胚胎外胚层的发育具有重要作用, 说明*otd*与CNS的形成与分化有关^[54-55]。

目前, *otd*对昆虫神经系统发育的研究主要是在黑腹果蝇中。Amelia等发现*otd*在原脑和后脑中表达; 除*otd*外, 还有其它的头部分隔基因和一些体节极性基因与CNS的发育也有关系, 如*tailless*、*empty spiracles*、*buttonhead*等^[49, 54]。Chang等发现调节CNS的部分基因的级联关系: *single minded*→*rhomboid*、*S* (*spi/Egfr*)、*spitz*→*Draf*→*pointed*→*otd*, 同时*pointed*→*argos*, 其中*argos*还能抑制*otd*的表达, 进一步证实了*otd*能在CNS的中线区域和腹部的神经外胚层细胞中表达^[55-56]。通过对黑腹果蝇*otd*突变体的研究, 发现*otd*突变体出现异常的神经纤维网, 并引起CNS中特定神经元的缺失, 同时导致小眼无法形成, 甚至导致胚胎的前脑和腹神经索缺失, 用*otd*超表达(Overexpression)进行遗传拯救(Genetic rescue), 能够使突变体胚胎的前脑和腹神经索得到一定程度的恢复^[2, 4, 34, 54, 57]。

2.4 *otd*基因与昆虫视觉发育

Vandendries等研究发现黑腹果蝇*otd*的突变体出现部分单眼的缺失, 而且单眼的缺失还与*otd*的亚等位基因(Hypomorphic allele) *ocelliless*有关^[12, 35, 57]。黑腹果蝇成虫的复眼由大约800个小眼组成, 每个小眼由20个细胞组成, 包括8个光感受器, 分别为R1~R8; 其中: R1~R6的感杆(指构成复眼中感杆束的视觉神经纤维)构成一个不等边四边形, 在这个四边形中心是由R7和R8构成, 因此小眼光感受器由两部分组成: (1)由R1~R6构成外部结构, 组成视神经叶的部分叶片, 功能是察觉外部活动; (2)由R7和R8构成内部结构, 功能是分辨不同的颜色, 并且R7和R8随机分布在视网膜上, 在30%的视网膜中有UV-*rh3* (在R7中)和*blue-rh5* (在R8中), 70%的视网膜中有UV-*rh4* (在R7中)和*green-rh6* (在R8中), 视网膜紫质的表达需要一系列高度保守的同源区域结合位点(Homeodomain binding sites), OTD蛋白质能够通过其同源域结合位点来激活特定小眼中的*rh3*和*rh5*的表达, 并通过这些位点来抑制外部的光感受器中的*rh6*的表达^[56-59], 而且*otd*对光感受器的后期分化还起着关键作用^[58]。

3 昆虫*otd*基因的进化

昆虫*otd*和脊椎动物*otx*调控个体的发育过程具有相似性, 例如: *otd*与昆虫的身体模式、体头部节形成、眼睛和神经系统发育有关^[60], *otx*与脊椎动物的前脑模式形成、视觉和神经元细胞的分化有关^[5]。追溯*otd*和*otx*的起源, 在大约6亿~8亿年前, 它们是从调节后口动物的光感受、脑发育和昼夜节律的基因中逐渐演变形成, 随后再分化成昆虫*otd*和脊椎动物*otx*^[60]。

Ranade等对长胚带 (Long-germ) 和短胚带 (Short-germ) 昆虫前后轴的进化研究中发现, 约两亿年前, 从双翅目昆虫中进化而来丽蝇蛹集金小蜂 (现属于膜翅目), 它与黑腹果蝇都属于长胚带昆虫, 但 *otd* 在两者胚胎发育过程中起的作用却不同^[62]。黑腹果蝇中 *otd* 属于间隙基因, 丽蝇蛹集金小蜂中 *otd* 却属于母体效应基因; 另外, 短胚带昆虫赤拟谷盗中 *otd* 也属于母体效应基因。随着昆虫的演变进化, 产生许多 *otd* 的同源基因, 功能也发生相应的变化, 形成一个 *otd* 基因家族^[61~62]; 黑腹果蝇 *otd* 突变型与野生型之间有61个基因的表达差异, 且都与黑腹果蝇胚胎发育有关, 其中37个基因表达出现下调, 24个基因表达出现上调, 有19个 (约占1/3) 基因的保守序列与 *otd* 同源性高, 这些基因中包含有与 *otd* 转录起始位点相结合的基因片段, 大小有1 kb, 它逐渐演变并保留下来^[61]。黑腹果蝇和拟暗果蝇 *otd* 突变体的基因表达差异性与上述研究结果相似^[60]。

4 研究展望

otd 是昆虫发育方面的一个重要功能基因, 它在正常组织中广泛表达, 尤其是在昆虫胚胎发育前期。目前, 对昆虫 *otd* 的表达模式和功能研究较为清楚的只涉及3个目, 即双翅目的黑腹果蝇、膜翅目的丽蝇蛹集金小蜂和鞘翅目的赤拟谷盗, 而其它昆虫 *otd* 基因的功能尚未研究。在已研究的昆虫中, *otd* 的表达模式和功能都表现出一定的差异。因此, 进一步研究系统发育地位不同的昆虫的 *otd* 基因, 对于 *otd* 基因和昆虫胚胎的演化都具有重要的意义。

References

- Dearden P, Akam M. Developmental evolution: Axial patterning in insects. *Curr Biol*, 1999, **9** (16): 591~594
- Finkelstein R, Smouse D, Capaci TM, Spradling AC, Errimon NP. The *orthodenticle* gene encodes a novel homeo domain protein involved in the development of the *Drosophila* nervous system and ocellar visual structures. *Genes Dev*, 1990, **4** (9): 1516~1527
- Simeone A, Acampora D, Mallamaci A, Stornaiuolo A, Apice MRD, Nigro V, Boncinelli E. A vertebrate gene related to *orthodenticle* contains a homeodomain of the *bicoid* class and demarcates anterior neuroectoderm in the gastrulating mouse embryo. *EMBO J*, 1993, **12** (7): 2735~2747
- Leuzinger S, Hirth F, Gerlich D, Acampora D, Simeone A, Gehring WJ, Finkelstein R, Furukubo-Tokunaga K, Reichert H. Equivalence of the fly *orthodenticle* gene and the human *OTX* genes in embryonic brain development of *Drosophila*. *Development*, 1998, **125** (9): 1703~1710
- Simeone A, Puelles E, Acampora D. The *Otx* family. *Curr Opin Genet Dev*, 2002, **12** (4): 409~415
- Li Y, Brown SJ, Hausdorf B, Tautz D, Denell RE, Finkelstein R. Two *orthodenticle*-related genes in the short-germ beetle *Tribolium castaneum*. *Dev Genes Evol*, 1996, **206**: 35~45
- Consortium HGS. Insights into social insects from the genome of the honeybee *Apis mellifera*. *Nature*, 2006, **443** (7114): 931~949
- Lynch J A, Brent AE, Leaf DS, Pultz MA, Desplan C. Localized maternal *orthodenticle* patterns anterior and posterior in the long germ wasp *Nasonia*. *Nature*, 2006, **439** (7077): 728~732
- Francks C, Fisher SE, Olson RK, Pennington BF, Smith SD, DeFries JC, Monaco AP. Fine mapping of the chromosome 2p12-16 dyslexia susceptibility locus: Quantitative association analysis and positional candidate genes *SEMA4F* and *OTX1*. *Psychiatr Genet*, 2002, **12** (1): 35~41
- Frantz GD, Weimann JM, Levin ME, McConnell SK. *Otx1* and *Otx2* define layers and regions in developing cerebral cortex and cerebellum. *J Neurosci*, 1994, **14** (10): 5725~5740
- Blitz IL, Cho KW. Anterior neuroectoderm is progressively induced during gastrulation: The role of the *Xenopus* homeobox gene *orthodenticle*. *Development*, 1995, **121** (4): 993~1004
- Li Y, Allende ML, Finkelstein R, Weinberg ES. Expression of two zebrafish *orthodenticle*-related genes in the embryonic brain. *Mech Dev*, 1994, **48** (3): 229~244
- Mori H, Miyazaki Y, Morita T, Nitta H, Mishina M. Different spatio-temporal expressions of three *otx* homeoprotein transcripts during zebrafish embryogenesis. *Brain Res Mol Brain Res*, 1994, **27** (2): 221~231
- Lemaire L, Kessel M. Gastrulation and homeobox genes in chick embryos. *Mech Dev*, 1997, **67** (1): 3~16
- Bally-Cuif L, Gulisano M, Broccoli V, Boncinelli E. *c-otx2* is expressed in two different phases of gastrulation and is sensitive to retinoic acid treatment in chick embryo. *Mech Dev*, 1995, **49** (1~2): 49~63
- Gan L, Mao CA, Wikramanayake A, Angerer LM, Angerer RC, Klein WH. An *orthodenticle*-related protein from *Strongylocentrotus purpuratus*. *Dev Biol*, 1995, **167** (2): 517~528
- Simeone A, Acampora D, Gulisano M, Stornaiuolo A, Boncinelli E. Nested expression domains of four homeobox genes in developing rostral brain. *Nature*, 1992, **358** (6388): 687~690
- Lynch J, Desplan C. Evolution of development: beyond *bicoid*. *Curr Biol*, 2003, **13** (14): 557~559
- Rivera-Pomar R, Jackle H. From gradients to stripes in *Drosophila* embryogenesis: Filling in the gaps. *Trends Genet*, 1996, **12** (11): 478~483
- Zhang QW (张青文). Insect Genetics. Beijing, China: Science Press (北京: 科学出版社), 2000
- Davis GK, Patel NH. Short, long, and beyond: Molecular and embryological approaches to insect segmentation. *Annu Rev Entomol*, 2002, **47**: 669~699
- Nüsslein-Volhard C, Frohnhofer HG, Lehmann R. Determination of anteroposterior polarity in *Drosophila*. *Science*, 1987, **238**: 1675~1681
- St Johnston D, Nüsslein-Volhard C. The origin of pattern and polarity in the *Drosophila* embryo. *Cell*, 1992, **68**: 201~219
- Frohnhofer HG, Nüsslein-Volhard C. Organization of anterior pattern in the *Drosophila* embryo by the maternal gene *bicoid*. *Nature*, 1986, **324**: 120~125
- Driever W, Siegel V, Nüsslein-Volhard C. Autonomous determination of anterior structures in the early *Drosophila* embryo by the *bicoid* morphogen. *Development*, 1990, **109**: 811~820
- Brown S, Fellers J, Shippey T, Denell R, Stauber M, Schmidt-Ott U. A strategy for mapping *bicoid* on the phylogenetic tree. *Curr Biol*, 2001, **11**: R43~44
- Stauber M, Prell A, Schmidt-Ott U. A single *Hox3* gene with composite *bicoid* and *zerknüllt* expression characteristics in non-Cyclorrhaphan flies. *Proc Natl Acad Sci USA*, 2002, **99**: 274~279

- 28 McGregor AP. How to get ahead: the origin, evolution and function of *bicoid*. *Bioessays*, 2005, **27**: 904~913
- 29 McGregor AP. Wasps, beetles and the beginning of the ends. *Bioessays*, 2006, **28** (7): 683~686
- 30 Schroder R. The genes *orthodenticle* and *hunchback* substitute for *bicoid* in the beetle *Tribolium*. *Nature*, 2003, **422** (6932): 621~625
- 31 Schinko JB, Kreuzer N, Offen N, Posnien N, Wimmer EA, Bucher G. Divergent functions of *orthodenticle*, *empty spiracles* and *buttonhead* in early head patterning of the beetle *Tribolium castaneum* (Coleoptera). *Dev Biol*, 2008, **317** (2): 600~613
- 32 Janody F, Reischl J, Dostadni N. Persistence of *Hunchback* in the terminal region of the *Drosophila* blastoderm embryo impairs anterior development. *Development*, 2000, **127** (8): 1573~1582
- 33 Lemke S, Schmidt-Ott U. Evidence for a composite anterior determinant in the hover fly *Episyrphus balteatus* (Syrphidae), a cyclorrhaphan fly with an anterodorsal serosa anlage. *Development*, 2009, **136** (1): 117~127
- 34 Finkelstein R, Perrimon N. The *orthodenticle* gene is regulated by *bicoid* and *torso* and specifies *Drosophila* head development. *Nature*, 1990, **346** (6283): 485~488
- 35 Wieschaus E, Perrimon N, Finkelstein R. *orthodenticle* activity is required for the development of medial structures in the larval and adult epidermis of *Drosophila*. *Development*, 1992, **115** (3): 801~811
- 36 Gao Q, Wang Y, Finkelstein R. *Orthodenticle* regulation during embryonic head development in *Drosophila*. *Mech Dev*, 1996, **56** (1~2): 3~15
- 37 Gallitano-Mendel A, Finkelstein R. Ectopic *orthodenticle* expression alters segment polarity gene expression but not head segment identity in the *Drosophila* embryo. *Dev Biol*, 1998, **199** (1): 125~137
- 38 Lehmann R, Nüsslein-Volhard C. *hunchback*, a gene required for segmentation of anterior and posterior regions of the *Drosophila* embryo. *Dev Biol*, 1987, **119**: 402~417
- 39 Berleth T, Burri M, Thoma G, Bopp D, Richstein S, Frigerio G, Noll M, Nüsslein-Volhard C. The role of localization of *bicoid* RNA in organizing the anterior pattern of the *Drosophila* embryo. *EMBO J*, 1988, **7**: 1749~1756
- 40 Lynch JA, Olesnick EC, Desplan C. Regulation and function of *tailless* in the long germ wasp *Nasonia vitripennis*. *Dev Genes Evol*, 2006, **216** (7~8): 493~498
- 41 Cohen SM, Jurgens G. *Drosophila* headlines. *Trends Genet*, 1991, **7**: 267~272
- 42 Finkelstein R, Perrimon N. The molecular genetics of headdevelopment in *Drosophila melanogaster*. *Development*, 1991, **112**: 899~912
- 43 Cohen SM, Jurgens G. Gap-like segmentation genes that mediate *Drosophila* head development. *Nature*, 1990, **346**: 482~485
- 44 Gao Q, Finkelstein R. Targeting gene expression to the head: the *Drosophila orthodenticle* gene is a direct target of the Bicoid morphogen. *Development*, 1998, **125** (21): 4185~4193
- 45 Wimmer EA, Jackle H, Pfeifle C, Cohen SM. A *Drosophila* homologue of human *Sp1* is a head-specific segmentation gene. *Nature*, 1993, **366** (6456): 690~694
- 46 Grossniklaus U, Cadigan KM, Gehring WJ. Three maternal coordinate systems cooperate in the patterning of the *Drosophila* head. *Development*, 1994, **120** (11): 3155~3171
- 47 Royet J, Finkelstein R. Pattern formation in *Drosophila* head development: the role of the *orthodenticle* homeobox gene. *Development*, 1995, **121** (11): 3561~3572
- 48 Younossi-Hartenstein A, Green P, Liaw GJ, Rudolph K, Lengyel J, Hartenstein V. Control of early neurogenesis of the *Drosophila* brain by the head gap genes *tlh*, *otd*, *ems*, and *btd*. *Dev Biol*, 1997, **182** (2): 270~283
- 49 Rudolph KM, Liaw GJ, Daniel A, Green P, Courey AJ, Hartenstein V, Lengyel JA. Complex regulatory region mediating *tailless* expression in early embryonic patterning and brain development. *Development*, 1997, **124** (21): 4297~4308
- 50 Royet J, Finkelstein R. *hedgehog*, *wingless* and *orthodenticle* specify adult head development in *Drosophila*. *Development*, 1996, **122** (6): 1849~1858
- 51 Struhl G, Struhl K, MacDonald PM. The gradient morphogen *bicoid* is a concentration-dependent transcriptional activator. *Cell*, 1989, **57**: 1259~1273
- 52 Driever W, Nüsslein-Volhard C. The *bicoid* protein is a positive regulator of *hunchback* transcription in the early *Drosophila* embryo. *Nature*, 1989, **337**: 138~143
- 53 Schroder R, Beermann A, Wittkopp N, Lutz R. From development to biodiversity-*Tribolium castaneum*, an insect model organism for short germband development. *Dev Genes Evol*, 2008, **218** (3~4): 119~126
- 54 Reichert H, Simeone A. Conserved usage of gap and homeotic genes in patterning the CNS. *Curr Opin Neurobiol*, 1999, **9** (5): 589~595
- 55 Chang J, Jeon SH, Kim SH. The hierarchical relationship among the *spitz/Egfr* signaling genes in cell fate determination in the *Drosophila* ventral neuroectoderm. *Mol Cells*, 2003, **15** (2): 186~193
- 56 Tahayato A, Sonnevile R, Pichaud F, Wernet MF, Papatsenko D, Beaufils P, Cook T, Desplan C. *Otd/Crx*, a dual regulator for the specification of ommatidia subtypes in the *Drosophila* retina. *Dev Cell*, 2003, **5** (3): 391~402
- 57 Vandendries ER, Johnson D, Reinke R. *orthodenticle* is required for photoreceptor cell development in the *Drosophila* eye. *Dev Biol*, 1996, **173** (1): 243~255
- 58 Xie B, Charlton-Perkins M, McDonald E, Gebelein B, Cook T. Senseless functions as a molecular switch for color photoreceptor differentiation in *Drosophila*. *Development*, 2007, **134** (23): 4243~4253
- 59 Sprecher SG, Pichaud F, Desplan C. Adult and larval photoreceptors use different mechanisms to specify the same *Rhodopsin* fates. *Genes Dev*, 2007, **21** (17): 2182~2195
- 60 Lichtneckert R, Reichert H. Insights into the urbilaterian brain: conserved genetic patterning mechanisms in insect and vertebrate brain development. *Heredity*, 2005, **94** (5): 465~477
- 61 Rosenberg MI, Lynch JA, Desplan C. Heads and tails: Evolution of antero-posterior patterning in insects. *Biochim Biophys Acta*, 2009, **1789** (4): 333~342
- 62 Ranade SS, Yang-Zhou D, Kong SW, McDonald EC, Cook TA, Pignoni F. Analysis of the *otd*-dependent transcriptome supports the evolutionary conservation of *CRX/OTX/OTD* functions in flies and vertebrates. *Dev Biol*, 2008, **315** (2): 521~534