

涡虫头部再生的细胞和分子机制研究

康静^{1,2}, 陈广文¹

(1.河南师范大学 生命科学学院,河南 新乡 453007;2.新乡医学院 生命科学技术学院,河南 新乡 453003)

摘要:涡虫因其拥有非凡的再生能力,成为实验室再生研究的一种常见模式动物。涡虫身体被切割后残存的任意部分都能再生出缺失组织,即使是小到虫体 1/279 的片段也能够在很短时间内再生出一个完整的个体,其中头部再生的研究更是备受关注。涡虫头部再生不仅是普通的组织再生,还包括一个功能完整的中枢神经系统再生。本文主要综述了涡虫头部再生的最新研究进展,阐明了涡虫在身体中线区域通过构建新的组织中心-前极,引导干细胞迁移,完成头部再生的细胞和分子机制。同时详细介绍了涡虫体内全能干细胞和功能干细胞的区别及它们分别在再生过程中的作用。

关键词:涡虫;头部再生;前极;干细胞;分子机制

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涡虫隶属于扁形动物门(Platyhelminthes),是扁形动物门的代表性成员,他们广泛分布在全球范围内,可以在海洋、湖泊、河流、池塘、甚至于土壤里生存^[1-2]。涡虫拥有非凡的再生能力,切割后身体残存的任意部分都能再生出缺失组织,即使是小到虫体 1/279 的片段也能够在很短时间内再生出一个完整的个体,且身体不留任何疤痕^[1-4]。而且材料易于获得,饲养方式简单,是实验室再生研究的优秀模式动物^[2-5]。动物再生现象在生物界普遍存在,从哺乳动物的脊髓、肝脏再生,到硬骨鱼和两栖类动物的整鳍或四肢的再生,再到涡虫的整体再生,我们都可以看到再生现象的存在^[5-10]。但是,从来没有一种生物可以像涡虫一样再生重建身体的任意组织或者器官,这也是涡虫再生受到关注的地方,因此涡虫再生被认为是再发育过程。特别是头部再生,不仅要再生一个完整的头部组织,还要再生出一个完整的中枢神经系统。在涡虫头部再生的过程中,有保守的再生网络存在^[11]。研究模式生物体(如涡虫)头部再生网络的细胞和分子机制,对于识别神经发育过程中潜在的细胞和分子网络至关重要^[12-17]。因此,研究涡虫头部再生过程不仅为涡虫的再生研究,同时也为高等动物神经发育研究提供了可能性。

涡虫头部再生的过程离不开干细胞和极性相关基因的调控。本文介绍了涡虫体内干细胞的最新研究进展,干细胞重新被定义为全能干细胞和功能干细胞两种,阐述了两者之间的区别及在再生过程中的作用;同时综述了涡虫再生过程中极性相关基因的研究概况。构建了涡虫头部再生的模型图,阐明了涡虫在身体中线区域通过构建新的组织中心-前极,引导干细胞迁移,完成头部再生的细胞和分子机制。

1 涡虫再生中干细胞研究概况

目前,涡虫常被认为是研究再生的理想材料,类似于高等动物胚胎发育过程,胚胎发育和一般的组织再生之间的本质区别是他们的起始阶段^[13]。胚胎发育起始于受精卵阶段,在大多数情况下,受精卵是对称分裂的^[11]。涡虫超强的再生能力是因为体内含有大量的干细胞(neoblasts),约占涡虫体内细胞总数 20%~30%。干细胞具有自我更新、增殖分化和迁移能力,而且对 X 射线异常敏感,伴随着辐射强度的增加,细胞数量急剧

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作者简介:康静(1980-),女,河南巩义人,河南师范大学博士研究生,研究方向为涡虫再生.

通信作者:陈广文,教授,博士生导师,E-mail:chengw0183@sina.com.

减少,最终完全消失,并且可以被 *piwi-1* 和 *H₂B* 基因标记,沿身体纵轴从前到后成簇分布于身体整个实质组织中^[12].干细胞(neoblasts)分为两种,全能干细胞(pluripotent stem cells, cNeoblasts)和功能干细胞(fate-specified cells, specialized neoblasts)^[1].全能干细胞能分化形成成体涡虫体内几乎所有细胞或组织,包括生殖细胞^[15],而功能干细胞则只能分化成相应功能的细胞.全能干细胞从功能上讲类似于胚胎干细胞,光镜下 cNeoblasts 呈圆形或卵圆形,直径约 5~8 μm ,具有较大的核质比,细胞质内具有拟染色体(Chromatoid bodies, CBs)结构^[1].辐照和移植实验表明,受辐射的动物不能再生出新的组织,但是移植了 cNeoblasts 之后,受致死辐射照射后的宿主动物恢复了再生能力,而移植功能性干细胞并不能使宿主恢复再生能力^[18].在对涡虫功能性干细胞研究过程中,最先被发现的是眼功能干细胞和原肾管功能性干细胞^[1].研究发现, *sp6-9*, *dlx*, *otxA*, *six1/2/-1*, *eya* 和 *ovo*, 等与眼点再生相关的基因仅在眼点功能干细胞表达,在别的功能性干细胞不表达^[1].与原肾管形成相关的基因 *POU2/3* 和 *six1/2-2* 仅在原肾管功能干细胞表达,在别的功能性干细胞不表达^[1].接着,5-羟色胺能^[19-20]、神经元^[21-23]、咽部^[24-25]、前极^[15,26-27]、肌肉^[28]、色素^[29],等功能性干细胞在涡虫体内被陆续鉴定.

当涡虫受伤后,体内会释放内含物,防止被致病菌或者病毒侵染,接着干细胞(neoblasts)感知体内发出的应急信号, cNeoblasts 从身体各处迅速向伤口迁移,分化形成产生神经元、表皮和肠等功能性干细胞,功能性干细胞大量增值,形成芽基(blastema)结构^[30](图 1).功能性干细胞对损伤的反应是增加其增殖率.增殖反应的初始高峰是广泛的,在受伤后 6 h 左右发生,然后是第二次伤口附近持续增生的阶段发生损伤后 48 h^[31].接下来近一周的时间,功能干细胞可以分化出不同的前体细胞(progeny cells)用于涡虫缺失部分的组织再生重塑,涡虫再生完成^[32-35].和干细胞相比,前体细胞在形态上和功能性干细胞类似,但是对 X 射线不敏感,同时不能被 *piwi-1* 和 *H₂B* 基因标记,却可以被 *piwi-1* 蛋白标记^[36].

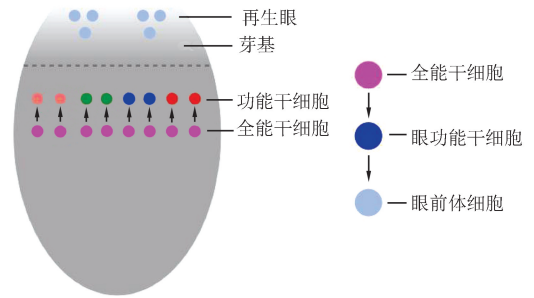


图1 全能干细胞、功能干细胞及前体细胞模型图
Fig. 1 Model of cNeoblasts, specialized neoblasts and the progeny cells

2 涡虫再生中极性相关基因研究概况

涡虫再生过程除了涉及到干细胞还涉及到极性(前后轴, antero-posterior axis, A/P; 背腹轴, dorsal-ventral axis, D/V, 中线轴, medial-lateral axis, M/L)再生问题.

在再生过程中,很多与涡虫极性再生相关的基因(表 1)及信号系统(signal pathway)被发现. Wnt 信号在涡虫的再生过程中,对 A/P 极性重建是必不可少的, Wnt 信号的正调控基因 *teashirt (tsh)* 被发现对涡虫的再生过程中 A/P 极性形成至关重要^[37-39], *teashirt* 对尾部再生有影响^[37].抑制 Wnt 信号导致所有芽基都再生分化为头部组织,相反过表达 Wnt 导致所有芽基都再生分为尾部组织^[40-41].影响 Wnt 配体分泌物表达的 *Evi/Wls* 基因被干扰后,再生的涡虫头部出现异位现象^[42];同样,调控 Wnt 配体形成的 *Wnt1* 基因被干扰后,再生出的涡虫头部出现异位现象^[42]. Wnt 信号系统的抑制基因 *notum* 被干扰后,涡虫再生时出现头部缺失或者两个尾部的表型现象^[43],而且 *notum* 是唯一在组织截肢后 6 至 12 h 就开始表达的基因^[44]. Hh 信号被干扰后影响 *wnt1* 表达和导致了早期阶段极性的变化,但并不影响早期的 *notum* 表达^[45].相反, β -*catenin-1* 基因的 RNAi 实验结果显示,影响 *notum* 早期表达,而影响 *wnt1* 表达^[17], β -*catenin-1* 被干扰后再生出许多头部^[1]. Hh 信号系统中的正向调控基因 *hedgehog (hh)*, *smoothened*, *gli-1* 缺失导致严重 A/P 极性再生失调,尾部再生失败^[45].相反,敲掉 Hh 的负调控基因 *patched (ptc)* 头部再生失败^[46].

在涡虫的再生过程中, D/V 极性重建主要依赖 Bmp 信号系统. *Bmp* 基因被抑制后,背部再生失败,出现两个腹部. Bmp 信号系统的成员 *bmp4*, *smad1*, *smad4* 被干扰后影响 D/V 的形成^[47-48],其中 *bmp4* 基因在涡虫背部,沿着中线到边缘梯度表达^[47-48].编码 Bmp 通路的其他基因也大多都在限定的区域(DV-and ML-

restricted-expression domains)内表达^[1].*Slit* 基因在中线轴表达,*wnt5* 基因在 *Slit* 基因两侧表达^[49].*slit* 和 *wnt5* 的表达被抑制后,M/L 轴再生异常.在涡虫的再生过程中,*slit* 和 *wnt5* 基因对 M/L 极性重建必不可少^[49].

表 1 极性相关基因 RNA 干扰后的表型

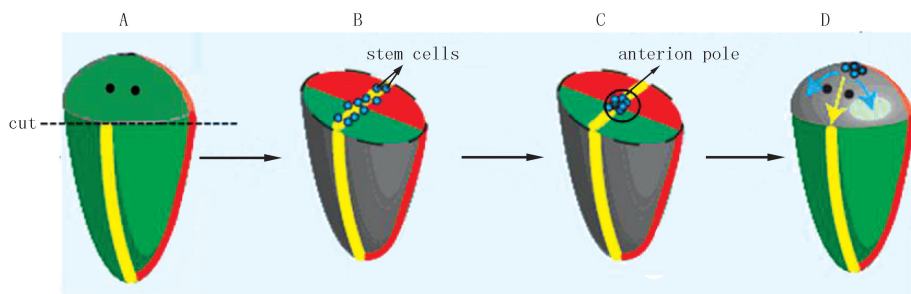
Tab.1 The phenotypes after polarity-related genes RNAi

基因	RNA 干扰后表型	参考文献	基因	RNA 干扰后表型	参考文献
<i>teashirt</i>	尾部再生失败	[24]	<i>patched</i>	头部再生失败	[45-46]
<i>Evi/Wls</i>	再生的涡虫头部出现异位现象	[29]	<i>bmp</i>	两个腹部	[47-48]
<i>wnt1</i>	再生的涡虫头部出现异位现象	[29]	<i>bmp4</i>	D/V 极性再生受到影响	[47-48]
<i>notum</i>	头部再生失败	[32]	<i>Smad1</i>	D/V 极性再生受到影响	[47-48]
<i>β-catenin-1</i>	再生动物出现许多头部	[1]	<i>Smad4</i>	D/V 极性再生受到影响	[47-48]
<i>hedgehog</i>	A/P 极性再生受到影响	[45-46]	<i>wnt5</i>	M/L 极性再生受到影响	[49]
<i>smoothed</i>	A/P 极性再生受到影响	[45-46]	<i>slit</i>	M/L 极性再生受到影响	[49]
<i>gli-1</i>	A/P 极性再生受到影响	[45-46]			

同时,我们需要注意生物物理性质在再生极性方面的影响,它们在许多生物体中胚胎发育和再生过程中具有关键作用^[50].例如,有机化合物处理可以引起动物再生过程中头部异位现象的发生,与头部再生相关基因敲除后的动物再生情况一致^[51].用吡喃唑酮药物处理后,动物细胞内钙含量增加,同时再生出两个头部.相反,降低细胞内钙水平,动物头部再生出现障碍^[52].

3 涡虫头部再生分子机制研究概况

涡虫的有一个相对原始的大脑和视觉系统,恢复头部不仅需要再生出各种功能性完整的神经元,而且需要神经元能够整齐地排列在特定的功能域.涡虫神经再生的同时要求其他器官协调形成,不仅涉及肠道及肠道分支重建,而且涉及到肾小管再生后必须恢复代谢废物清除和渗透压调节的功能.此外,体壁肌肉纤维,眼点,以及内部的肌肉纤维间质,必须重新建立.涡虫头部被切割后,创伤引起的 Wnt 信号系统抑制蛋白 *notum* 的表达^[53-54],随后,转录因子 *foxD* 和 *zic1/zicA* 开始表达,在涡虫背腹侧的轴心形成 anterior pole 信号中心,干细胞(neoblast)集中在背腹轴的中线,向背腹侧的轴心称为前极(anterior pole)的区域迁移^[25,37,55](图 2).cNeoblasts 从身体各处迅速向伤口迁移,分化形成产生眼点、神经元、表皮和肌肉等功能性干细胞,功能性干细胞大量增值,形成芽基(blastema)结构^[30].接下来近一周的时间,功能干细胞可以分化出眼点、神经元、表皮和肌肉等前体细胞(progeny cells)用于涡虫缺失部分的组织再生重塑,涡虫头部再生完成^[32-35].



A: 涡虫沿黑色虚线位置被切割;B: stem cells (蓝色) 沿着中线(黄色)向anterior pole中心位置迁移; C: stem cells 迁移至背腹侧(红色)的中心anterior pole位置(红绿交汇点);D: 头部再生完成.

图 2 stem cells 的迁移模型(根据参考文献[13]修改)

Fig.2 Model of the stem cells migration (modified from reference[13])

前极(anterior pole)可以调节 Wnt 和 Activin 信号系统中的两种关键因子 *notum*^[22,56] 及 *follistatin*^[57-58] 的表达,而 *notum*^[56] 及 *follistatin*^[59-60] 的表达对涡虫头部再生是必需的. anterior pole 可以通过影响邻近组织对中心轴的形成发挥一个独特的影响,类似于信号中心的作用,抑制 Wnt 信号可能是前极(ante-

rior pole)主要的分子功能^[53].然而,anterior pole的特殊空间形式目前能仍然不清楚,推测其可能是一个类似于胚胎的组织结构.当涡虫身体被倾斜切割时,anterior pole形成在原有组织的背腹侧的轴心位置,而不是在截肢平面的中点.截肢后可能某一种信号系统控制涡虫背腹侧中轴的形成进而影响anterior pole前极形成.slit基因干扰后抑制anterior pole的形成,wnt5基因被干扰后可以激活anterior pole的形成,而bmp4通过调控slit和wnt5的表达控制涡虫背腹侧的轴中心位置.一套来自截肢平面的原有组织通过基因调控anterior pole的形成,进而调控头部芽基顺利再生,这种机制确保身体外侧的和背腹侧的芽基,与伤口处预先存在的组织严谨地无缝连接.但是涡虫的再生可能来自不同截肢片段,非对称切割的涡虫碎片能够重新生成一个对称的头部^[39].

对于切割的涡虫碎片来说,极性相关基因确定anterior pole的唯一位置,这个唯一取决于成体涡虫的原有组织.一旦anterior pole重建成功,其他下游基因继续工作,功能性干细胞分化形成相应的功能干细胞和前体细胞,进而形成缺失的组织,再生完成.Neoblasts必须严格按照正确的机制进行增值和分化,才能使再生顺利进行,同时维持体内平衡.同时,许多功能性干细胞分化相关的转录因子,包括FoxA,gata4/5/6,myoD,在分化后的咽、内脏、肌肉^[9,55],以及神经^[61]功能干细胞都有表达.同样,coe编码的转录因子在眼功能性干涉及前体细胞表达.ovo,sine oculis及eyes absent(eya)3种基因对光感受神经元和色素细胞的分化形成是必需的,而egfr-1(epidermal growth factor receptor 1),tph(tryptophan hydroxylase),sp6-9(specificity protein 6-9)and dlx(distal-less homeobox)对色素细胞的形成是必不可少的^[62],分别在相应的功能性干细胞和前体细胞表达.

4 结论与展望

涡虫的几乎所有截肢后的片段可以再生,这需要一个正确的系统正确指导干细胞取代缺失的组织.总之,最新的研究表明涡虫头部切割后,需要三个重要步骤来恢复.首先,必须确定,缺失的是头部组织,而不是其他部位的组织,需要在伤口部位生成一个新的头部(head-versus-tail确定).第二,极性相关基因快速对损伤做出反应,之后重建极性中心(anterior pole).第三,全能干细胞迁移至极性中心(anterior pole),分化形成功能性干细胞,严格控制各种前体细胞的数量,类型和相对位置,完成组织重建.头部再生的是一个复杂的过程,需要多基因共同参与的网络协作,并且很多基因都是保守性,从低等的无脊椎动物到高等的哺乳动物中都存在.所以,关于涡虫头部再生需要更多的学者做进一步深入研究,不仅为涡虫再生,同时也为高等脊椎动物乃至人类的神经发育研究提供更多的理论依据和参考.

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The cellular and molecular mechanism for planarians head regeneration

Kang Jing^{1,2}, Chen Guangwen¹

(1.College of Life Science, Henan Normal University, Xinxiang 453007, China;
2.College of Life Science, Xinxiang Medical University, Xinxiang 453003, China)

Abstract: The planarian has a powerful regenerative capability, and is an organism that is able to regenerate a new individual from a tiny fragment of its own body, no matter that the minimum fragment size is as small as 1/279th of a planarian. The planarian species can regenerate a head de novo including a functional brain and central nervous system. Here, the latest advances of planarian head regenerative are reviewed. New findings indicate after decapitation, planarians build an organizing center-anterior pole from stem cells at the old midline that directs head patterning and outgrowth. A stem cell population (neoblasts) generates new cells and is comprised of pluripotent stem cells (cNeoblasts) and fate-specified cells. Their mechanism was also introduced in planarian regeneration.

Keywords: planarian; head regeneration; anterior pole; stem cell; cellular and molecular mechanism

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Study on moderate scale of grain management in agricultural area of central plain based on DEA model: A case of wheat-corn rotation in Henan province

Zhang Xinyi¹, Meng Junjie², Wang Jing², Meng Yao²

(1.The university of Sheffield, The School of Mathematics and Statistics, Sheffield S10 2TN, UK;
2.Agricultural Economics and Information Research Institute, Henan Academy of Agriculture Sciences, Zhengzhou 450002, China)

Abstract: Taking wheat-corn rotation in Henan as an example, farmers' questionnaire and DEA model were used to measure appropriate grain production scale of crop growing areas in Central China Plain. 4 input indexes including land, labor, direct materials, and indirect materials and 2 output indexes including total grain yield and net profit were chosen, and the index data of different land scale farmers were counted and collected. Comprehensive efficiency, technical efficiency and scale efficiency were measured so the appropriate scale of production were found out. Meanwhile, input structure and output characteristics of different scale groups were analyzed, and characteristics of DEA effective group and the reasons of invalid group were explored. The results showed that there were great differences among farmers' input structure in different planting scale, and that the best cultivated area of general grain producers was (3.67, 4.67] hm², and the most suitable scale for large scale grain producers who had large investment in infrastructure and agricultural machinery was (66.67, 100.00] hm². Through the research, some policy recommendations were put forward such as choosing suitable planting scale, utilizing scale advantage to breed better seeds and plant high-quality special varieties, and strengthening social services, and so on.

Keywords: moderate scale management; wheat-corn rotation; data envelopment analysis; surveying peasant household; agricultural area in central plain

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