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RNA-Protein Interactions. ZHANG Qing-Shuo, WANG Er-Duo (*State Key Laboratory of Molecular Biology, Shanghai Institute of Biochemistry, The Chinese Academy of Sciences, Shanghai 200031, China*)

Abstract RNA-protein interactions play crucial roles in many fundamental cellular processes. Recently studies on RNA-protein interactions are getting considerable progress with the improvement of techniques and the appearance of new methods. Many protein-binding sites of RNAs have been characterized, some RNA-binding domains of proteins have been found, and the structural features of them have been investigated in detail. The results from above work can provide important information to understand the molecular mechanism of RNA-protein interactions and the related cellular processes.

Key words recognition, domain, RNA-binding protein

白血病抑制因子促进胚泡植入的研究进展*

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摘要 白血病抑制因子是一多效性细胞因子, 能促进哺乳动物的早期胚胎发育和启动胚泡植入, 其基因表达和生物合成受母体因素 (如甾体激素和其他细胞因子) 的控制. gp130 是白血病抑制因子家族受体的亲和力转化亚基, 其同源/异源亚基的二聚体能够激活酪氨酸激酶, 通过不同途径调节靶基因的表达.

关键词 白血病抑制因子, 胚泡植入, gp130

学科分类号 Q492.1, Q516

白血病抑制因子 (leukemia inhibitory factor, LIF) 是子宫内膜腺体分泌、分子质量为 45~56 ku 的糖蛋白^[1]. 它是一种多效性细胞因子, 可作用于多种靶细胞, 而且, 在体内许多组织/器官都有其分布.

哺乳动物的胚泡植入是一复杂的生理过程, 它要求有侵入能力的胚泡和具接受性的子宫内膜相互作用^[2], 即双方建立起“对话”机制. 一些细胞因子, 如 LIF、白介素 (interleukine, IL)、表皮生长因子 (epidermal growth factor, EGF)、转化生长因子 (transforming growth factor, TGF) 等在子宫内

膜的“植入窗口”期具有重要的生理功能.

本文试图就 LIF 在围植入期的基因表达、生理功能及其受体信号转导方面的近期进展加以综述, 为探讨 LIF 对胚泡植入的调节机理提供思路.

1 子宫内膜的 LIF 基因表达

Bhatt 等^[2]研究表明, LIF 在妊娠第 4 天小鼠的子宫内膜腺体中表达最高. 当延缓植入时, LIF

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的突发性表达也相应延迟,说明 LIF 在子宫内膜的表达和胚泡植入的时间紧密相连,具时空特异性.人子宫上皮细胞的 LIF 含量依不同的生理时期而异,具有月经周期依赖性^[3].分泌期 LIF 含量比增生期高,而且在子宫内膜的上皮丰富区(epithelium-enriched fraction, EF)比基质丰富区(stroma-enriched fraction, SF)高^[4].

甾体激素(E_2/P_4)能够促进胚泡发育,但是必须有子宫内膜单层上皮的存在,提示甾体激素可能间接作用于胚泡^[5].细胞因子[白介素-1(interleukin-1, IL-1),肿瘤坏死因子 α/β (tumor necrosis factor α/β , TNF- α/β)]和甾体激素,如雌二醇(estradiol, E_2)能够刺激人子宫内膜细胞的 LIF 表达,并且,这种刺激作用能被蛋白激酶 C(protein kinase C, PKC)抑制剂所阻断^[6],即 PKC 参与 LIF 基因的表达调节.

2 LIF 在围植入期的生理功能

Stewart 等^[7]采用基因重组技术,发现 LIF 基因缺陷的雌鼠(LIF⁻/LIF⁻)能够排卵,其卵子亦能够受精,但胚泡不能正常植入及发育;若转移到野生型假孕鼠中,则胚泡能够正常植入和发育,说明 LIF 是动物胚泡植入过程所需的.

目前认为,在围植入期 LIF 主要有两种作用:一是作为胚胎营养因子,调节其生长发育;二是启动胚泡植入的进行^[2,5].

2.1 调节胚胎生长发育

大量证据表明, LIF 是植入前期母体环境中的胚胎营养因子,能调节胚胎生长发育. LIF 在胚胎生成中有两方面作用: a. 抑制内细胞团(inner cell mass, ICM)的分化,维持胚胎的多潜能性; b. 刺激 ICM 和滋养外胚层的增殖^[5]. LIF 的这种功能差异可能是其受体下游信号转导途径不同造成的.

2.2 启动胚泡植入

LIF 在小鼠子宫内膜腺体中的表达与胚泡的形成相吻合,对胚泡植入有重要调节作用^[3]. LIF 和 EGF 能刺激培养 3 d 胚泡的尿激酶型纤溶酶原激活因子(urokinase-type plasminogen activator, uPA)和明胶酶-B(gelatinase-B)活性,进一步影响胚泡植入^[7].还有报道 LIF 能够刺激人滋养层细胞的纤粘连蛋白(fibronectin, FN)合成增加,使其向锚定的表型(anchoring phenotype)转化^[8];或者 LIF 能够抑制合体滋养层的分化,使其向浸润的表型发展,进而启动胚泡植入^[9].

3 LIF 的受体转导通路

有关 LIF 下游激活途径的研究目前集中在 LIF 受体(leukemia inhibitory factor receptor, LIFR)亚基 gp130 上. gp130 是一种糖蛋白,它是 LIF、IL-6、制瘤素 M(oncostatin M, OSM)、睫状神经营养因子(ciliary neurotrophic factor, CNTF)等一类细胞因子家族共同存在的受体亲和力“转换器”,它能形成同源(如 IL-6 受体)或异源(如 LIF, OSM 受体)二聚体. gp130 不能直接和 LIF 结合,它与 LIFR 的 β 亚基结合后,能够把低亲和力受体转换成高亲和力形式,这种异二聚体受体能够激活细胞质中酪氨酸蛋白激酶(如 TYK-2, JAK-2, JAK-1)^[10],被激活的酪氨酸激酶可以磷酸化转录的信号转导因子和活化蛋白(signal transducer and activator of transcription, STAT),调节特异的基因表达.另有认为,致裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)参与 LIF 的受体转导通路^[11].由此可知, LIF 的受体下游信号通路比较复杂,推测一条通路不可能完成其复杂的生物学功能,这可能是 LIF 多功能性的主要原因.

4 展 望

胚泡植入是动物生殖过程中的关键,其中一些细胞因子起重要作用,它们能够充当子宫内膜微环境的“局部调节者”(local mediators). LIF 在“植入窗口”期的子宫内膜中特异性表达,促进胚胎生长发育和启动胚泡植入. LIF 是一多效性细胞因子,其受体亚基的异源二聚化能激活酪氨酸蛋白激酶,进而调节特异基因的表达,但是其多功能性的分子细胞学机理很令人费解.另外, LIF 在围植入期的上游及下游信号传导途径也有待进一步探讨,比如,甾体激素 E_2 能够调节 LIF 的基因表达,但序列分析未能显示出 LIF 基因上有 E_2 结合区^[12];再如,胚泡植入涉及一系列酶解活动,影响子宫内细胞外基质的重建(remodelling)^[7], LIF 能够促进这一过程, LIF 如何增加蛋白酶的水解活动,这是一个很有价值的课题.总之,通过研究 LIF 这一“热门分子”的作用机理,有望打开胚泡植入的细胞分子调节通路之门.

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Effects of Leukemia Inhibitory Factor on the Blastocyst Implantation. CAI Li-Quan, DUAN Er-Kui, ZHU Cheng (*State Key Laboratory of Reproductive Biology, Institute of Zoology, The Chinese Academy of Sciences, Beijing 100080, China*).

Abstract Leukemia inhibitory factor (LIF), mainly secreted by endometrium gland during peri-implantation, is a glycoprotein with pleiotrophic activity on a wide variety of cell types. The principal function of LIF *in vivo* may be to regulate the growth and to initiate implantation of blastocyst. LIF expression is under maternal control, which is influenced by steroid hormones and cytokines. Gp130, a signal transducer receptor component shared by the cytokines such as LIF, IL-6, OSM and CNTF, can convert the low affinity LIFR β into a high affinity form, and its homodimerization (in the case of IL-6) or heterodimerization (in the case of LIF, OSM and CNTF) can activate tyrosine kinases, which further regulate expression of target genes by some kinds of pathway.

Key words leukemia inhibitory factor, blastocyst implantation, gp130

分析基因表达图式的新方法

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摘要 随着基因组研究的深入进行, 基因的分子生物学除了要寻找在生物学上重要的个别基因并研究其结构与功能外, 更重要的应是了解整个基因组的功能活动, 即细胞全部基因的表达图式. 要解决如此复杂的问题就必须在研究方法上有所创新, 基因表达系列分析法、cDNA 微阵列分析法、DNA 微芯片分析法等正是近几年发展起来的分析基因表达图式的新方法.

关键词 基因表达图式, 基因表达系列分析法, cDNA 微阵列分析法, DNA 微芯片分析法

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