



IGF-1在哺乳动物卵泡发育中的作用

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摘要: 在哺乳动物的发情周期中有大量的卵泡被募集, 每个发情周期单胎动物一般只有一个卵泡优势化排卵, 而多胎动物也只有少数卵泡被优势化选择, 剩余的大量卵泡发生闭锁。近些年来, 围绕卵泡优势化选择的研究取得了一系列重要进展, 但相关机理尚未完全揭示。胰岛素样生长因子1(insulin-like growth factor 1, IGF-1), 被证实卵泡发育过程中起到重要作用, 本文综述了IGF-1在哺乳动物卵泡发育中的作用及机制, 主要论述其在卵泡的优势化选择, 促进卵泡生长发育, 抑制颗粒细胞凋亡和维持雌性哺乳动物正常繁殖力方面的研究进展。

关键词: IGF-1; 哺乳动物; 卵泡发育; 激素调控; 内分泌

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The Role of IGF-1 in Mammalian Follicular Development

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Abstract: During the estrous cycle of mammals, a large number of follicles are recruited. Typically, only one follicle is selected for dominance and ovulation in monotocous (single-offspring) species per cycle, while only a few follicles are selected for dominance in polytocous (multiple-offspring) species. The vast majority of the remaining follicles undergo atresia. In recent years, significant progress has been made in research focusing on follicular dominance selection, although the underlying mechanisms have not yet been fully elucidated. Insulin-like growth factor 1 (IGF-1) has been demonstrated to play a crucial role in follicular development. This review summarizes the roles and mechanisms of IGF-1 in mammalian follicular development, focusing on its involvement in dominant follicle selection, promotion of follicular growth and development, inhibition of granulosa cell apoptosis, and maintenance of normal reproductive performance in female mammals.

Keywords: IGF-1; mammal; follicular development; hormonal regulation; endocrine

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近年来, 畜牧业在提升人类生活品质与丰富饮食文化方面发挥着日益重要的作用。该产业的发

展高度依赖于动物的繁殖效率, 而雌性哺乳动物的卵泡发育作为生殖过程的核心环节, 直接决定繁殖

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性能。在卵巢中,卵泡是由卵母细胞及其外围包裹的颗粒细胞群构成的基本功能单位。其发育过程始于原始卵泡,历经募集、生长、分化阶段,最终形成可排卵的成熟卵泡。这一动态进程是一个复杂的过程,受多重生理调节因子精密调控。其中,胰岛素样生长因子-1(insulin-like growth factor 1, IGF-1),也叫做生长调节素 C,在多种卵巢功能的调节中起着重要作用,可以影响卵泡发育和成熟,包括原始卵泡的激活、卵泡生成、卵巢类固醇生成、卵母细胞成熟和胚胎植入^[1],IGF-1作为关键旁分泌/自分泌信号分子,通过协同促性腺激素、调节类固醇生成及细胞代谢^[2],主导卵泡的募集、优势化选择^[3]并抑制颗粒细胞凋亡^[4]。值得注意的是,环境内分泌干扰物(如邻苯二甲酸二正丁酯)可抑制卵巢 IGF-1 信号传导,导致卵泡数量减少及卵巢储备下降^[5],而间充质干细胞治疗则通过上调 IGF-1 表达,同步提高抗缪勒管激素(anti-müllerian hormone, AMH)、雌二醇(estradiol, E₂)水平及卵泡数量,为卵巢功能修复提供新策略^[6]。本文主要论述卵泡的优势化选择,探讨 IGF-1 在哺乳动物卵泡发育中的作用及机制,旨在改善畜牧生产和辅助生殖技术领域提供新的策略。

1 IGF-1 概述

1.1 IGF-1 的生物特性

IGF-1 是一种与胰岛素分子结构相似的激素。IGF-1 由一个单链上的 70 个氨基酸组成,有 3 个分子的二硫化物桥。IGF-1 的分子量是 7.649 ku^[7]。人的 IGF-1 基因位于第 12 条染色体上,小鼠的 IGF-1 基因位于第 10 条染色体上^[8-9],猪和牛的 IGF-1 基因在第 5 号染色体上。IGF-1 有 7 种结合蛋白,其中胰岛素样生长因子结合蛋白 2(insulin-like growth factor-binding protein 2, IGFBP2)和胰岛素样生长因子结合蛋白 3(insulin-like growth factor-binding protein 3, IGFBP3)对胰岛素样生长因子(insulin-like growth factors, IGFs)的作用有促进作用,而其余的都对 IGFs 有不同程度的抑制作用,如 IGFBP2 和胰岛素样生长因子结合蛋白 5(insulin-like growth factor-binding protein 5, IGFBP5),它与 IGF-1 的亲合性远高于胰岛素样生长因子 1 受体(insulin-like growth factor 1 receptor, IGF-1R),属竞争性抑制。大约 98% 的 IGF-1 与胰岛素样生

因子结合蛋白家族(insulin-like growth factor-binding protein family, IGFBPs)结合。IGFBP3 大量存在,它与 IGF-1 以 1:1 的比例结合,能结合 80% 的 IGFs。胰岛素可以调节胰岛素样生长因子结合蛋白 1(insulin-like growth factor-binding protein 1, IGFBP1)的合成^[10]。

1.2 IGF-1 的生理作用

IGF-1 主要来源于肝脏,通过内分泌、旁分泌、自分泌等形式作用于靶标组织。IGF-1 是生长激素作用的主要介质。生长激素在垂体前叶生成,释放到血流中,刺激肝脏产生 IGF-1,随后刺激全身的生长,并且对身体中的几乎每个细胞都起作用。IGF-1 的产生受生长激素(growth hormone, GH)的刺激, GH 是 IGF-1 的主要调节因子,肝脏是其主要生产者,反过来,垂体 GH 的释放通过负反馈回路机制受到循环 IGF-1 的控制^[11],营养不足、生长激素不敏感、生长激素受体缺乏或下游信号传导通路的失败,都可能使 IGF-1 的产生受阻。胰岛素水平、基因构成、时间、年龄、性别、运动状态、压力水平、营养水平和体重指数、疾病状态、种族、雌激素状态和外来物摄入都能影响 IGF-1 的水平^[12-14]。近年研究发现,IGF-1 在畜牧生产中具有重要作用,有研究证实,IGF-1 可促进早产仔猪肾脏成熟并减轻其出生后第一周的肾功能损害^[15];生长发育迟缓仔猪的血浆中 IGF-1 水平显著低于同日龄正常个体^[16];对于绵羊胎儿而言,输注 IGF-1 可维持体内正常胰岛素及血糖水平^[17];围产期母牛的营养均衡供给可有效提高其后代血清中的 IGF-1 水平^[18]。

IGF-1 通过与 IGF-1R 结合发挥作用。其信号通路的激活始于 IGF-1 与细胞表面 IGF-1R 的结合,激活磷脂酰肌醇-3 激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B(protein kinase b, AKT)或细胞外信号调节激酶(extracellular signal-regulated kinases, ERK)/丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路,刺激细胞生长和增殖并抑制程序性细胞死亡^[19]。IGF-1 和 IGF-1R 的 mRNA 和蛋白在人体各个组织中的表达模式如图 1 所示。IGF-1 和 IGF-1R 的 mRNA 和蛋白在女性和男性的生殖器官的表达水平相对其他组织较高,这表明 IGF-1 和 IGF-1R 在雌性生殖系统中发挥着重要的作用。IGFs、IGFBPs 和 IGFBP 蛋白酶共同构成 IGF 系统。

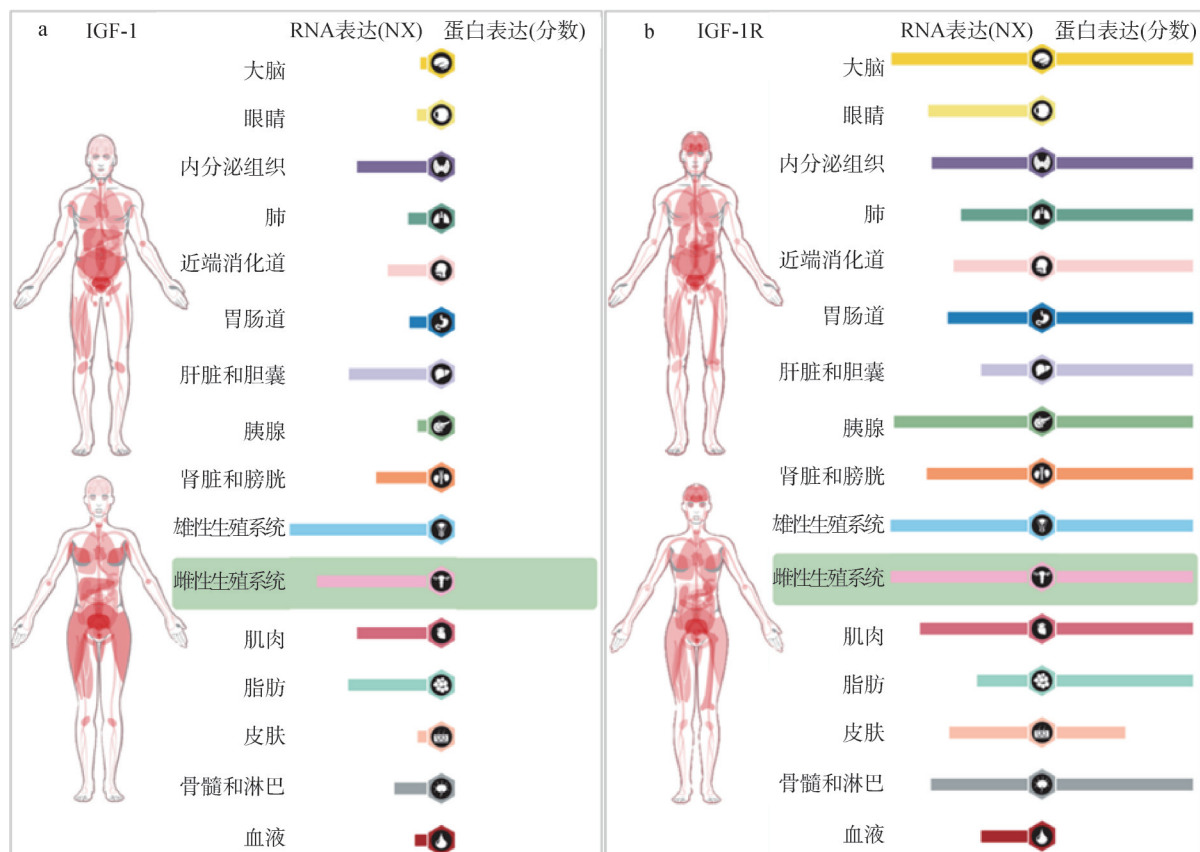


图1 IGF-1和IGF-1R的mRNA和蛋白在人体重要组织中的表达模式(图改自 The Human Protein Atlas 网站: <https://www.proteinatlas.org>)

Fig. 1 Expression patterns of IGF-1 and its receptor (IGF-1R) at the mRNA and protein levels in major human tissues (Image from The Human Protein Atlas website: <https://www.proteinatlas.org>)

2 IGF-1在卵泡中的表达情况

IGF1对多种动物物种的卵泡发育非常重要。在小鼠和大鼠的次级卵泡、腔前卵泡、小腔卵泡中IGF-1 mRNA大量并均匀分布在颗粒细胞中,而在大的有腔卵泡、成熟的有腔卵泡中IGF-1 mRNA集中分布在靠近卵泡腔和卵子周围的颗粒细胞中,在靠近基底膜的位置很少表达^[20]。在一些大的早期闭锁卵泡中IGF-1 mRNA很少或者检测不到,在黄体颗粒细胞中也检测不到^[21]。随着卵泡生长,各级生长卵泡和成熟卵泡中都大量表达IGF-1R的mRNA,且次级卵泡的生长速率与IGF-1R mRNA的表达水平相关^[22]。颗粒细胞与卵子产生的IGF-1R与IGF-1相互作用促进了卵子的代谢活动,不同的是IGF-1 mRNA均匀地分布在成熟卵泡的壁层颗粒细胞和靠近卵泡腔的颗粒细胞中。在退化闭锁的卵泡中,IGF-1R mRNA在IGF-1 mRNA停止

表达后的一段时间内依然表达。IGF-1R mRNA在成熟的黄体颗粒细胞中也大量表达,而在膜细胞中检测不到。卵泡膜细胞和颗粒细胞之间的直接相互作用促进了IGF-1表达。IGF-1R mRNA也在卵子中表达;Spicer等^[23]研究发现,马的大卵泡的卵泡液中游离IGF-1含量显著高于小卵泡中的含量;Yuan等^[24]研究表明,牛的大卵泡液有大量的IGF-1 mRNA表达,卵泡直径越小IGF-1 mRNA的表达越少。Han等^[25]研究证实,断奶时IGF-1浓度较高的母猪比断奶时IGF-1水平较低的母猪在断奶时卵泡更大;在绵羊物种中,IGF-1 mRNA定位于窦卵泡的颗粒层和膜层,也位于窦前卵泡的卵母细胞和颗粒细胞中,然而,IGF-1蛋白位于山羊窦前和胃窦卵泡中^[26]。因此IGF-1在哺乳动物的卵泡发育过程中很重要,并且IGF-1表达和作用存在物种依赖性变异。

3 IGF-1在卵泡发育中的作用

3.1 参与卵泡的优势化选择

单胎动物的卵泡优势化过程中,只有一个卵泡发育并继续生长和排卵。其中的关键事件就是卵泡直径发生偏差,即最大直径和第二大直径的卵泡发生区分。在卵泡发育期间,超声波可观测到发育中的优势卵泡的持续生长,而其他卵泡(从属卵泡)的生长减缓,这被称为卵泡直径偏差^[27-28]。

牛的IGF系统通过IGFBPs的蛋白酶A (pregnancy-associated plasma protein-a, PAPP-A)而保持或增强活性,并在最大和第二大直径的卵泡发生直径偏离前增加雌激素和促黄体激素受体(luteinizing hormone receptor, LHR)表达^[29];马的卵泡直径发生偏离前最大卵泡有多种因子高于第二大卵泡,但是只有IGF系统是唯一一个对卵泡直径偏离有积极效应的机制^[30]。促卵泡激素(follicle-stimulating hormone, FSH)通过促卵泡激素受体(follicle-stimulating hormone receptor, FSHR)促进IGFBPs蛋白酶的表达,IGFBPs蛋白酶可以降解IGFBPs从而使游离态的IGF增加,游离的IGF增强颗粒细胞对促性腺激素的敏感性从而促进卵泡生长。研究发现,促卵泡素FSH诱导的颗粒细胞分化需要IGF-1受体的活性^[31]。Beg等^[32]的研究也表明,牛的最大卵泡中游离的IGF-1浓度没有随着直径偏离而增加,但第二大卵泡中的游离IGF-1浓度则下降。Ginther等^[33]发现,给马的第二大卵泡注射IGF-1可以使其也继续发育并排卵,且增加了第二大卵泡中激活素-A、抑制素-A、血管内皮生长因子的浓度。然而,用IGFBP-3注射到马直径最大的卵泡里,发现最大的卵泡生长停滞,而第二大卵泡继续生长成为优势卵泡并排卵^[34]。通过研究最大的卵泡和第二大卵泡中IGF-1水平的不同以及用IGF-1诱导第二或第三大卵泡生长并排卵的试验,足以表明IGF-1是引起卵泡直径偏差进而引发卵泡优势化选择的发起者^[27]。

3.2 促进卵泡生长发育

Walters等^[35]为了研究IGF-1在早期有腔卵泡发育中的作用,将不同直径大小的牛的有腔卵泡进行体外培养并添加高浓度($1\text{ mg}\cdot\text{mL}^{-1}$)或低浓度($10\text{ ng}\cdot\text{mL}^{-1}$)的IGF-1处理,结果发现添加了高浓度的卵泡生长显著加快,并且IGF-1的添加提高了卵子质量。另外,大卵泡的IGFBP2在转录和翻译

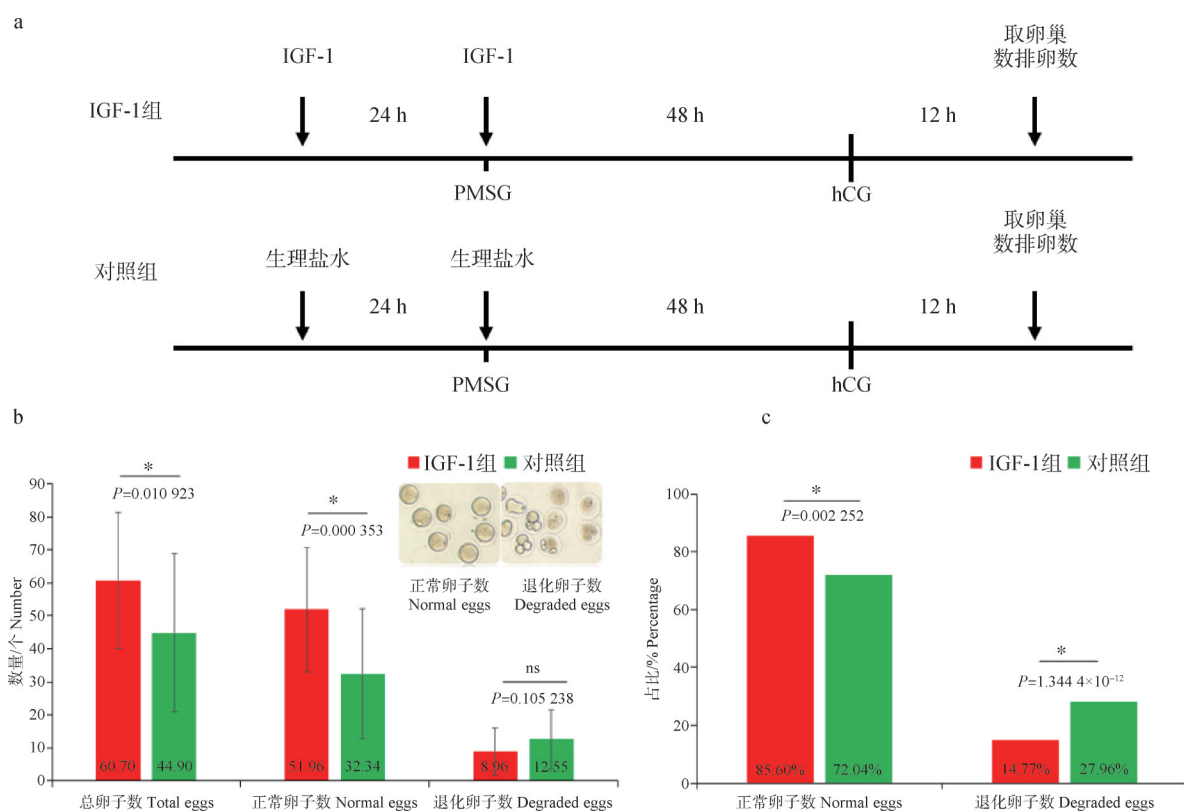
水平上都显著低于小卵泡。IGF-1增加了两种大小卵泡颗粒细胞中*ESR2*、*FSHR*和*CYP19a1*的mRNA表达,中等大小卵泡中的*FSHR*的mRNA除外。IGF-1显著提高了颗粒细胞中*HSD-3 β* 、*CYP11A1*和*CYP19A1*的mRNA表达^[36-37]。此外,IGF-1增加了雄烯二酮和黄体酮的产生,但没有影响在睾酮中小型卵泡膜细胞中的产生^[38]。

早在1996年,Baker等^[39]就研究了IGF-1敲除母鼠的生殖表型,结果发现,敲除鼠的卵巢可以正常发育,但小鼠不表现出青春期,可以产生正常卵子并有腔前卵泡,但其卵泡发育停滞在腔前或小腔卵泡阶段,并且没有成熟卵泡及黄体生成。此研究充分表明IGF-1在卵泡发育过程中至关重要的作用。IGF-1敲除鼠与FSH敲除鼠在卵泡发育上的表型相似^[40]。研究发现,IGF-1能够增加*FSH*的表达^[41]。此外,IGF-1可上调在含FSH培养基中培养的大鼠颗粒细胞中*LHR*的表达,而单独使用IGF-1则无法诱导*LHR* mRNA的表达^[42]。

Zhou等^[43]提出了IGF-1基因在卵泡发育中作用:卵子能够产生一些信号分子,促进颗粒细胞增殖和IGF-1的产生,IGF-1和IGF-1R在卵母细胞及其滤泡细胞中的局部表达也可以促进卵泡的早期发育,IGF-1促进*FSHR*的表达,增强了*FSH*的敏感性,*FSH*可促进IGF-1R和*FSHR*的表达,这种正反馈调节被认为对于卵泡的生长和优势化选择至关重要。*FSH*活性的增强增加了颗粒细胞芳香化酶和*LHR*的表达,雌激素的水平也会上升,升高的雌激素引起促黄体生成素峰的出现,从而发生排卵^[44-45]。如果IGF-1缺乏或不足则会引起卵泡的发育停滞。Rawan等^[46]报道,低浓度($1\text{ ng}\cdot\text{mL}^{-1}$)和高浓度($100\text{ ng}\cdot\text{mL}^{-1}$)的IGF-1能够促进各种大小直径卵泡中颗粒细胞*LHR* mRNA的表达,并能促进小卵泡的颗粒细胞中雄烯二酮和雌二醇的产生,对卵泡的优势化选择有重要作用。根据IGF-1可上调卵泡颗粒细胞*FSHR*和*LHR*的理论,本研究团队设计了IGF-1注射试验:在小鼠超数排卵处理前进行IGF-1腹腔注射,如图2a所示,每只小鼠提前24 h注射80 μg 的IGF-1在注射孕马血清促性腺激素(pregnant mare serum gonadotropin, PMSG)时再次注射80 μg 的IGF-1,48 h后注射人绒毛膜促性腺激素(human chorionic gonadotropin, hCG)进行超数排卵处理,14 h后,刺破输卵管获取卵子并计数。结果显示,在超排处理时用IGF-1注射可显著提高小

鼠的排卵总数,平均排卵数从对照组的44.90个提高到了60.70个,优质卵子数增加约10个且占比显著增多,而退化卵子数显著降低(图2b和2c)。此试验有力地证明了IGF-1在卵泡发育和卵泡过程中的重要作用。进一步地,本研究团队探索了IGF-1对三维培养小鼠卵泡的影响,本团队发现添加低浓度IGF-1($5\text{ ng}\cdot\text{mL}^{-1}$ 和 $10\text{ ng}\cdot\text{mL}^{-1}$)与对照组相比对卵泡体积增长没有显著影响($P>0.05$),但添加高浓度($50\text{ ng}\cdot\text{mL}^{-1}$)IGF-1时会显著抑制卵泡生长($P<0.05$)(图3a和3b)并降低卵泡存活率(图3c),在卵泡培养过程中添加适宜浓度的IGF-1有助于促

进卵泡发育并提高卵母细胞质量,具体表现为,培养6天后的卵泡经体外成熟后,其卵母细胞的成熟率显著提升(图3d),同时其退化率相应降低(图3e)。IGF-1在培养过程中显著促进了卵泡类固醇合成相关基因*STAR*,*CYP19a1*和*HSD-3 β* 的mRNA的表达,并促进了 17β -雌二醇和孕激素的分泌,下调了*AMH*的mRNA的表达并抑制AMH分泌,促进了卵母细胞分泌因子*BMP-15*,*GDF-9*和*FGF-8*的mRNA的表达,并提高了*LHCGR*和*FSHR*的mRNA的表达。IGF-1处理后,与对照组相比,*BCL2/BAX*的mRNA比率升高^[47]。



a. IGF-1腹腔注射处理小鼠的试验流程;b. IGF-1注射组和对照组小鼠总排卵数,正常卵子数,退化卵子数统计图;c. IGF-1注射组和对照组小鼠正常和退化卵子占比对比图,采用卡方检验

a. Experimental timeline of IGF-1 intraperitoneal injection in mice; b. Comparison of the total number of oocytes ovulated, normal oocytes, and degenerated oocytes between the IGF-1-injected group and the control group; c. Comparison of the percentages of normal and degenerated oocytes between the IGF-1-injected group and the control group, analyzed by the chi-square test

图2 IGF-1处理显著提高小鼠的排卵数和卵子质量

Fig. 2 IGF-1 treatment significantly improved ovulation number and oocyte quality in mice

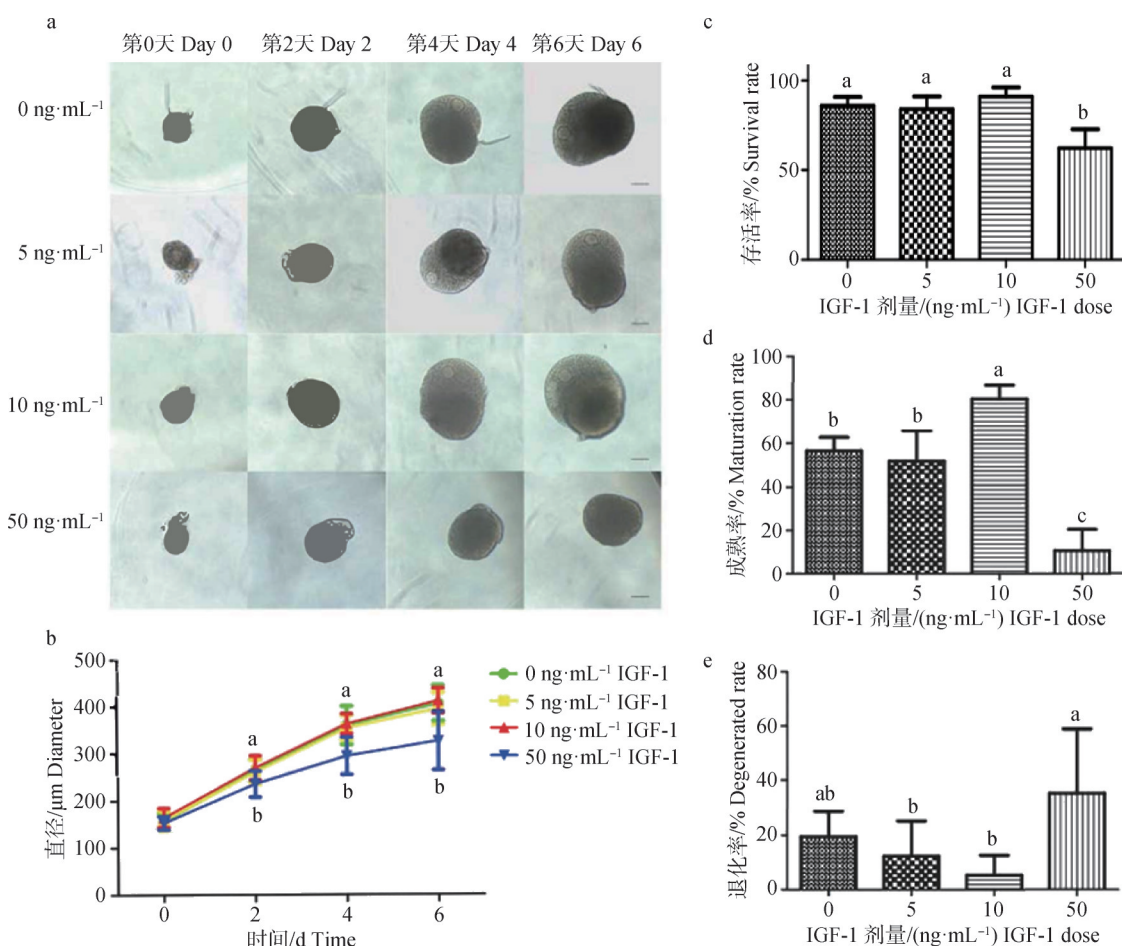
然而,也有研究认为IGF-1可能不是卵泡发育所必需的,例如Dor等^[48]1992年报道了一名患有侏儒型侏儒症(IGF-1缺乏二级到GH受体异常)的患者,其血清中及卵泡液中IGF-1的含量非常低,但该

患者发育出了正常的卵泡,经过和正常排卵的排卵诱导以后采出了成熟的、可受精的卵子。因此,作者提出IGF-1可能不是卵泡发育所必需的,而可能是FSH的一种调节因子。

3.3 抑制颗粒细胞凋亡

IGF-1 可以通过翻译后修饰来调节 Bcl-2 相互作用髓细胞白血病样蛋白(Bcl-2 interacting mediator of cell death, extra-long isoform, BimEL)的降解,防止猪原代颗粒细胞凋亡。首先,IGF-1 通过激活细胞外信号调节激酶 1 和 2 (extracellular signal-regulated kinase 1 and 2, ERK1/2) 通路诱导 BimEL

磷酸化。然后,磷酸化的 BimEL 通过泛素-蛋白酶体和自噬-溶酶体途径降解^[49]。有研究表明,IGF-1 通过激活 ERK1/2 通路,促进猪颗粒细胞中 BimEL Ser65 位氨基酸残基的磷酸化进而诱导 BimEL 蛋白的降解,从而保护颗粒细胞免受凋亡^[50];在水牛颗粒细胞中添加 IGF-1 同样可以促进颗粒细胞增殖,抑制颗粒细胞凋亡^[51]。



a. 不同浓度 IGF-1 (0~50 ng·mL⁻¹) 处理卵泡第 0、2、4、6 天的代表图像, 标尺 100 μm。b. 从第 0 天到第六天卵泡发育的直径变化。c. 培养第六天卵泡存活率。d~e. IGF-1 处理 6 天的卵泡体外成熟后产生卵母细胞的成熟率(d)和退化率(e)。不同字母之间代表显著性差异 ($P < 0.05$)。N=10 个卵泡, 5 次重复

a. Representative images of follicles treated with different concentrations of IGF-1 (0-50 ng·mL⁻¹) on days 0, 2, 4, and 6. Scale bar=100 μm. b. Changes in follicular diameter from day 0 to day 6 of development. c. Follicular survival rate on day 6 of culture. d-e. Maturation rate (d) and degeneration rate (e) of oocytes derived from follicles treated with IGF-1 for 6 days after in vitro maturation. Different letters indicate significant differences ($P < 0.05$). N=10 follicles with 5 replicates

图 3 不同浓度的 IGF-1 对三维培养的卵泡发育的影响^[47]

Fig. 3 Effects of different concentrations of IGF-1 on the development of three-dimensional cultured follicles^[47]

3.4 维持雌性哺乳动物正常繁殖力

在哺乳动物卵泡生长和成熟过程中, IGF-1 能促进颗粒细胞增殖、分化和类固醇激素合成^[52]。成年母畜的繁殖性能与血液中 IGF-1 水平密切相关。

例如, 产仔时体重较轻和泌乳期间体重损失较大的初产母猪在断奶前后, 血液中 IGF-1 水平明显低于对照组, 繁殖障碍发生率明显升高^[53]; 母牛在产后两周内, 排卵组血液中 IGF-1 水平比未排卵组高

40%~50%^[54]; 体况评分高的母马血清中 IGF-1 含量明显高于体况差的马, 前者繁殖力明显高于后者^[55]。正常雌性动物注射一定量的生长激素(诱导内源性 IGF-1 释放)或 IGF-1 能提高排卵率或早期胚胎质量。例如, 给青年母猪注射外源生长激素后排卵数明显增加^[56]; 在超排过程中母羊^[57]或母牛^[58]注射外源生长激素能提高囊胚率和胚胎移植受胎率; 小鼠^[59]和大鼠^[60]用外源生长激素处理后排卵数明显增加。同时有研究表明, 注射(20 $\mu\text{g}\cdot\text{d}^{-1}$) IGF-1 可提高母兔的窝产子数^[61]; 与注射 0.1 mL 生理盐水的对照组相比, 注射妊娠杂交母马血清来源 IGF-1 的母鼠平均窝仔数更多, 且呈剂量依赖性: (10 $\text{ng}\cdot\text{mL}^{-1}$) 组为 5.40 ± 1.67 只; (20 $\text{ng}\cdot\text{mL}^{-1}$) 组增至 7.40 ± 1.95 只; (40 $\text{ng}\cdot\text{mL}^{-1}$) 组达 8.40 ± 2.97 只^[62]。以上研究表明, IGF-1 不仅能显著提升雌性哺乳动物的繁殖力(如增加排卵数、窝仔数), 且对维持正常繁殖功能具有关键调控作用。

4 总结与展望

综上所述, IGF-1 通过调控卵泡的优势化选择、促进卵泡生长发育、提高促排卵的卵子数量与质量、抑制颗粒细胞凋亡、在维持雌性哺乳动物正常繁殖力中发挥着关键作用, 如图 4 (IGF-1 对卵泡发育影响的汇总图) 所示。鉴于 IGF-1 在哺乳动物卵泡发育过程中的核心地位, 未来研究可重点关注以

下方向: 1) 研究 IGF-1 及其 IGF-1R 在卵泡不同发育阶段(原始→初级→窦卵泡)的表达动态, 结合单细胞转录组/蛋白组技术, 绘制颗粒细胞、卵母细胞及膜细胞中 IGF-1R 下游通路(如 PI3K/AKT *vs.* MAPK)的激活图谱; 2) 验证 IGF-1 是否作为卵母细胞分泌因子的关键介质, 通过缝隙连接调控颗粒细胞的增殖与分化, 并利用卵母细胞特异性 IGF-1 基因敲除模型验证其必要性; 3) 比较 IGF-1 在单胎(人/牛)与多胎(猪/鼠)物种卵泡发育中的剂量效应差异, 挖掘关键响应元件(如启动子区 STAT5 结合位点)的种属特异性。深入探索 IGF-1 在卵泡发育过程中的作用机制, 其在畜牧生产和辅助生殖技术领域的巨大应用潜力值得高度关注。

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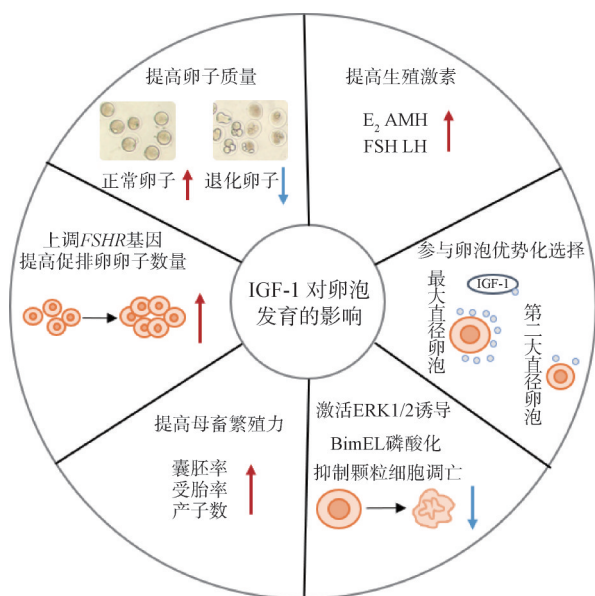


图4 IGF-1对卵泡发育的影响汇总图

Fig. 4 Summary diagram of the effect of IGF-1 on follicular development

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