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哺乳动物卵泡卵母细胞发育的调控机制研究

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摘要 卵巢卵泡是维持雌性哺乳动物生殖功能的核心结构, 其围绕卵母细胞的形成、发育及成熟展开的一系列过程, 从胚胎期开始, 贯穿性成熟直至衰老, 机制复杂且精密. 在发育过程中, 卵泡经历了多次选择、阻滞与激活等阶段, 这些过程确保了雌性个体能够排出质量最优的卵母细胞以繁衍后代. 在胚胎期, 伴随着卵母细胞的减数分裂阻滞及数量调控, 卵巢内形成了原始卵泡库, 作为有限的生殖储备. 此后, 大部分卵泡处于休眠状态, 并在生命周期内逐步被激活和生长, 以平衡生育质量与生殖能力的持续时间. 激活后, 卵泡内的卵母细胞快速生长, 并在内分泌与旁分泌信号的调控下, 经历周期性的阻滞与激活, 最终发育为具备受精能力的成熟卵母细胞. 本文对卵泡及其核心细胞——卵母细胞发育的最新研究进展进行了简要综述, 为深入理解其生物学机制和潜在应用提供了参考.

关键词 雌性生殖, 卵巢发育, 卵泡, 卵母细胞, 生殖调控

生殖是生命延续的基础, 哺乳动物繁殖则有赖于通过产生特化的雌雄配子的有性生殖. 在有性生殖的角色上, 两性功能上的差异使得配子发生和发育的方式产生了极大的不同: 雄性睾丸持续生成大量甚至在生命周期内数量无限的精子以应对生殖竞争, 从而使其在未知的生殖竞争占据优势的短暂时间段中繁育更多的后代. 雌性则在胚胎期生成有限且不可再生的卵母细胞, 随后通过与体细胞的结合形成精密的功能复合体卵泡, 供给其终生的生殖活动[1~3]; 而这种极为精巧的策略, 使得雌性哺乳动物个体在成年后无需在每个繁殖周期中都消耗大量的能量形成配子, 从而将有限的能量投入到交配成功后的后代繁育中.

由于卵母细胞在胚胎期形成, 如何在漫长的生育寿命中保持卵母细胞的健康成为哺乳动物雌性面临的重要挑战. 在包括哺乳动物的高等生命中, 卵母细胞普遍需要与周围的体细胞互做形成紧密且协同发育的功能复合体, 而此类结构被称为卵泡(follicle). 以卵泡为单位, 卵母细胞的形成、发育及成熟在不同生命阶段展现出特定的周期性发育特征, 并贯穿整个生命周期. 具体而言, 包括胚胎期卵泡储备的建立、出生后卵泡的募集和激活, 以及发情周期或月经周期中的生长和最终排卵[4]. 同时, 伴随着增龄所导致的卵泡消耗, 女性在中年期进入生殖衰老并最终失去生育能力[5].

尽管卵泡和卵母细胞的在体发育直接决定了雌性生殖的质量和寿命, 但由于卵泡发育周期长, 体内动态变化复杂, 对其发育规律及机制, 特别是早期发育规律一直以来仍存在较多空白. 但是, 鉴于现代社会生育习惯的改变, 以及日益加剧的不孕不育问题, 对卵泡在体发育、消耗和耗竭规律的认知显得极为迫切. 近年来, 基因修饰模型、高分辨率成像及组学技术极大推动了对相关研究, 本文则综述了卵巢卵泡发生研究的新进展, 聚焦于卵泡卵母细胞选择、阻滞与激活三者的平衡.

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1 胚胎期原始卵泡的建立和卵母细胞选择与阻滞

雌性卵巢的形成始于原始生殖细胞向卵原细胞的转化, 这些卵原细胞随后进入减数分裂成为卵母细胞. 此过程标志着雌性配子发育路径的开始. 随后, 雌性生殖细胞经历减数分裂阻滞与卵母细胞的选择, 大约三分之二的卵母细胞被淘汰, 剩余卵母细胞构成个体一生的卵巢储备. 这一过程中, 减数分裂阻滞和卵母细胞选择的有序发生, 直接决定了性成熟后卵母细胞的数量和质量[6].

1.1 原始卵泡形成中的卵母细胞选择

通过牺牲一些卵母细胞来选择最佳的生殖细胞, 以形成可受精卵子是有性繁殖物种中普遍存在的过程, 从线虫到哺乳动物都遵循这一规律. 在哺乳动物中, 大约三分之二的卵母细胞在胚胎期被淘汰, 仅少数存活[7,8]. 在果蝇中, 最终存活的卵母细胞只有16个生殖细胞中的1个. 研究表明, 卵母细胞选择不仅是简单的存活或死亡过程, 还涉及受损卵母细胞向存活卵母细胞转移细胞器和细胞质, 这种“选择与滋养”机制确保并增强了存活卵母细胞的初始质量.

在果蝇中, 生殖细胞合胞体的形成是卵母细胞选择的关键结构基础. 一个生殖细胞分裂形成16个细胞的合胞体, 其中一个被指定为卵母细胞, 其余15个成为滋养细胞. 这一选择依赖于细胞间桥的连接和物质转移[9]. 近期研究发现, Patronin/CAMSAP蛋白通过调控非中心体微管网络的形成, 在决定果蝇卵母细胞命运中发挥重要作用[10]. 滋养细胞在生成piRNA、促进卵母细胞极性形成和发育方面也起关键作用[9,11,12]. 破坏生殖细胞合胞体结构或功能会导致雌性果蝇不育[9].

在哺乳动物中, 早期的卵母细胞选择机制尚不完全明确. 目前, 基于对小鼠胎儿卵巢中卵母细胞选择过程追踪的研究表明: 最初的较大生殖细胞合胞体会碎裂成更小的合胞体, 每个合胞体选择一个卵母细胞存活, 而其他细胞成为滋养细胞, 并最终死亡[8,13,14]. 最近, 通过单细胞RNA测序解析了合胞体分解和卵母细胞选择过程中的分子机制[15]. 该研究显示, 在胎儿卵巢结构刚形成、性细胞进入减数分裂时, 滋养细胞和卵母细胞的基因表达已开始出现差异. 胚胎14.5天(14.5 days postcoitum, 14.5 dpc)至出生后第1天(postpartum day 1, PD1)的滋养细胞mRNA含量较其他卵母细胞低. 该研究表明, 与卵母细胞存活相关的转录因子*Nobox*, 早在18.5 dpc时就特异性地在合胞体内某个卵母细胞中表达. 此外, *Follistatin*在滋养细胞中上调, 而表达于细胞间桥的基因*Tex14*在滋养细胞中下调, 并在卵母细胞选择过程中发挥作用[15]. 除了近期利用组学技术的研究, 早期的研究也通过体外小鼠胚胎卵巢培养系统, 发现了多个参与生殖细胞合胞体破裂和卵母细胞选择的调节因子, 例如组蛋白去甲基化酶1(lysine-specific demethylase 1, LSD1)[16]和糖原合成激酶3β[17]参与调控卵母细胞的命运选择, JNK信号通路[18]、ADAM10-Notch信号通路[19], 以及间隙连接蛋白(gap junction)[20]等通过调控体细胞与卵母细胞互作影响合胞体的破裂进程. 值得注意的是, 所有这些研究均表明, 干扰正常的合胞体破裂和卵母细胞选择会导致卵巢储备的构建失败, 凸显了早期选择在雌性繁殖中的不可或缺性.

尽管不同物种的卵母细胞选择过程具有保守性, 哺乳动物的机制则表现出一些特异性. 例如, 哺乳动物原始生殖细胞向性腺迁移的时间并不同步, 导致不同区域的生殖细胞进入减数分裂的时序不一致[8]. 此外, 哺乳动物卵母细胞存活率高于果蝇, 以及*Tex14*敲除小鼠仍具有生育能力等现象表明细胞间桥在哺乳动物中的作用可能不如果蝇重要[21,22]. 因此, 哺乳动物可能进化出其他机制, 以适应其更长的生殖寿命, 提高卵母细胞质量.

1.2 卵母细胞减数分裂的启动与阻滞

在哺乳动物性别分化中, 生殖细胞在胎儿卵巢中进入减数分裂是关键步骤. 原始生殖细胞迁移至性腺后, 通过几轮有丝分裂增加数量[23]. 雌性生殖细胞进入减数分裂后成为不可再生资源, 这与雄性生殖细胞保持有丝分裂状态的特性不同[24]. 减数分裂的启动对卵巢发育至关重要, 为后续阻滞、休眠和激活奠定基础, 这也决定了雌性生殖寿命[25].

视黄酸(retinoic acid, RA)由肾脏和卵巢产生, 是减数分裂启动的主要调控因子[26]. 大约在胚胎期12.5天, RA在性腺中形成浓度梯度, 刺激减数分裂启动所必需基因*Stra8*的表达[27]. 这一过程沿卵巢轴形成自前至后的减数分裂启动波[28]. 有趣的是, 近期的三维成像研究揭示了这一模式之前还存在一个额外的径向波. 细胞间桥在这一阶段协调生殖细胞从多能状态向减数分裂状态的过渡, 确保了启动的有序性[29]. 减数分裂的启动受到胞质分裂蛋白调控因子(protein regulator of cyto-

kinesis 1, PRC1)等表观遗传因子的严格调控. PRC1通过沉默*Stra8*等关键基因防止RA提前诱导减数分裂, RA信号达到阈值后PRC1抑制解除, 减数分裂启动[30,31]. 此外, 广泛的表观遗传修饰(如DNA甲基化和组蛋白修饰)也在此阶段发生, 从而调控染色质状态和基因表达, 确保卵母细胞减数分裂启动的正常进程和同步性[32]. 虽然RA是减数分裂启动的关键因子, 但其并非唯一调控路径. 研究发现, 即使在缺乏RA受体的情况下, 减数分裂仍能进行, 提示存在其他路径[33]. 例如, 骨形态发生蛋白信号通路(bone morphogenetic proteins, BMP)信号通路通过锌指蛋白(zinc finger GATA-like protein 1, ZGLP1)促进减数分裂基因激活[34,35]. 此外, MEIOSIN, Retinoblastoma等蛋白质在减数分裂启动中也发挥着重要作用[36,37]. 这些信号的协同作用确保了减数分裂的精确调控.

进入减数分裂后, 卵母细胞在减数第一次分裂中期的核网期(dictyotene stage)阻滞, 直到排卵前恢复并继续完成减数分裂[38]. 这一长时间的阻滞由高水平的环磷酸腺苷(cAMP)维持, 具体机制为GPR3-ADCY信号通路负责产生和维持这些高水平的cAMP, 从而激活蛋白激酶A(protein kinase A, PKA)抑制成熟因子(maturation promoting factor, MPF)的活性, 确保卵母细胞在减数第一次分裂中保持阻滞状态[39]. 此外, 卵母细胞邻近的颗粒细胞通过C型(NPPC)/钠肽受体2(NPR2)信号系统产生的环鸟苷酸(cGMP)抑制cAMP的水解, 从而维持卵母细胞减数分裂的阻滞状态[40,41]. 尽管大量关于减数分裂阻滞的研究集中在卵母细胞成熟的最后阶段, 但调控早期减数分裂阻滞的机制仍然不甚明了. 对围产期小鼠的研究表明, cAMP水平的升高也参与调控早期减数分裂的进程[42].

此外, 在阻滞期间卵母细胞维持低水平的DNA甲基化, 直至恢复减数分裂, 卵母细胞中的组蛋白修饰和DNA甲基化发生上调. 这个延长的阻滞过程对于维持卵母细胞在整个雌性生殖寿命中的休眠状态至关重要, 但它也给卵母细胞质量的维持带来了挑战[43]. 因此, 继续深入研究长期减数分裂阻滞的机制是理解雌性生殖过程中独特生物学过程的关键.

2 生育旺盛期卵母细胞在原始卵泡中的休眠与激活平衡

在卵母细胞选择后, 存活下来的卵母细胞仍处于一个未成熟的发育状态. 在这个阶段, 这些卵母细胞的大小和关键细胞器仅占成熟卵细胞的约百分之一, 并且它们的线粒体数量仅为成熟卵子的万分之一. 此外, 这些处在减数第一次分裂阻滞的卵母细胞表现出低水平的转录和翻译活性水平, 表明它们处于休眠状态. 值得注意的是, 仅依靠卵母细胞本身来维持这种休眠状态是一个相当大的挑战.

2.1 卵母细胞休眠的进入与原始卵泡形成

在卵巢胚胎发育过程中, 卵母细胞在减数第一次分裂阻滞, 并开始与前颗粒细胞相互作用, 启动原始卵泡的形成[44,45]. 这一过程建立了原始卵泡库, 作为终生且不可再生的生殖储备. 原始卵泡形成的时间在不同物种之间差异显著. 在小鼠中, 这一过程大约从胚胎第17.5天(17.5 dpc)开始, 并持续至出生后第3~5天(PD3~5), 此时原始卵泡库完全建立[46,47]. 恒河猴的原始卵泡的形成始于胚胎第90天, 并在出生后两周内完成[48]. 相比之下, 人类原始卵泡的形成早在妊娠16周时就开始了, 并于妊娠26周时建立完成[49,50]. 然而, 关于原始卵泡库完全建立的确切时间仍然存在争议.

在结构上, 原始卵泡由一个休眠的卵母细胞和一层扁平的前颗粒细胞围绕组成, 保护它们免受周围卵巢微环境的影响, 这对于维持卵母细胞的休眠至关重要. 原始卵泡的形成由一系列复杂的信号通路调控, 包括WNT, NOTCH, KIT和JNK信号通路等, 以及其他分子因素[6,47,51,52]. 其中, 一些特异性表达于卵母细胞或颗粒细胞的转录因子被证明在原始卵泡形成的调控中发挥着关键作用. 近年来, 组学技术的进展使得转录组学和表观遗传学可以深入揭示这一关键发育过程中的分子机制[53]. 例如转录因子*Figla*, *Lhx8*和*Sohlh1*不仅互相调节, 而且共同形成卵母细胞内的核复合物, 协调原始卵泡的组装[54]. 此外, 鼠类卵母细胞的顺式调控组图谱还识别了其他关键转录因子, 如*Tcf3*/*12*, 这些因子与顺式调控元件相互作用, 并在原始卵泡形成的调控中起着重要作用[55](表1).

卵母细胞在原始卵泡中的休眠持续时间在不同物种之间差异极大. 在小鼠中, 卵母细胞的休眠期可以持续一年以上; 而在人类中, 这一休眠期最长可达到50年以上. 研究表明, 卵母细胞在如此长时间内维持休眠状态与其蛋白质稳定性和稳态密切相关. 卵母细胞通过将蛋白质聚集物隔离在内溶酶体小泡中, 并抑制线粒体复合物I的活性, 从而保持无ROS胁迫的环境[72,73]. 近期的研究进一步阐明, 卵母细胞中蛋白质极端的寿

表 1 转录因子调控原始卵泡形成的作用机制

Table 1 Transcription factors involved in primordial follicle formation.

基因	表达细胞	小鼠突变体表型[a)]	参考文献
Figla	卵母细胞	PF形成缺陷及卵母细胞丢失	[56]
Nobox	卵母细胞	PF形成延迟及卵母细胞丢失	[57]
Lhx8	卵母细胞	卵母细胞丢失	[58,59]
Sohlh1	卵母细胞	PF数量降低及卵母细胞丢失	[60,61]
Id1/2	卵母细胞	PF形成延迟及卵母细胞丢失	[62]
Tcf3/12	卵母细胞	卵母细胞丢失	[55]
Foxl2	颗粒细胞	PF形成缺陷及卵母细胞丢失	[63,64]
Taf4b	颗粒细胞	PF形成延迟及卵母细胞丢失	[65]
Hnrnpk	卵母细胞和颗粒细胞	PF形成缺陷及卵母细胞丢失	[66]
Ahr	卵母细胞和颗粒细胞	加速PF形成	[67,68]
SP1	卵母细胞和颗粒细胞	PF数量降低及卵母细胞丢失	[69]
Irx3/5	动态表达在卵母细胞和颗粒细胞	PF形成缺陷及卵母细胞丢失	[70,71]

a) PF, 原始卵泡(primordial follicle)

命是保持其功能完整性和长期休眠的关键因素[74]. 原始卵泡的休眠不仅有助于保持卵母细胞的质量, 还对维持女性在长期生殖寿命中的生育能力至关重要.

在早期发育过程中形成数量有限的原始卵泡库, 并在整个生殖生命周期内将其保持在休眠状态, 是哺乳动物生殖的一个基本策略. 这一策略最大程度地减少了成年后持续生产生殖细胞的需求, 从而节省了代谢能量. 然而, 这一策略也使得雌性动物的生殖寿命相对于其整体寿命较短, 可能作为一种进化机制, 用以确保后代的质量.

2.2 原始卵泡激活的分子调控

原始卵泡库是女性生殖储备的重要组成部分, 其有序激活决定了生育能力与生殖寿命的平衡. 卵母细胞从休眠状态转为生长阶段, 同时伴随前颗粒细胞的分化与增殖, 称为原始卵泡的激活或始动募集[4,5]. 原始卵泡激活时, 卵母细胞体积增加、转录增强, 前颗粒细胞由扁平状转为立方状并迅速增殖.

研究显示, 原始卵泡的激活由卵母细胞、前颗粒细胞和卵巢微环境的复杂相互作用调控. 其中, mTORC1(mammalian target of rapamycin 1)信号通路是前颗粒细胞激活的关键调控因子[75](图1(a)). 在休眠卵泡中, mTORC1受抑制; 激活信号触发其活性后, 前颗粒细胞分化、增殖并上调KITL(c-Kit Ligand)的表达. KITL与卵母细胞的KIT受体结合后, 激活卵母细胞中的PI3K(Phosphatidylinositol 3 Kinase)/AKT(Serine/Threonine Kinase B)信号通路[75]. 随后, AKT磷酸化并将FOXO3蛋白隔离于细胞质, 防止其入核启动细胞周期抑制因子p27Kip1, 从而恢复卵母细胞的生长[76]. 因此, 前颗粒细胞mTORC1-KITL-卵母细胞KIT-PI3K/AKT通路级联调控卵泡的激活, 该通路的异常会导致卵泡激活障碍. 例如, 敲除前颗粒细胞中mTORC1的关键组分*Rptor*, 或敲除卵母细胞中PI3K的激活因子*Pdk1*, 均会抑制卵泡激活, 导致卵巢功能衰退[77]. 相反, 敲除前颗粒细胞中mTORC1的负调节因子*Tsc1/2*, 或卵母细胞中的*Pten*, 均会引发原始卵泡的过早激活[78,79]. 在人类中, TSC/mTOR通路异常与早发性卵巢功能不全疾病相关[80]. 因此, mTORC1和PI3K/AKT通路的精确调控对于维持卵泡休眠与激活的平衡至关重要.

此外, 其他上游因子和信号通路也参与了卵泡激活. 原始卵泡休眠时位于卵巢皮质, 激活后迁移至髓质. 微环境因素如低氧和细胞外基质(extracellular matrix, ECM)介导的机械应力在其中发挥重要作用. 低氧条件下, 缺氧诱导因子(hypoxia inducible factor, HIFs)通过维持FOXO3的核定位, 保持卵泡的休眠[81]. ECM的消化可激活卵母细胞, 而高气压培养又能逆转这一现象, 恢复FOXO3核定位, 维持原始卵泡的休眠[82]. 同时, Hippo信号通路也受细胞环境的物理和机械特性调控, 并参与原始卵泡激活[83]. 临床研究利用卵巢碎片化结合AKT刺激破坏Hippo信号通路, 已被用于促进早发性卵巢功能不全(premature ovarian insufficiency, POI)患者的卵泡生长, 为不孕不育女性患者提供了一种潜在的治疗方案[84]. 这些发现表明, 机械应力可以调控卵母细胞的休眠状态, 但具体机制仍待深入研究.

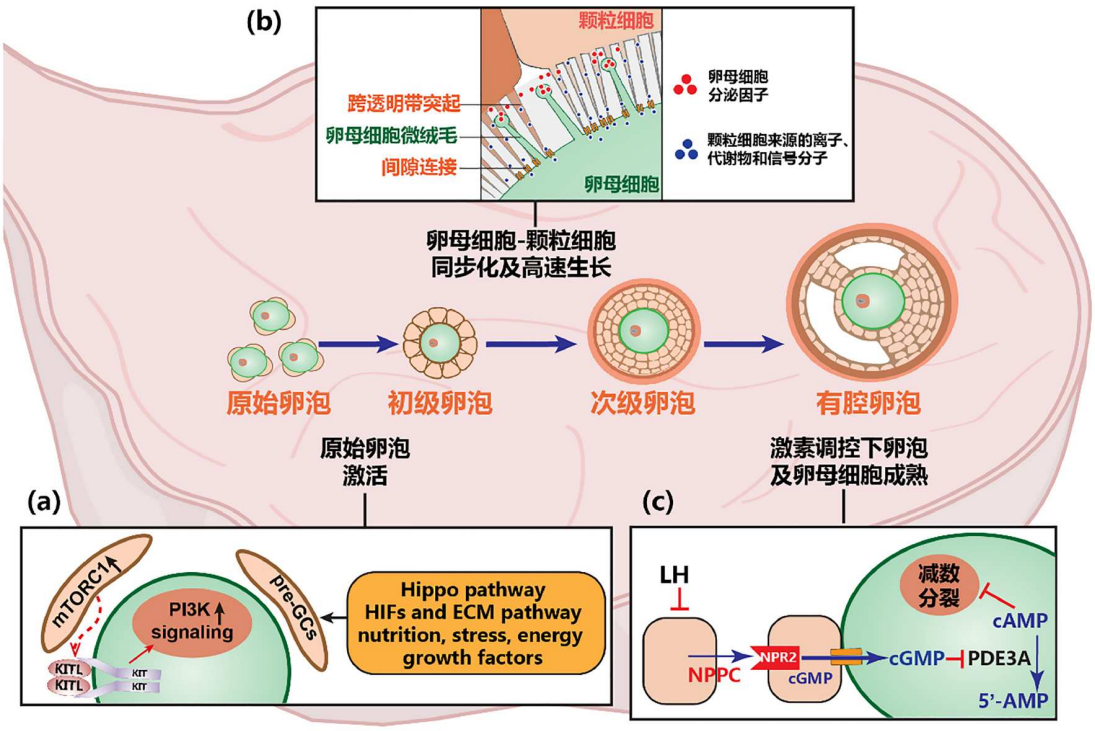

图 1 哺乳动物卵泡卵母细胞发育的调控机制. (a) 哺乳动物原始卵泡受到前颗粒细胞mTORC1-KITL-卵母细胞KIT-PI3K信号级联通路和其他微环境因素调控, 激活为初级卵泡. (b) 激活后的初级卵泡, 卵母细胞与颗粒细胞通过卵母细胞微绒毛与颗粒细胞的跨透明带突起结构建立互作通讯, 进行同步化发育和生长, 进入卵泡的高速生长阶段. 该阶段的颗粒细胞大量增殖和卵母细胞体积迅速增长, 卵泡发育到腔前卵泡阶段. (c) 随后卵泡进入激素依赖期, 周期募集的优势卵泡继而发育为有腔卵泡, 并在LH峰的作用下开始成熟. 壁颗粒细胞接收到LH峰信号后, 通过C型钠肽系统, 将信号逐步传递到卵母细胞中, 解除其对减数分裂阻滞的抑制作用. 卵母细胞完成第一次减数分裂到达核成熟, 并且从卵泡中排出贡献于生育

Figure 1 The mechanisms of mammalian follicular oocyte development. (a) In mammals, the activation of primordial follicles is regulated by the canonical mTORC1-KITL-KIT-PI3K/AKT pathway, along with other microenvironmental factors. (b) Once activated, the primary follicle establishes the communication between the oocyte and granulosa cells (GCs)through the Oo-mvi and TZPs. The oocyte and GCs of growing follicle synchronized development, initiating the rapid follicular growth phase. During this stage, GCs undergo extensive proliferation, and the volume of oocyte experiences a significant increase. (c) Subsequently, the follicles enter the hormone-dependent phase. After cyclic recruitment, an antral follicle progresses to undergoing maturation under the influence of the LH surge. The LH signal is received by mural granulosa cells, which transmit the signal to the oocyte through the NPPC-NPR2 system. This signaling cascade results in the resumption of meiosis I. The maturated oocyte is then released from the follicle, contributing to fertility

以上这些研究揭示了前颗粒细胞、卵母细胞与局部卵巢微环境之间复杂的调控相互作用, 这些相互作用共同控制着原始卵泡的激活. 理解原始卵泡在卵巢皮质中的空间分布和激活机制, 不仅为卵母细胞的发育和激活提供了新的视角, 而且对生殖生物学和医学均具有重要意义.

2.3 原始卵泡激活的异质性

原始卵泡库在围产期形成, 大多数进入休眠, 等待后续的激活招募以贡献生育能力, 然而也有一些卵母细胞在形成后立即被激活. 值得注意的是, 在哺乳动物中, 出生与性成熟之间存在较长的间隔, 这意味着这些新生期招募的卵母细胞和卵泡在青春期之前无法完全发育. 新生期和成年期卵泡之间的这种发育差异促成了"两波卵泡发育"概念的提出[85]. 即新生期卵巢髓质中的卵泡代表第一波, 而卵巢皮质中的原始卵泡形成第二波. 第一波卵泡在青春期前被激活, 支持早期生育能力; 第二波卵泡则在成年后逐步激活, 为生育提供长期支持[46,85].

最近十年的研究利用细胞谱系追踪等技术, 深入揭示了两波卵泡在起源、发育动力学和分子调控上的差异. Mork等人[46]和Niu等人[86]的研究表明, 卵泡激活的异质性与两波卵泡中前颗粒细胞的不同来源密切相关. 具体而言, 第一波卵泡的颗粒细胞由胚胎肾脏间充

质细胞分化而来, 这些卵泡在出生后迅速激活, 启动青春期并支持早期生育能力; 第二波卵泡的前颗粒细胞则来源于出生后卵巢的表皮细胞, 这些卵泡在原始卵泡库中休眠, 并在整个生育期中逐步激活[46]. 有研究通过内源性荧光报告小鼠标记卵母细胞和前颗粒细胞, 证明第一波卵泡在青春期启动时耗尽, 而第二波卵泡逐渐选择性激活, 维持雌性的生育寿命[87]. 因此, 第一波卵泡贡献于青春期的始动和早期生育能力, 而第二波则卵泡维持雌性哺乳动物的长期生殖功能.

最新研究进一步揭示了两波卵泡激活机制的差异. 通过追踪胎儿卵巢卵母细胞的发育, 发现胚胎期卵母细胞的不同步发育导致了两波卵泡的异质性[88]. 第一波卵泡来源于快速发育的胚胎生殖细胞, 这些细胞较早进入减数分裂, 并在出生后立即激活; 而第二波卵泡则与较慢发育的胚胎卵母细胞相关, 这些细胞在被前颗粒细胞包裹后进入休眠状态. 相关的机制研究表明, 第一波卵泡的激活主要依赖卵母细胞的内在信号, 而非外部信号通路(如KITL-KIT信号通路)[88]. 实验表明, 即使缺失关键分子KITL, 第一波卵泡仍能自发激活; 相比之下, 第二波卵泡的激活严格依赖于经典信号通路—前颗粒细胞mTORC1-KITL-卵母细胞KIT-PI3K级联反应[88].

尽管这些发现主要基于小鼠模型, 尚需进一步研究以探索这些机制在人类中的适用性. 了解人类卵巢中卵泡激活的异质性, 对于探究生育寿命、生殖衰老以及青春期始动时间的调控均具有重要意义.

3 卵泡和卵母细胞激活后的生长和成熟

3.1 卵泡生长: 生殖细胞与体细胞之间的相互调控

原始卵泡激活后, 会经历初级、次级和有腔卵泡等阶段发育, 最终获得排出成熟卵子的能力. 尽管卵泡激活由前颗粒细胞触发, 但后续发育则由卵母细胞主导[76]. 此阶段卵母细胞迅速增大, RNA和蛋白质合成增加, 其直径接近成熟卵母细胞大小[89,90]. 卵母细胞分泌的卵母细胞分泌因子(oocyte secreted factors, OSFs), 如GDF9, BMP15和RSPO2等, 引发周围体细胞的增殖与分化, 从而促进卵泡发育[91,92]. 这些信号通路的紊乱会导致生育能力下降和卵巢功能障碍, 进一步说明了卵母细胞在卵泡发育中的核心作用[93].

在卵母细胞的早期发育阶段, 其分泌透明带蛋白形成透明带, 这一结构在防止多精受精中至关重要[94]. 尽管透明带限制了卵母细胞与颗粒细胞的直接接触, 颗粒细胞通过跨透明带突起结构(translucent zone protrusion structure, TZPs)与卵母细胞膜相连[95]. TZPs通过间隙连接蛋白, 如CX37和CX43, 使得卵母细胞与颗粒细胞之间的离子、代谢物和信号分子发生交换[96]. CX37和CX43在支持卵母细胞发育中具有互补作用. 研究表明, 缺失CX37会导致卵母细胞发育障碍, 而回补CX43可部分恢复细胞间沟通和生育能力[97,98].

尽管TZPs和间隙连接的研究已有深入进展, 但卵母细胞如何调控这些细胞间通信仍未完全清楚. 最近研究发现了一种特殊的卵母细胞表面结构, 称为卵母细胞微绒毛(Oo-Mvi), 它在卵母细胞分泌OSFs有序释放中发挥重要作用[99]. Oo-Mvi呈蘑菇状, 由基部茎和顶端小泡组成, 顶端小泡周期性破裂释放OSFs, 这种方式可确保颗粒细胞高效接收OSFs以激活下游信号通路, 促进颗粒细胞增殖及卵泡生长[99](图1(b)). Oo-Mvi的形成依赖于卵母细胞中RADIXIN蛋白的高表达, *Radixin*缺失会阻碍Oo-Mvi形成, 导致卵泡发育异常和生殖功能障碍[99].

因此, 卵母细胞在透明带形成后通过Oo-Mvi调控OSFs释放, 而颗粒细胞则通过TZPs与卵母细胞建立连接. 这一通信网络的协调对卵泡的同步发育至关重要[99,100]. 任何环节的异常, 包括OSFs, TZPs、间隙连接或Oo-Mvi, 都会导致卵泡发育障碍和生育问题.

3.2 卵母细胞成熟: 内分泌与旁分泌的协同作用

在卵母细胞激活和生长后, 卵母细胞成熟是卵母细胞获得成功受精和早期胚胎发育能力的关键最后一步[101]. 这一复杂过程包括核成熟和细胞质成熟两个方面.

核成熟的关键是第一次减数分裂阻滞的恢复, 该过程受到促黄体生成素(LH)激增的调控[102]. LH通过信号级联反应引发颗粒细胞内cGMP水平下降, 进而导致卵母细胞内cAMP水平降低, 激活促进减数分裂的相关因子, 推动核成熟[103,104]. 同时, LH还刺激颗粒细胞分泌表皮生长因子(epidermal growth factor, EGF)样因子, 这些因子通过激活EGFR通路进一步支持减数分裂恢复[105,106]. 组蛋白去乙酰化酶3(histone deacetylase 3, HDAC3)在LH激增后通过调控EGF样因子(如双调蛋白Amphiregulin, AREG)的表达, 对减数分裂恢复起关键作用[107]. 此外, 卵泡中的壁颗粒细胞分泌C-型利钠肽, 并通过卵丘颗粒细胞上的受体NPR2产生cGMP, 抑制

cAMP-磷酸二脂酶PDE3A的活性，从而阻止卵母细胞内cAMP的水解，维持卵母细胞的减数分裂阻滞．只有当LH峰出现时下调C-型钠肽的分泌，才能解除其对卵母细胞减数分裂阻滞的抑制，进而引起卵母细胞的核成熟和排卵(图1(c))．进一步的研究结果证实，C-型钠肽及其受体NPR2缺失将导致卵泡中卵母细胞的提前成熟[41]．此外，一系列翻译后修饰，包括泛素化[108]、SUMO(small ubiquitin-like modifier)化[109]、乙酰化[110]和糖基化[111]，均在减数分裂成熟的精细调控中起重要作用.

与核成熟相比，尽管细胞质成熟的研究相对较少，但其对调控后续胚胎发育母源因子的积累过程起着重要的作用. 研究表明, 成熟卵母细胞中富含母源mRNA, 这些mRNA在早期胚胎细胞分化和组织形成中起重要作用[112,113]．母源mRNA在线粒体相关的核糖核蛋白复合物结构域内储存, 并受特定调控因子如LSM14B的严格控制[114,115]．此外，细胞皮层下母源因子复合物(the subcortical maternal complex, SCMC)的发现进一步揭示了细胞质成熟的复杂性, SCMC对早期胚胎发育至关重要[116]．任何单一SCMC组件的缺失通常会导致卵母细胞和胚胎发育异常，进而影响雌性生育能力[117,118]．研究表明，SCMC组件还与母源效应基因(如*Zar1*和*Zar2*)协同作用，促进减数分裂成熟和细胞质成熟的过程[119]．

总之，卵母细胞的成熟是受到核成熟与质成熟的精细调控，其中每个环节在确保卵母细胞的活力和发育潜力方面发挥着至关重要的作用．深入理解这些过程不仅有助于揭示基本的生物学现象，还为临床干预改善人类生殖健康带来了新的希望.

4 结论与展望

在哺乳动物中，卵母细胞的选择和激活是维持生育能力的基本过程．有限的卵母细胞在胎儿发育过程中被选择, 并随之进入休眠状态, 直到整个生殖期内逐渐被募集激活．这些过程通过复杂的分子和细胞机制被精细调控, 涉及卵母细胞与周围体细胞, 尤其是颗粒细胞之间的相互作用．这些过程不仅决定了可供受精的卵母细胞的质量和数量, 还影响女性的生殖衰老[120]．

尽管生殖是生命中最基本和最本能的功能之一，现代社会却面临日益增加的生育挑战．全球不孕症的发生率不断上升，与此同时，卵巢疾病(如POI和多囊卵巢综合征(polycystic ovarian syndrome, PCOS))的发病率也显著增加, 加之晚育趋势, 使得生育健康与自然生殖能力之间的矛盾日益突出[121,122]．深入理解这些调控机制对于解决现代社会日益增加的不孕症和卵巢相关疾病的挑战同样重要[123,124]．

从卵巢生物学的角度，开发延缓卵巢储备耗竭和防止休眠卵泡过早激活的策略或许能够延长生殖寿命, 并降低与年龄相关的生殖疾病风险．基于前体颗粒细胞mTORC1-KITL-卵母细胞KIT-PI3K/AKT信号通路等卵泡激活机制的研究已经带来了创新性的生育治疗技术，如“体外激活(*in vitro* activation of primordial follicles, IVA)”，它为POI患者或缺乏生长卵泡的女性提供了潜在治疗方案[125,126]．然而，IVA技术仍存在低成功率和侵入性手术操作的限制[127]．未来需要提高技术效率并开发更少侵入性的替代方法，以更好应对卵巢储备耗竭相关的生育挑战. 此外, 卵母细胞和胚胎冷冻保存已被广泛应用，但它们仍需要侵入性操作，且这类方法无法保护卵巢的长期功能[124,128]．相比之下，通过非侵入方式来调控卵母细胞激活保护卵巢储备，为延长生育寿命和降低卵巢功能障碍提供了新方向[129]．因此，开发新方法来调节卵母细胞休眠并防止卵泡过早激活，对于延长女性生育力和提高治疗效果具有关键意义.

未来研究应关注以下几个关键领域. 首先, 应探索调控卵母细胞选择和有序激活的分子和细胞的机制. 了解这些过程如何在不同发育阶段及器官水平上进行协调，将为卵巢储备的维持和整体女性生育力提供重要见解. 其次, 需要深入研究卵泡细胞与周围体细胞的通信机制，尤其是调控长期卵母细胞储存和质量的分子通路[129]．此外，卵母细胞通常会长时间处于休眠状态，理解控制休眠的机制以及为何有些卵母细胞在这一阶段死亡至关重要．发现卵母细胞死亡调控通路并开发防止其发生的策略，将是延长生育寿命和延缓卵巢衰老的关键. 新技术的应用, 如高分辨率成像、多层组学和体内细胞命运追踪，将为解析卵泡发育的时间和空间动态提供支持，从而为卵巢储备如何有序调动和发育提供全面理解．而将生殖医学与生物工程进行交叉融合，如利用3D培养技术和卵巢类器官结合微流控芯片技术，构建更接近自然生理状态卵巢卵泡发育的体外研究平台，将为深入探究卵泡发育和成熟新机制以及开发生育力保存和个性化治疗新方法带来了机遇．最后，将这些研究成果转化为临床应用，对提高女性生殖健康非常关键．临床医师与研究人员的协作将

推动不孕症、卵巢疾病和生殖衰老相关治疗的进步.

总之, 尽管在卵母细胞选择和激活机制的研究方面取得了显著进展, 但仍有许多领域亟待探索. 通过调节卵母细胞休眠与激活的靶向疗法, 以及开发新型生育保护技术, 有望延长女性生殖健康寿命, 改善与年龄或卵巢疾病相关的生育治疗效果.

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Summary for “哺乳动物卵泡卵母细胞发育的调控机制研究”

Mechanisms of ovarian follicle and oocyte development in mammal

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Ovarian follicles are the essential structures that maintain female mammalian reproduction. Their development is a highly intricate and dynamic process that spans from the embryonic stage through to old age. Throughout their development, follicles undergo multiple stages of selection, arrest, and activation, which ensure that only the healthiest oocytes are ovulated for successful reproduction. This complex process plays a pivotal role in maintaining the reproductive potential of female mammals. During the embryonic stage, the formation of the primordial follicle pool occurs alongside the initiation and arrest of oocyte meiosis, a process critical for determining the oocyte quantity that will serve as a finite reproductive reserve throughout the female’s lifespan. Following this initial establishment, the majority of follicles enter a dormant state, forming a quiescent pool of primordial follicles. Over the course of the lifespan, these follicles are gradually recruited and activated in a highly regulated manner, maintaining a balance between reproductive quality and the length of reproductive capability. Once activated, the oocytes within follicles grow rapidly. This growth involves significant metabolic and structural changes, such as cytoplasmic and organelle enrichment, which are crucial for the development of a fully competent oocyte capable of fertilization. These processes are tightly controlled by endocrine and paracrine signaling pathways, which regulate the periodic cycles of arrest and activation, ultimately culminating in the development of fertilizable oocytes. The proper regulation of these developmental processes is essential for female fertility. Disruptions in any stage of follicular development, whether during primordial follicle formation, dormancy, activation, or oocyte growth —can result in infertility or reproductive disorders. Over the past two decades, substantial progress has been made in understanding the molecular and cellular mechanisms underlying follicle and oocyte development. Advances in genetically modified animal models, high-resolution imaging techniques, and multi-omics technologies have provided valuable insights into these mechanisms. These studies have elucidated key pathways involved in follicle activation, oocyte maturation, and the intricate interplay of signals that regulate these processes. This review aims to summarize the latest research findings on ovarian follicle development, with a specific focus on the developmental stages of the oocyte and the regulatory mechanisms governing follicle activation. By exploring these advances, we highlight the critical role of oocyte quality and follicular dynamics in maintaining female reproductive health and provide a foundation for understanding disorders related to female infertility. Moreover, the insights gained from these studies have the potential to inform therapeutic strategies for addressing infertility and age-related reproductive decline in females. In conclusion, the development of ovarian follicles is a lifelong process that ensures the continuity of female reproduction. It involves multiple intricate and highly regulated steps, from the establishment of the primordial follicle pool during embryogenesis to the periodic recruitment and activation of dormant follicles. As our understanding of these processes continues to deepen, further research will undoubtedly contribute to improving reproductive health and developing novel approaches to combat infertility.

female reproduction, ovarian development, follicle, oocyte, reproductive regulation

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