

· 综述 ·

17 β -HSDs 的种类和功能概述及其在贝类中的研究进展

曾臻^{1,2,3}, 余美舜¹, 谭强来^{1,2*}, 史博^{3,4},
李建波¹, 李伟杰¹, 蔡广¹

(1. 厦门医学院, 海洋生物医药资源福建省高校工程研究中心, 福建 厦门 361023;

2. 厦门医学院, 天然化妆品福建省高校工程研究中心, 福建 厦门 361023;

3. 厦门大学, 近海海洋环境科学国家重点实验室, 福建 厦门 361102;

4. 集美大学水产学院, 福建 厦门 361021)

摘要: 为深入解析 17 β -HSDs (17 β -羟基类固醇脱氢酶) 对贝类性腺发育和生殖内分泌的调控机制, 本文综述了 17 β -HSDs 的种类和功能, 对迄今已报道的所有亚型进行了分类归纳, 并对贝类等水产动物中 17 β -HSDs 的克隆表达、功能阐述、机制推测进行了调研总结。目前, 虽然 17 β -HSDs 调控贝类生殖过程研究已取得一定的进展, 但仍有很多重要的科学问题尚待解答, 需要重点加强“发现贝类中 17 β -HSDs 新亚型、分析时空表达特征、解析构效关系、明晰环境污染物影响、制定相应对策、指导产业实践应用”等方面的研究。本综述结合了其他物种的成熟研究和最新成果, 为深入探究 17 β -HSDs 调控贝类性腺发育和生殖内分泌的机理及应用提供了借鉴。

关键词: 贝类; 17 β -羟基类固醇脱氢酶 (17 β -HSDs); 性类固醇激素; 生殖

中图分类号: S 917.4

文献标志码: A

17 β -HSDs (17 β -hydroxysteroid dehydrogenase, 17 β -羟基类固醇脱氢酶) 是一类催化性类固醇激素合成时最后步骤的氧化还原酶, 因其作用于第 17 位碳而得名^[1]。17 β -HSDs 依赖 NAD(P)H/NAD(P)⁺ 将 C17 醇氧化为无活性或活性较低的酮, 或将 C17 酮还原为有活性的类固醇, 从而实现性类固醇激素活性高低的调节, 如雌二醇与雌酮、去氢表雄酮与雄烯二醇、双氢睾酮与 3 α -雄烷二醇、睾酮与雄烯二酮等之间的相互转化, 对于维持生物体内性类固醇激素合成与代谢发挥着重要作用^[2-3]。17 β -HSDs 广泛分布于各种生物体及其组织中, 迄

今已发现 15 种亚型并按最初被识别的顺序进行编号^[4]。根据催化结构及功能可分两类: 一类属于醛酮还原酶 (AKR) 超家族, 仅包含 17 β -HSD5 这 1 种亚型; 一类属于短链脱氢酶/还原酶 (SDR) 超家族, 包含其余 14 种亚型^[5]。

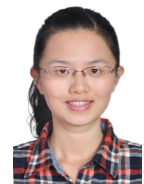
性类固醇激素在贝类中广泛存在, 其含量随生殖阶段的不同而发生变化, 对性腺发育和性别决定等过程具有重要作用^[6-8]。研究者也陆续在长牡蛎 (*Crassostrea gigas*)、九孔鲍 (*Haliotis diversicolor supertexta*) 和栉孔扇贝 (*Chlamys farreri*) 中发现 17 β -HSDs 的部分亚型, 并对其功能进行推

收稿日期: 2020-11-23 修回日期: 2021-04-18

资助项目: 国家自然科学基金 (31702314); 福建省卫生健康中青年骨干人才培养项目 (2019-ZQNB-21); 福建省中青年教育科研项目 (JT180661, JAT190849); 海洋生物医药资源福建省高校工程研究中心 (厦门医学院) 开放课题 (XMMC-MBS201901); 天然化妆品福建省高校工程研究中心 (厦门医学院) 开放课题 (XMMC-NC201901)

第一作者: 曾臻 (照片), 从事贝类生殖发育研究, E-mail: zengzhen@xmmc.edu.cn

通信作者: 谭强来, 从事海洋营养功效因子评估研究, E-mail: tanqianglai@xmmc.edu.cn



测^[9-12]。相比在哺乳动物中的系统研究^[2, 13-14], 17 β -HSDs 在贝类中的报道相对有限, 主要集中在基因序列克隆、生殖周期及组织内表达分析、功能预测及鉴定等方面^[15-17], 仍有待深入探讨。

贝类是动物界软体动物门中最为主要的类群, 在海洋资源开发利用、水产经济发展、生态环境保护等方面占据着重要地位, 因此其育种和生殖调控在产业界和学术界备受关注^[18-20]。然而, 17 β -HSDs 等性类固醇激素合成与代谢关键酶在贝类性腺发育、性别分化的具体机制目前研究较为滞后, 严重制约了相关领域的进一步发展。因此, 本文综合其他物种的成熟研究和最新成果, 对 17 β -HSDs 的种类和功能及其在贝类中的研究进展进行综述, 以期对深入研究贝类 17 β -HSDs、精准调控贝类性腺发育和生殖内分泌提供参考。

1 17 β -HSDs 种类和功能概述

17 β -HSDs 家族成员最早于 1962 年由 Jarabak 等^[21]从胎盘中分离得到, 此后又陆续克隆出其他亚型。随着已发现的亚型不断增多, 研究者开始对其进行规范命名和功能分类^[22-24]。迄今已报道 15 种 17 β -HSD 亚型, 其中仅 17 β -HSD5 亚型属于醛酮还原酶 (AKR) 超家族, 其余 14 种亚型均属于短链脱氢酶/还原酶 (SDR) 超家族^[5]。此外, 根据催化作用形式大致可将 17 β -HSD1、3、5、7、12、15 等 6 种亚型归为还原酶; 17 β -HSD2、4、6、8、9、10、11、13、14 等 9 种亚型归为氧化酶^[4, 22]。

17 β -HSDs 作用于性类固醇激素合成的最后步骤及之后代谢的初步阶段, 通过依赖 NAD(P)H/NAD(P)⁺辅助因子, 催化第 17 位碳上的羟基或酮基的氧化还原反应, 使其在活性和非活性形式之间相互转换, 进而发挥多重生物学功能^[12-14]。17 β -

HSDs 各亚型在组织分布、亚细胞定位、表达模式、功能表现、辅助因子依赖、底物特异性要求等方面存在不同, 从而形成了一个能确保细胞专一性运用和调节调控的复杂系统, 实现性类固醇激素的局部水平调节^[1, 5, 25-26] (图 1)。

在人和哺乳动物中, 性类固醇激素对性器官发育、性功能维持以及子宫内膜异位症、乳腺癌、前列腺癌、卵巢癌、子宫内膜癌等疾病的发生发展具有重要的生理意义^[13, 27]。对于水产动物, 性类固醇激素与性腺发育和生殖内分泌过程密切相关^[25-12]。因此, 近年来 17 β -HSDs 的研究较多关注结构与功能的关系^[28]、时空表达与癌症的关联^[29]、特异性抑制剂的开发利用^[30], 以及贝类等水产动物中新亚型的克隆表达、功能阐述、机制推测^[31-32]等方面。以下依次对 17 β -HSD1~15 亚型的发现、分布和功能进行概述。

17 β -HSD1。17 β -HSD1 与雌酮具有高亲和性, 是雌酮还原合成雌二醇的主要关键酶, 也能还原原脱氢表雄酮转化为 5 α -雄烯二醇^[33]。在一定条件下 17 β -HSD1 还具有较弱的氧化能力, 可逆向将雌二醇氧化为雌酮^[1]。17 β -HSD1 分布广泛, 在人胎盘、卵巢、乳腺以及啮齿类、鱼类中均有发现^[25, 34-36]。17 β -HSD1 在人体组织内的表达及与乳腺癌、宫颈癌、子宫内膜异位症等雌激素依赖性疾病的关系明确, 因此, 其抑制剂的开发是目前的研究热点^[37-38]。在水产动物中, 目前主要关注该基因的克隆表达、功能鉴定以及环境污染物暴露对其表达水平的影响^[39-40]。梁冬冬等^[35]和 Zou 等^[32]发现, 17 β -HSD1 在牙鲆 (*Paralichthys olivaceus*) 卵巢中高表达, 外源信号分子 cAMP 及转录因子 NR5a2 使其表达显著下调, 而注射雄激素受体抑制剂氟他胺可使其表达显著上调。周林燕^[36]和

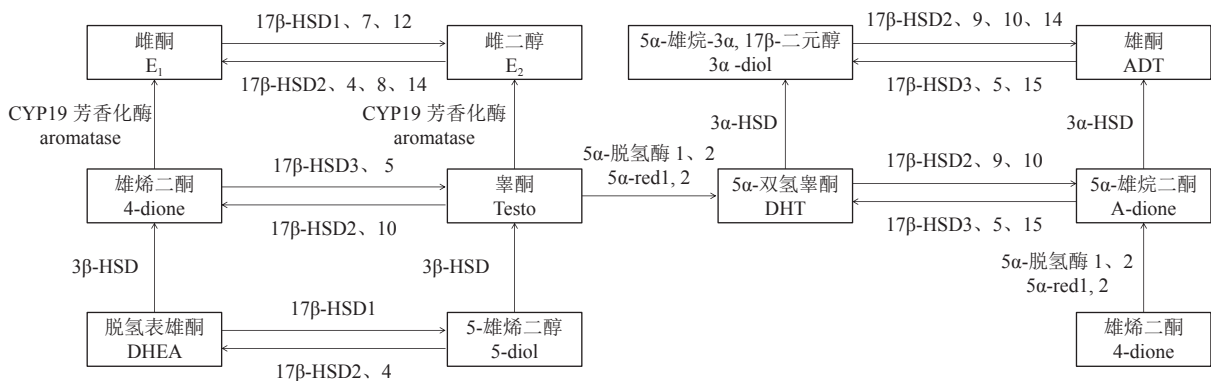


图 1 17 β -HSDs 各亚型在性类固醇激素合成与代谢中的作用

Fig. 1 Roles of 17 β -HSDs subtypes in the synthesis and metabolism of sex steroids

Ribeiro 等^[39]发现, 17 β -HSD1 存在于尼罗罗非鱼 (*Oreochromis niloticus*) 中, 且可被双酚 A 等环境污染物直接诱导表达。Rajakumar 等^[40]也从胡子鲶 (*Clarias batrachus*) 性腺中克隆出 17 β -HSD1, 并推测其可调节性腺发育和配子发生过程。

17 β -HSD2。Lehmann 等^[41]于 1967 年报道了人胎盘中的 17 β -HSD2, 后续证实其他生物体及组织中也广泛分布^[42]。17 β -HSD2 是家族中主要的氧化酶, 在 NAD⁺辅助下以雌二醇为最适底物生成雌酮; 也能催化睾酮为雄烯二酮、5 α -雄烯二酮为脱氢表雄酮, 实现高活性激素向对应低活性形式的转化, 从而避免胎盘、前列腺、乳腺等效应部位过度积累高活性的性类固醇激素^[43]。17 β -HSD2 的表达水平与某些癌症存在一定关联^[44], 因此其抑制剂的开发也是目前的研究热点^[45]。在水产动物中仅见零星的报道, 如 Mindnich 等^[46]从斑马鱼 (*Danio rerio*) 卵巢组织中克隆出 17 β -HSD2。

17 β -HSD3。17 β -HSD3 在睾丸中高表达, 对睾酮合成至关重要, 主要以 NADPH 为辅助因子催化雄烯二酮为睾酮, 也能催化 5 α -雄烯二酮为 5 α -双氢睾酮, 人一旦出现缺失可导致 46,XY 性发育障碍^[47]。17 β -HSD3 在激素依赖性前列腺癌中过表达, 催化合成的过量睾酮最终刺激前列腺癌细胞生长, 因此被认为是潜在有效的前列腺癌治疗靶点^[48]。在水产动物中, 周林燕^[36]从尼罗罗非鱼精巢中克隆出 17 β -HSD3。Ings 等^[49]监测了 17 β -HSD3 在不同时期的斑马鱼卵巢卵泡中的表达。Ma 等^[50]发现, 斑马鱼中 17 β -HSD3 的表达可被内分泌干扰物三唑锡影响。

17 β -HSD4。17 β -HSD4 是唯一被定位为过氧化物酶体的 17 β -HSDs, 含脱氢酶、水合酶和脂质转移等三个功能结构域, 具有较为独特的多功能酶活性, 可依赖 NAD⁺氧化雌二醇为雌酮、5 α -雄烯二酮为脱氢表雄酮, 并参与长链和支链脂肪酸的过氧化物酶体 β 氧化^[5]。17 β -HSD4 在肝癌组织中高表达, 可通过抑制雌二醇活性促进肝癌细胞增殖^[51-52]。王丹等^[53]对栉孔扇贝 17 β -HSD4 进行了克隆表达分析, 结果表明, 17 β -HSD4 在精巢、卵巢、肌肉、外套膜、鳃、肝胰腺和肾脏中均可合成, 且对精巢发育成熟的作用明显。Madureira 等^[54]采用实时 PCR 法 (RT-PCR) 检测了雌激素/抗雌激素对褐鳟 (*Salmo trutta*) 肝细胞 17 β -HSD4 mRNA 水平的影响。Song 等^[55]发现 17 β -HSD4 参与脂肪酸 β 氧化, 在瘦素介导的黄颡鱼 (*Pelteoba-*

grus fulvidraco) 卵母细胞成熟过程中发挥了重要作用。Abdelmoneim 等^[56]研究表明 17 α -乙炔雌二醇可使 17 β -HSD4 在性腺分化期的青鳉 (*Oryzias latipes*) 体内差异表达。

17 β -HSD5。17 β -HSD5 又称 AKRIC3、3 α -HSD2, 是唯一属于醛酮还原酶 (AKR) 超家族的 17 β -HSDs 亚型, 主要以 NADPH 为辅助因子催化雄烯二酮为睾酮, 也能将 5 α -雄烯二酮转化为 5 α -双氢睾酮, 可在外周组织产生强效雄激素, 激活雄激素受体或作为芳香化酶底物, 与去势抵抗性前列腺癌、多囊卵巢综合征、急性髓细胞白血病等疾病密切相关^[57]。因此其抑制剂的开发及临床应用备受关注^[58]。17 β -HSD5 被认为对人类特异^[24, 32], 在水产动物中未见相关报道。

17 β -HSD6。17 β -HSD6 早期被认为仅存在于啮齿类动物中^[1]。17 β -HSD6 在雄激素氧化代谢中具有重要作用, 同时表现出 17 β -HSD、3 α -HSD 和 3 β -HSD 活性; 在肝脏中含量丰富, 是合成 5 α -双氢睾酮的关键酶, 与多囊卵巢综合征、非小细胞肺癌及肝癌的发生发展相关^[59]。

17 β -HSD7。17 β -HSD7 是内质网膜上 NADPH 依赖的还原酶, 主要还原雌酮为雌二醇, 还具有 3 β -HSD 和 20 α -HSD 活性, 参与孕激素灭活^[60]。Thériault 等^[61]通过外源表达 17 β -HSD7, 证实其在雌激素激活和雄激素失活中的双重作用。双功能性的 17 β -HSD7 可调节雌二醇和 5 α -双氢睾酮的平衡, 因此被认为是治疗雌激素依赖性乳腺癌的新靶点^[62]。在水产动物中, Zou 等^[32]在牙鲆中鉴定出 17 β -HSD7。Nyuji 等^[63]发现 17 β -HSD7 在远东拟沙丁鱼 (*Sardinops melanostictus*) 的精巢中高表达。

17 β -HSD8。17 β -HSD8 在哺乳动物中广泛存在, 早期称作 Ke6, 以 NAD⁺为辅助因子, 主要氧化雌二醇为雌酮^[64]。但 Pletnev 等^[65]基于序列结构推测其功能主要是参与脂肪酸代谢, 而不是性类固醇激素代谢。17 β -HSD8 在斑马鱼、青鳉、尼罗罗非鱼、远东拟沙丁鱼及栉孔扇贝中均被克隆和鉴定出^[11, 16, 63, 66]。Nyuji 等^[63]发现 17 β -HSD8 在远东拟沙丁鱼的卵巢中高表达。季爱昌等^[66]通过对栉孔扇贝胚胎和幼虫中 17 β -HSD8 的表达进行分析, 推测其在栉孔扇贝起始关键器官的发生中具有重要作用, 并参与脂肪酸代谢调节, 进而调控胚胎和幼虫的发育过程。

17 β -HSD9。17 β -HSD9 最早从小鼠肝脏 cDNA 文库转染而来, 也曾被认为对啮齿类动物特异^[1, 32],

兼具 17 β -HSD、3 α -HSD 和视黄醇脱氢酶活性, 既参与 5 α -双氢睾酮氧化为 5 α -雄烷二酮, 也催化视黄醇为视黄醛^[67]。Zou 等^[32]在牙鲆体内鉴定出 17 β -HSD9, 主要在双眼中表达, 且只具有一个跨膜区, 与具有两个跨膜区的人 17 β -HSD9 明显不同。

17 β -HSD10。17 β -HSD10 被认为是家族中底物特异性最低的酶, 可催化短链和支链脂肪酸、胆汁酸、雌激素、雄激素、孕激素、皮质类固醇等多种底物, 以 NAD⁺为辅助因子可催化睾酮为雄烯二酮、5 α -双氢睾酮为 5 α -雄烷二酮、5 α -雄烷-3 α ,17 β -二醇为雄酮, 也能将雌二醇氧化成雌酮^[68]。由于最早是被认作一种 β -淀粉样肽 (A β) 结合蛋白, 因此过往研究主要关注 17 β -HSD10 与阿尔茨海默病的关联性及其抑制剂的开发利用^[68-69]。Zhang 等^[70]和 He 等^[71]从文昌鱼 (*Branchiostoma belcheri*) 体内分离出 17 β -HSD10, 与斑马鱼等脊椎动物的氨基酸序列高度相似。Zou 等^[32]和 Nyuji 等^[63]发现, 该基因在牙鲆和远东拟沙丁鱼的卵巢中高表达。Ribas 等^[72]通过转录组学研究表明 17 β -HSD10 是舌齿鲈 (*Dicentrarchus labrax*) 早期卵巢分化的可靠标志物。Zhang 等^[73]发现, 17 β -HSD10 在紫贻贝 (*Mytilus galloprovincialis*) 消化腺和性腺中高表达, 但暴露于双酚 A 或 2,2',4,4'-四溴二苯醚等内分泌干扰物时表达下调。

17 β -HSD11。17 β -HSD11 以 NADH 为辅助因子催化雌二醇为雌酮、5 α -雄烷-3 α ,17 β -二醇为雄酮, 也参与脂肪酸代谢^[74]。Zhai 等^[15]从九孔鲍中克隆出该基因, 与其他物种的同源性较高, 同样具有将 5 α -雄烷-3 α ,17 β -二醇转化为雄酮、睾酮转化为雄烯二酮的活性。

17 β -HSD12。17 β -HSD12 较早被认为仅参与脂肪酸代谢, 之后发现在类固醇代谢中也具有重要作用, 可催化雌酮还原为雌二醇^[24]。Zhou 等^[10]从九孔鲍中分离出该基因, 在产卵前、中、后 3 个繁殖阶段均有差异表达。Zou 等^[32]和 Nyuji 等^[63]分别在牙鲆和远东拟沙丁鱼体内鉴定出 17 β -HSD12a 和 17 β -HSD12b, 均在卵巢中高表达。Zhang 等^[73]发现, 该基因在紫贻贝中广泛分布, 在消化腺和性腺中的表达量较高, 但暴露于双酚 A 或 2,2',4,4'-四溴二苯醚等内分泌干扰物时表达下调。Aranyakanont 等^[75]发现, 该基因在尼罗罗非鱼卵母细胞成熟过程中参与成熟诱导类固醇合成。Suzuki 等^[76]研究表明日本鳗鲡 (*Anguilla japonica*) 体内 17 β -HSD12a 参与精巢 11-酮睾酮的合成。

17 β -HSD13。17 β -HSD13 早期称作 SCDR9, 与 17 β -HSD11 具有高度相似性, 但二者特性和功能却并不相同; 结构分析表明 17 β -HSD13 与除 17 β -HSD5 外的其他家族成员一样, N 端含有 NAD(P)⁺/NAD(P)H 结合域和一个酶激活位点, 可催化雌二醇为雌酮^[24]。此外, 该酶被认为是一种新的小鼠和人肝脏特异性脂滴相关蛋白, 在非酒精性脂肪肝患者中表达显著上调, 推测可参与类固醇和脂质代谢, 在调节肝脏脂质稳态中发挥重要作用^[77]。

17 β -HSD14。17 β -HSD14 早期称作 DHRS10、retSDR3, 能以 NAD⁺为辅助因子催化雌二醇为雌酮、5 α -雄烷-3 α ,17 β -二醇为雄酮, 也能参与脂肪酸代谢^[2]。因其对调节乳腺中生物活性类固醇, 具有重要意义, 被认为是雌激素受体阳性乳腺癌三苯氧胺反应的预测标志物^[78]。王丹^[5]从栉孔扇贝中克隆了该基因, 并发现其在生长期和成熟期的精巢中的表达量明显比同时期卵巢的更高, 从而推测 17 β -HSD14 在栉孔扇贝中具有羟基类固醇脱氢酶活性, 参与调节雌二醇水平。Zou 等^[32]在牙鲆中鉴定出 17 β -HSD14, 在精巢和卵巢中的表达水平随性腺发育而变化。

17 β -HSD15。17 β -HSD15 是目前最新的家族成员, 因最早在人前列腺中被鉴定而被称为前列腺短链脱氢酶 1, 主要参与雄激素合成, 可催化 5 α -雄烷二酮为 5 α -双氢睾酮、雄烯二酮为睾酮^[26]。赵刚^[4]探讨了 17 β -HSD15 在乳腺癌及癌旁组织中的表达, 认为其作为检测指标有助于提高乳腺癌恶性表型判断的准确性。Zou 等^[32]在牙鲆中鉴定出了 17 β -HSD15, 在精巢和卵巢中的表达水平随性腺发育而变化。

2 17 β -HSDs 在贝类中的研究进展

17 β -HSDs 种类和功能的研究前期主要集中在哺乳动物, 随后发现该酶在多种生物体及其组织中广泛分布, 目前共发现 15 种亚型, 是一类催化性类固醇激素合成的氧化还原酶^[2-4]。贝类是软体动物门 (Mollusca) 中最为主要的类群, 也是全世界重要的海洋经济物种, 对海洋资源开发利用、水产经济发展、生态环境保护至关重要, 其育种和生殖调控在产业界和学术界备受关注^[18-20]。性腺发育相关基因的克隆表达及功能鉴定是该领域的研究基础, 关注研究 17 β -HSDs 及其所调控的性类固醇激素, 可为阐明贝类生殖内分泌机理及

性腺发育和性别分化机制提供参考依据^[5-12]。

早在 20 世纪初,研究者就已关注到性类固醇激素在贝类中广泛存在^[79]。但其来源存在一定争议,部分研究者认为是通过环境摄食获取,而不是自身合成的,理由是贝类的固着及滤食生活方式使其易从环境污染物或细菌及微藻中摄入,且贝类基因组中不包含关键合成转化和受体基因^[80-81]。然而,多数研究者通过同位素标记、气相色谱-质谱联用、液相色谱-质谱联用、串联质谱和放射免疫等多种技术验证了贝类具有合成性类固醇激素的能力^[82]。Fernandes 等^[83]综合研究认为,贝类具有与脊椎动物类似的性类固醇激素合成与代谢途径,参与生殖过程。贝类中性类固醇激素的含量随着生殖阶段的不同而发生变化,对其排卵、性腺发育和性别决定等起着重要作用^[6-8]。Zheng 等^[6]利用超高效液相色谱-串联质谱证实栉孔扇贝存在性类固醇激素,且在生殖过程中睾酮在雄性、17 β -雌二醇在雌性的浓度与性腺体细胞指数的变化趋势相似,推测发挥了内分泌调节功能。Ni 等^[84]发现在福建牡蛎(*C. angulata*)中 17 β -雌二醇和睾酮浓度的波动与其生殖周期密切相关,推测对其性别决定、发育和成熟过程中发挥了内源性调节作用;并扩增得到雌激素受体的全长 cDNA,经在卵巢中表达最高。Smolarz 等^[85]研究表明蓝贻贝(*M. trossulus*)中睾酮、17 β -雌二醇、雌酮和雌三醇的含量随季节、配子发生阶段、性别、组织(性腺和体细胞)和贻贝床深度的变化而变化。外源性类固醇激素处理也会调控贝类的生殖过程^[86]。Wang 等^[87-91]开展了一系列关于注射或浸泡性类固醇激素对海扇贝(*Placopecten magellanicus*)生殖过程影响的研究。通过注射雌二醇、睾酮、孕酮和脱氢表雄酮均能加速早期发育阶段的海扇贝性腺分化,并使性别比向雄性更多转变;对于雌性海扇贝卵母细胞,雌二醇能刺激其生长,而睾酮则诱导其退化^[88]。对于成熟期的海扇贝,注射雌二醇可促进 5-羟色胺诱导雌雄配子的排放,孕酮则会阻止雌雄配子的排放,而注射睾酮仅诱导雄性配子的排放^[89]。Teaniniuraitemoana 等^[92]发现,连续注射 17 β -雌二醇可调控成体珠母贝(*Pinctada margaritifera*)的配子发生和性别分化。此外,环境污染物可通过干扰贝类的性类固醇激素合成与代谢途径或相关受体介导信号通路,进而影响其生殖过程^[93-95]。利用 2,2',4,4'-四溴二苯醚连续处理菲律宾蛤仔(*Ruditapes philippinarum*),

可导致在一定时期雌雄个体的血淋巴睾酮水平显著降低,但 17 β -HSD mRNA 表达水平无显著变化^[94]。Yang 等^[95]发现,雌性栉孔扇贝暴露于苯并[a]芘后,在生长期和成熟期时孕酮、睾酮和 17 β -雌二醇含量显著降低,且与 3 β -HSD、CYP17 和 17 β -HSD 等性类固醇激素生成酶的表达下调有关。

性类固醇激素合成与代谢途径受 17 β -HSD、11 β -HSD、3 β -HSD 和 CYP19 等多种性腺发育相关基因调控^[94-97]。相比脊椎动物,性腺发育相关基因在无脊椎动物中的研究还不够系统,但研究者在蛤、鲍、牡蛎、贻贝、扇贝等贝类中已陆续发现多个 17 β -HSDs 亚型,并对其基因序列克隆、生殖周期及组织内表达分析、功能预测及鉴定等方面进行了探讨^[9-12, 15-17]。在贝类中 17 β -HSDs 通过调节性类固醇激素水平从而影响其排卵、性腺发育和性别决定等相关生理活动,如 Hathaway 等^[98]早在 1965 年就发现牡蛎精子制备物能氧化 17 β -雌二醇等 17 β -羟基类固醇转化底物。de Longcamp 等^[99]将紫贻贝性腺匀浆与性类固醇激素体外孵育,利用同位素标记发现其可将雌二醇转化为雌酮,表明性腺中存在性类固醇激素生物合成,从而证明紫贻贝存在 17 β -HSDs。Matsumoto 等^[9]采用高效液相色谱法测定了扇贝和牡蛎性腺在生殖周期中的雌激素含量,在卵巢中检测到雌酮、17 β -雌二醇和少量的雌三醇,而在精巢中只检测到 17 β -雌二醇;卵巢中 17 β -雌二醇含量始终高于雌酮,且随性成熟而升高;并通过体外实验证实扇贝和牡蛎的卵巢中均存在 17 β -HSD,可催化雌二醇转化为雌酮,且其酶活性高低与生殖周期有关,在个体分化早期较高。Le Curieux-Belfond 等^[100]结合薄层层析法和高效液相色谱联用放射检测仪分析,发现长牡蛎中 17 β -HSD 具有性类固醇激素转化活性,其活性随性成熟而增加,在产卵后下降。

17 β -HSDs 在贝类中的研究早期主要集中在酶催化活性检测,然而在不同物种中其酶催化活性存在较大差异,导致其内源性合成与代谢易被质疑。随着现代分子生物学技术的迅速发展,17 β -HSDs 多种亚型在贝类的不同物种中被克隆表达,如 Zhang 等^[101]于 2012 年获得长牡蛎的全基因组,其中包含 17 β -HSD4、17 β -HSD7 和 17 β -HSD14 等序列信息。曾臻等^[12]利用 cDNA 末端快速扩增技术(RACE)克隆了福建牡蛎 17 β -HSD 的全长序列,并通过 RT-PCR 对其时空表达特征进行监测,结果表明,其在福建牡蛎生殖周期的排放期时表达

量较高,在鳃、性腺、闭壳肌、外套膜和内脏团中均有表达,在性腺中的表达量最高。高云峰^[31]、Zhai等^[15]和Zhou等^[10,102]在九孔鲍中克隆和鉴定了17 β -HSD11和17 β -HSD12,通过瞬时转染人胚胎肾细胞293(HEK-293),证实17 β -HSD11可将5 α -雄烷-3 α ,17 β -二醇转化为雄酮、睾酮转化为雄烯二酮,17 β -HSD12可将雌酮转化为雌二醇;体内表达分析表明17 β -HSD11和17 β -HSD12在生殖期前、中、后3个阶段均有差异表达,推测二者在性类固醇激素介导调控生殖过程中具有重要作用;此外,当雌雄配子暴露于内分泌干扰物邻苯二甲酸二甲酯时,其17 β -HSD11、17 β -HSD12和cyp3a的表达模式发生变化,预示邻苯二甲酸二甲酯对配子受精过程和后续的胚胎发生具有不利影响。在紫贻贝中,Zhang等^[73]克隆出17 β -HSD10和17 β -HSD12,可在鳃、性腺、消化腺、闭壳肌、外套膜和血细胞中检测出,在消化腺和性腺的表达量较高;但当暴露于内分泌干扰物双酚A或2,2',4,4'-四溴二苯醚时,二者在消化腺中表达均下调。Prisco等^[103]和Rosati等^[104]均关注意大利那不勒斯湾的紫贻贝,定位分析表明17 β -HSD在生殖期存在于精巢的支持细胞、间质细胞、生殖细胞和脂肪颗粒细胞中,在静息期仅存在于脂肪颗粒细胞中;无论是生殖还是非生殖阶段,17 β -HSD均存在于卵巢中。王丹等^[5,53]、刘建国等^[11,16]和季爱昌等^[66]围绕栉孔扇贝17 β -HSDs开展研究,陆续克隆表达出17 β -HSD4、17 β -HSD8和17 β -HSD14;其中17 β -HSD4和17 β -HSD8在鳃、精巢、卵巢、肌肉、肾脏、外套膜、肝胰腺中均有表达,但17 β -HSD4在肝胰腺和肾脏中的表达量较高,而17 β -HSD8在消化腺、肾脏和卵巢中表达量较高;三者生长期和成熟期精巢中的表达量均显著高于同时期的卵巢,在成熟期精巢中表达量最高。17 β -HSD8在栉孔扇贝胚胎和幼虫中可通过调节脂肪酸代谢参与调控早期发育过程,在初始未受精卵中高表达,随即在受精卵和卵裂期胚胎中显著下降,在囊胚中又显著提高;至D形幼虫阶段,17 β -HSD8 mRNA阳性信号由均匀分布于所有细胞转变为集中在内脏团附近。虾夷扇贝(*Mizuhopecten yessoensis*)中17 β -HSD8、17 β -HSD11和17 β -HSD14近期被Thitiphuree等^[17]克隆及鉴定出,三者虾夷扇贝各组织中普遍分布,在脑和足神经节、内脏神经节、性腺和消化腺中表达量较高;17 β -HSD8和17 β -HSD11随着卵巢成熟而表达量逐渐增加,但在精巢中整个生殖期均

不高;然而17 β -HSD14表达模式与生殖期的成熟度无关。此外,Lima等^[105]从狗岩螺(*Nucella lapillus*)中成功扩增出17 β -HSD12,且在所有检测组织中普遍表达,在肾脏和消化腺中表达量较高,预示在贝类中,17 β -HSD12同样参与脂质代谢。

3 总结与展望

17 β -HSDs是一类参与性类固醇激素合成与代谢的关键酶,也可参与脂质代谢,广泛存在于各种生物体及其组织中。贝类育种和生殖调控对海洋资源开发利用、水产经济发展、生态环境保护至关重要,20世纪六、七十年代已发现贝类中存在17 β -HSDs,但迄今仅在少数贝类中开展了17 β -HSDs基因克隆与表达、结构与功能分析等。目前,17 β -HSDs调控贝类性腺发育和生殖内分泌研究已取得一定的进展,如:①贝类中17 β -HSDs新亚型的发现。目前仅在少数几种贝类中明确了为数不多的17 β -HSDs亚型,还存在着未知序列、结构与功能的亚型有待克隆表达及功能鉴定。②贝类中17 β -HSDs时空表达特征的分析。目前17 β -HSDs在生殖与非生殖周期、性腺与非性腺组织内等时空表达特征分析还不够深入,各项研究在分阶段和分类型采样时并不完全统一,需要更系统地研究其组织分布、亚细胞定位及表达模式等。③贝类中17 β -HSDs构效关系的解析。目前研究大多停留在简单的一级结构分析和空间结构预测层面,与贝类生殖调控功能的关系有待深入解析,需要进一步明晰其底物特异性要求、受体类型、完整的合成与代谢功能途径及其分子机制等。④环境污染影响的明晰及相应对策的制定。有实验表明某些外源性类固醇激素和环境污染可调控贝类中17 β -HSDs的表达水平,进而影响生殖过程,但已开展的研究较有限,需要更全面地评估其具体影响,从而制定对策开发利用相应的激活剂、抑制剂。⑤对产业实践应用的指导。如何综合利用已有的研究成果来指导贝类中17 β -HSDs后续的创新研发、服务贝类产业发展等亟待开展的重要课题。

(作者声明本文无实际或潜在的利益冲突)

参考文献 (References):

- [1] 苏文,许华敏,康继宏,等. 17 β -羟基类固醇脱氢酶的功能[J]. 生理科学进展, 2014, 45(1): 27-31.

- Su W, Xu H M, Kang J H, *et al.* Function of 17 β -hydroxysteroid dehydrogenase[J]. *Progress in Physiological Sciences*, 2014, 45(1): 27-31 (in Chinese).
- [2] Lukacik P, Kavanagh K L, Oppermann U. Structure and function of human 17 β -hydroxysteroid dehydrogenases[J]. *Molecular and Cellular Endocrinology*, 2006, 248(1-2): 61-71.
- [3] Hilborn E, Stål O, Jansson A. Estrogen and androgen-converting enzymes 17 β -hydroxysteroid dehydrogenase and their involvement in cancer: with a special focus on 17 β -hydroxysteroid dehydrogenase type 1, 2, and breast cancer[J]. *Oncotarget*, 2017, 8(18): 30552-30562.
- [4] 赵刚. 15 型 17 β 羟化类固醇脱氢酶和 1 型 5 α -还原酶在乳腺癌和癌旁组织中的表达 [D]. 长春: 吉林大学, 2010.
- Zhao G. Expression of 17 β -hydroxysteroid dehydrogenase type 15 and 5 α -reductase type 1 in breast cancer and adjacent non-malignant tissues[D]. Changchun: Jilin University, 2010 (in Chinese).
- [5] 王丹. 栉孔扇贝 (*Chlamys farreri*) 三个性腺发育相关基因的克隆及表达分析 [D]. 青岛: 中国海洋大学, 2013.
- Wang D. Cloning and expression analysis of three gonad development-related genes in *Chlamys farreri*[D]. Qingdao: Ocean University of China, 2013 (in Chinese).
- [6] Zheng B H, An L H, Chang H, *et al.* Evidence for the presence of sex steroid hormones in Zhikong scallop, *Chlamys farreri*[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2014, 143: 199-206.
- [7] Zhu X J, Guo C Y, Lin C Y, *et al.* Estradiol-17 β and testosterone levels during the annual reproductive cycle of in *Mytilus coruscus*[J]. *Animal Reproduction Science*, 2018, 196: 35-42.
- [8] Xu R Y, Pan L Q, Yang Y Y, *et al.* Characterizing transcriptome in female scallop *Chlamys farreri* provides new insights into the molecular mechanisms of reproductive regulation during ovarian development and spawn[J]. *Gene*, 2020, 758: 144967.
- [9] Matsumoto T, Osada M, Osawa Y, *et al.* Gonadal estrogen profile and immunohistochemical localization of steroidogenic enzymes in the oyster and scallop during sexual maturation[J]. *Comparative Biochemistry and Physiology-Part B: Biochemistry and Molecular Biology*, 1997, 118(4): 811-817.
- [10] Zhou J, Gao Y F, Li L, *et al.* Identification and functional characterization of a putative 17 β -hydroxysteroid dehydrogenase 12 in abalone (*Haliotis diversicolor supertexta*)[J]. *Molecular and Cellular Biochemistry*, 2011, 354(1-2): 123-133.
- [11] 刘建国. 栉孔扇贝 (*Chlamys farreri*) 性类固醇激素和 17 β -羟类固醇脱氢酶 8 在性腺发育过程中的潜在作用 [D]. 青岛: 中国海洋大学, 2014.
- Liu J G. Potential roles of sex steroids and 17 β -hydroxysteroid dehydrogenase 8 in *Chlamys farreri* during gonadal development[D]. Qingdao: Ocean University of China, 2014 (in Chinese).
- [12] 曾臻, 倪健斌, 谭强来, 等. 福建牡蛎 17 β -HSD 基因的克隆及其生殖周期表达 [J]. 应用海洋学学报, 2020, 39(1): 12-19.
- Zeng Z, Ni J B, Tan Q L, *et al.* Cloning of 17 β -HSD gene and its characterization in the Fujian oyster, *Crassostrea angulata*, during gonad development[J]. *Journal of Applied Oceanography*, 2020, 39(1): 12-19 (in Chinese).
- [13] Moeller G, Adamski J. Multifunctionality of human 17 β -hydroxysteroid dehydrogenases[J]. *Molecular and Cellular Endocrinology*, 2006, 248(1-2): 47-55.
- [14] Hiltunen J K, Kastaniotis A J, Autio K J, *et al.* 17 β -hydroxysteroid dehydrogenases as acyl thioester metabolizing enzymes[J]. *Molecular and Cellular Endocrinology*, 2019, 489: 107-118.
- [15] Zhai H N, Zhou J, Cai Z H. Cloning, characterization, and expression analysis of a putative 17 beta-hydroxysteroid dehydrogenase 11 in the abalone, *Haliotis diversicolor supertexta*[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2012, 130(1-2): 57-63.
- [16] Liu J G, Zhang Z F, Ma X S, *et al.* Characteristics of 17 β -hydroxysteroid dehydrogenase 8 and its potential role in gonad of Zhikong scallop *Chlamys farreri*[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2014, 141: 77-86.
- [17] Thitiphuree T, Nagasawa K, Osada M. Molecular identification of steroidogenesis-related genes in scallops and their potential roles in gametogenesis[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2014, 141: 77-86.

- logy, 2019, 186: 22-33.
- [18] 苏海林, 王扬帆, 胡晓丽, 等. 贝类全基因组遗传育种评估与分析系统的开发[J]. 中国海洋大学学报, 2016, 46(10): 65-72.
- Su H L, Wang Y F, Hu X L, *et al.* Development of the genomic analysis and evaluation system for shellfish genetic breeding[J]. Periodical of Ocean University of China, 2016, 46(10): 65-72 (in Chinese).
- [19] Kim E J, Kim S J, Park C J, *et al.* Characterization of testis-specific serine/threonine kinase 1-like (TSSK1-like) gene and expression patterns in diploid and triploid Pacific abalone (*Haliotis discus hannai*; Gastropoda; Mollusca) males[J]. PLoS One, 2019, 14(12): e0226022.
- [20] 付璐璐, 王峥, 王磊, 等. 近10年水产动物抗逆育种研究进展[J]. 江苏农业科学, 2020, 48(16): 52-58.
- Fu L L, Wang Z, Wang L, *et al.* Research progress of resistance breeding of aquatic animals in recent ten years[J]. Jiangsu Agricultural Sciences, 2020, 48(16): 52-58 (in Chinese).
- [21] Jarabak J, Adams J A, Williams-Ashman H G, *et al.* Purification of a 17 β -hydroxysteroid dehydrogenase of human placenta and studies on its transhydrogenase function[J]. Journal of Biological Chemistry, 1962, 237(2): 345-357.
- [22] Peltoketo H, Luu-The V, Simard J, *et al.* 17 β -hydroxysteroid dehydrogenase (HSD)/17-ketosteroid reductase (KSR) family; nomenclature and main characteristics of the 17HSD/KSR enzymes[J]. Journal of Molecular Endocrinology, 1999, 23(1): 1-11.
- [23] Adamski J, Jakob F J. A guide to 17 β -hydroxysteroid dehydrogenases[J]. Molecular and Cellular Endocrinology, 2001, 171(1-2): 1-4.
- [24] Moeller G, Adamski J. Integrated view on 17 β -hydroxysteroid dehydrogenases[J]. Molecular and Cellular Endocrinology, 2009, 301(1-2): 7-19.
- [25] 张万飞, 叶建新. 人类17 β -羟基类固醇脱氢酶的功能[J]. 海南医学, 2008, 19(1): 127-130.
- Zhang W F, Ye J X. Function of human 17 β -hydroxysteroid dehydrogenase[J]. Hainan Medical Journal, 2008, 19(1): 127-130 (in Chinese).
- [26] Luu-The V, Labrie F. The intracrine sex steroid biosynthesis pathways[J]. Progress in Brain Research, 2010, 181: 177-192.
- [27] Dobbs R W, Malhotra N R, Greenwald D T, *et al.* Estrogens and prostate cancer[J]. Prostate Cancer and Prostatic Diseases, 2019, 22(2): 185-194.
- [28] Li T, Stephen P, Zhu D W, *et al.* Crystal structures of human 17 β -hydroxysteroid dehydrogenase type 1 complexed with estrone and NADP⁺ reveal the mechanism of substrate inhibition[J]. The FEBS Journal, 2019, 286(11): 2155-2166.
- [29] Collin L J, Ulrichsen S P, Ahern T P, *et al.* 17 β -hydroxysteroid dehydrogenase 1: 2 and breast cancer recurrence: a Danish population-based study[J]. Acta Oncologica, 2020, 59(3): 329-333.
- [30] Hernández-López H, Leyva-Ramos S, Gómez-Durán C F A, *et al.* Synthesis of 1, 4-biphenyl-triazole derivatives as possible 17 β -HSD1 inhibitors: an *in silico* study[J]. ACS Omega, 2020, 5(23): 14061-14068.
- [31] 高云峰. 鲍鱼 17 β 羟基类固醇脱氢酶 12 的结构与功能鉴定 [D]. 北京: 清华大学, 2010.
- Gao Y F. Identification and characterization of the 17 β -hydroxysteroid dehydrogenase 12 (17 β HSD12) structure and function in abalone[D]. Beijing: Tsinghua University, 2010 (in Chinese).
- [32] Zou C C, Wang L J, Zou Y X, *et al.* Characteristics and sex dimorphism of 17 β -hydroxysteroid dehydrogenase family genes in the olive flounder *Paralichthys olivaceus*[J]. The Journal of Steroid Biochemistry and Molecular Biology, 2020, 199: 105597.
- [33] Han H, Thériault J F, Chen G, *et al.* Substrate inhibition of 17 β -HSD1 in living cells and regulation of 17 β -HSD7 by 17 β -HSD1 knockdown[J]. The Journal of Steroid Biochemistry and Molecular Biology, 2017, 172: 36-45.
- [34] 张哲, 王宏竹, 刘永惠, 等. 大鼠肾脏细胞17 β -HSD1的表达及参与性激素合成的能力[J]. 南方医科大学学报, 2016, 36(2): 265-268.
- Zhang Z, Wang H Z, Liu Y H, *et al.* Expression of 17 β -hydroxysteroid dehydrogenase type 1 in the kidney of rats: the capacity of the kidney for synthesizing sex hormones[J]. Journal of Southern Medical University, 2016, 36(2): 265-268 (in Chinese).
- [35] 梁冬冬, 范兆飞, 邹玉霞, 等. 牙鲆17 β -HSD1基因克隆及其表达调控的初步研究[J]. 海洋科学, 2017, 41(9): 65-73.
- Liang D D, Fan Z F, Zou Y X, *et al.* Molecular charac-

- terization, expression, and regulation of 17 β -HSD1 in the olive flounder *Paralichthys olivaceus*[J]. *Marine Sciences*, 2017, 41(9): 65-73 (in Chinese).
- [36] 周林燕. 罗非鱼三种 17 β -羟类固醇脱氢酶 (17 β -HSD1, 17 β -HSD3, 17 β -HSD8) 的克隆、表达及酶活性鉴定 [D]. 重庆: 西南师范大学, 2004.
- Zhou L Y. Molecular cloning, gene expression and enzyme activity characterization of three types of 17 β -hydroxysteroid dehydrogenase (17 β -HSD1, 17 β -HSD3, 17 β -HSD8) from Nile tilapia, *Oreochromis niloticus*[D]. Chongqing: Southwest University, 2004 (in Chinese).
- [37] He W H, Gauri M, Li T, *et al.* Current knowledge of the multifunctional 17 β -hydroxysteroid dehydrogenase type 1 (HSD17B1)[J]. *Gene*, 2016, 588(1): 54-61.
- [38] Lespérance M, Barbeau X, Roy J, *et al.* Chemical synthesis of C3-oxiranyl/oxiranylmethyl-estrane derivatives targeted by molecular modeling and tested as potential inhibitors of 17 β -hydroxysteroid dehydrogenase type 1[J]. *Steroids*, 2018, 140: 104-113.
- [39] Ribeiro C, Urbatzka R, Castro L F C, *et al.* *In vitro* exposure of Nile tilapia (*Oreochromis niloticus*) testis to estrogenic endocrine disrupting chemicals: mRNA expression of genes encoding steroidogenic enzymes[J]. *Toxicology Mechanisms and Methods*, 2012, 22(1): 47-53.
- [40] Rajakumar A, Senthilkumaran B. cloning and expression analysis of 17 β -hydroxysteroid dehydrogenase 1 and 12 during gonadal development, recrudescence and after *in vivo* hCG induction in catfish, *Clarias batrachus*[J]. *Steroids*, 2014, 92: 81-89.
- [41] Lehmann W D, Breuer H. Metabolism of 16-oxoestrone in rat liver cell fractions[J]. *Hoppe-Seyler's Zeitschrift für physiologische Chemie*, 1967, 348(10): 1268-1272.
- [42] Wang C L, Ying S J, Wang Z Y, *et al.* Molecular cloning and expression of 17 β -hydroxysteroid dehydrogenase type 2 gene in Hu sheep[J]. *Molecular Biology Reports*, 2013, 40(2): 1073-1080.
- [43] Zhang C Y, Calvo E L, Yang C Q, *et al.* Transcriptome of 17 β -hydroxysteroid dehydrogenase type 2 plays both hormone-dependent and hormone-independent roles in MCF-7 breast cancer cells[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2019, 195: 105471.
- [44] Drzewiecka H, Jarmolowska-Jurczyszyn D, Kluk A, *et al.* Altered expression of 17 β -hydroxysteroid dehydrogenase type 2 and its prognostic significance in non-small cell lung cancer[J]. *International Journal of Oncology*, 2020, 56(6): 1352-1372.
- [45] Salah M, Abdelsamie A S, Frotscher M. Inhibitors of 17 β -hydroxysteroid dehydrogenase type 1, 2 and 14: structures, biological activities and future challenges[J]. *Molecular and Cellular Endocrinology*, 2019, 489: 66-81.
- [46] Mindnich R, De Angelis M H, Adamski J. Functional genome analysis indicates loss of 17 β -hydroxysteroid dehydrogenase type 2 enzyme in the zebrafish[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2007, 103(1): 35-43.
- [47] Mendonca B B, Gomes N L, Costa E M F, *et al.* 46, XY disorder of sex development (DSD) due to 17 β -hydroxysteroid dehydrogenase type 3 deficiency[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2017, 165: 79-85.
- [48] Cheng Y T, Yang Y, Wu Y N, *et al.* The curcumin derivative, H10, suppresses hormone-dependent prostate cancer by inhibiting 17 β -hydroxysteroid dehydrogenase type 3[J]. *Frontiers in Pharmacology*, 2020, 11: 637.
- [49] Ings J S, Van Der Kraak G J. Characterization of the mRNA expression of StAR and steroidogenic enzymes in zebrafish ovarian follicles[J]. *Molecular Reproduction & Development*, 2006, 73(8): 943-954.
- [50] Ma Y N, Cao C Y, Wang Q W, *et al.* Effects of azocyclostin on gene transcription and steroid metabolome of hypothalamic-pituitary-gonad axis, and their consequences on reproduction in zebrafish (*Danio rerio*)[J]. *Aquatic Toxicology*, 2016, 179: 55-64.
- [51] Pan L C, Xiao H Y, Yin W J, *et al.* Correlation between HSD17B4 expression in rat liver cancer tissues and inflammation or proliferation[J]. *European Review for Medical and Pharmacological Sciences*, 2018, 22(11): 3386-3393.
- [52] Lu X, Kong L Y, Wang X, *et al.* 17 β -hydroxysteroid dehydrogenase 4 induces liver cancer proliferation-associated genes via STAT3 activation[J]. *Oncology Reports*, 2019, 41(3): 2009-2019.

- [53] 王丹, 李海龙, 毕颖, 等. 栉孔扇贝17 β -HSD4基因的克隆和表达分析[J]. *水产学报*, 2013, 37(3): 367-375.
Wang D, Li H L, Bi Y, *et al.* Cloning and expression analysis of 17 β -HSD4 gene in *Chlamys farreri*[J]. *Journal of Fisheries of China*, 2013, 37(3): 367-375 (in Chinese).
- [54] Madureira T V, Malhão F, Pinheiro I, *et al.* Estrogenic and anti-estrogenic influences in cultured brown trout hepatocytes: focus on the expression of some estrogen and peroxisomal related genes and linked phenotypic anchors[J]. *Aquatic Toxicology*, 2015, 169: 133-142.
- [55] Song Y F, Tan X Y, Pan Y X, *et al.* Fatty acid β -oxidation is essential in leptin-mediated oocytes maturation of yellow catfish *Pelteobagrus fulvidraco*[J]. *International Journal of Molecular Sciences*, 2018, 19(5): 1457.
- [56] Abdelmoneim A, Abdu A, Chen S, *et al.* Molecular signaling pathways elicited by 17 α -ethinylestradiol in Japanese medaka male larvae undergoing gonadal differentiation[J]. *Aquatic Toxicology*, 2019, 208: 187-195.
- [57] Penning T M. AKR1C3 (type 5 17 β -hydroxysteroid dehydrogenase/prostaglandin F synthase): roles in malignancy and endocrine disorders[J]. *Molecular and Cellular Endocrinology*, 2019, 489: 82-91.
- [58] Liu Y, He S Y, Chen Y, *et al.* Overview of AKR1C3: inhibitor achievements and disease insights[J]. *Journal of Medicinal Chemistry*, 2020, 63(20): 11305-11329.
- [59] Lv L, Zhao Y J, Wei Q Q, *et al.* Downexpression of HSD17B6 correlates with clinical prognosis and tumor immune infiltrates in hepatocellular carcinoma[J]. *Cancer Cell International*, 2020, 20(1): 210.
- [60] Liu H, Robert A, Luu-The V. Cloning and characterization of human form 2 type 7 17 β -hydroxysteroid dehydrogenase, a primarily 3 β -keto reductase and estrogen activating and androgen inactivating enzyme[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2005, 94(1-3): 173-179.
- [61] Thériault J F, Lin S X. The dual sex hormone specificity for human reductive 17 β -hydroxysteroid dehydrogenase type 7: synergistic function in estrogen and androgen control[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2019, 186: 61-65.
- [62] Wang X Q, Gérard C, Thériault J F, *et al.* Synergistic control of sex hormones by 17 β -HSD type 7: a novel target for estrogen-dependent breast cancer[J]. *Journal of Molecular Cell Biology*, 2015, 7(6): 568-579.
- [63] Nyuji M, Hongo Y, Yoneda M, *et al.* Transcriptome characterization of BPG axis and expression profiles of ovarian steroidogenesis-related genes in the Japanese sardine[J]. *BMC Genomics*, 2020, 21(1): 668.
- [64] Ohno S, Nishikawa K, Honda Y, *et al.* Expression in *E. coli* and tissue distribution of the human homologue of the mouse Ke 6 gene, 17 β -hydroxysteroid dehydrogenase type 8[J]. *Molecular and Cellular Biochemistry*, 2008, 309(1-2): 209-215.
- [65] Pletnev V Z, Duax W L. Rational proteomics IIV: modeling the primary function of the mammalian 17 β -hydroxysteroid dehydrogenase type 8[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2005, 94(4): 327-335.
- [66] 季爱昌, 刘建国, 刘丹雯, 等. 栉孔扇贝胚胎和幼虫中的17 β -HSD8表达分析[J]. *海洋湖沼通报*, 2018(5): 125-129.
Ji A C, Liu J G, Liu D W, *et al.* Expression analysis of 17 β -HSD8 in embryos and larvae of *Chlamys farreri*[J]. *Transactions of Oceanology and Limnology*, 2018(5): 125-129 (in Chinese).
- [67] Napoli J L. 17 β -hydroxysteroid dehydrogenase type 9 and other short-chain dehydrogenases/reductases that catalyze retinoid, 17 β -and 3 α -hydroxysteroid metabolism[J]. *Molecular and Cellular Endocrinology*, 2001, 171(1-2): 103-109.
- [68] He X Y, Isaacs C, Yang S Y. Roles of mitochondrial 17 β -hydroxysteroid dehydrogenase type 10 in Alzheimer's disease[J]. *Journal of Alzheimer's Disease*, 2018, 62(2): 665-673.
- [69] Boutin S, Maltais R, Roy J, *et al.* Synthesis of 17 β -hydroxysteroid dehydrogenase type 10 steroidal inhibitors: selectivity, metabolic stability and enhanced potency[J]. *European Journal of Medicinal Chemistry*, 2021, 209: 112909.
- [70] Zhang Y, Wang L, Shao M, *et al.* A comparative study on the developmental expression of *hadh2* in amphioxus and zebrafish[J]. *Journal of Fish Biology*, 2008, 72(5): 1215-1222.
- [71] He X, Yang S. Comments on 'significance of developmental expression of amphioxus *Branchiostoma belcheri*

- eri* and zebrafish *Danio rerio* *Hsd17b10* in biological and medical research[J]. *Journal of Fish Biology*, 2009, 74(8): 1689-1692.
- [72] Ribas L, Crespo B, Sánchez-Baizán N, *et al.* Characterization of the European sea bass (*Dicentrarchus labrax*) gonadal transcriptome during sexual development[J]. *Marine Biotechnology*, 2019, 21(3): 359-373.
- [73] Zhang Y Y, Wang Q, Ji Y L, *et al.* Identification and mRNA expression of two 17 β -hydroxysteroid dehydrogenase genes in the marine mussel *Mytilus galloprovincialis* following exposure to endocrine disrupting chemicals[J]. *Environmental Toxicology and Pharmacology*, 2014, 37(3): 1243-1255.
- [74] Chai Z L, Brereton P, Suzuki T, *et al.* 17 β -hydroxysteroid dehydrogenase type XI localizes to human steroidogenic cells[J]. *Endocrinology*, 2003, 144(5): 2084-2091.
- [75] Aranyakanont C, Ijiri S, Hasegawa Y, *et al.* 17 β -hydroxysteroid dehydrogenase type 12 is responsible for maturation-inducing steroid synthesis during oocyte maturation in Nile tilapia[J]. *General and Comparative Endocrinology*, 2020, 290: 113399.
- [76] Suzuki H, Ozaki Y, Ijiri S, *et al.* 17 β -hydroxysteroid dehydrogenase type 12a responsible for testicular 11-ketotestosterone synthesis in the Japanese eel, *Anguilla japonica*[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2020, 198: 105550.
- [77] Su W, Mao Z, Liu Y, *et al.* Role of HSD17B13 in the liver physiology and pathophysiology[J]. *Molecular and Cellular Endocrinology*, 2019, 489: 119-125.
- [78] Sivik T, Gunnarsson C, Fornander T, *et al.* 17 β -hydroxysteroid dehydrogenase type 14 is a predictive marker for tamoxifen response in oestrogen receptor positive breast cancer[J]. *PLoS One*, 2012, 7(7): e40568.
- [79] Hagerman D D, Wellington F M, Villet C A. Estrogens in marine invertebrates[J]. *The Biological Bulletin*, 1957, 112(2): 180-183.
- [80] Scott A P. Do mollusks use vertebrate sex steroids as reproductive hormones? Part I: critical appraisal of the evidence for the presence, biosynthesis and uptake of steroids[J]. *Steroids*, 2012, 77(13): 1450-1468.
- [81] Fodor I, Urbán P, Scott A P, *et al.* A critical evaluation of some of the recent so-called 'evidence' for the involvement of vertebrate-type sex steroids in the reproduction of mollusks[J]. *Molecular and Cellular Endocrinology*, 2020, 516: 110949.
- [82] Hallmann A, Konieczna L, Swiezak J, *et al.* Aromatisation of steroids in the bivalve *Mytilus trossulus*[J]. *PeerJ*, 2019, 7: e6953.
- [83] Fernandes D, Loi B, Porte C. Biosynthesis and metabolism of steroids in molluscs[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2011, 127(3-5): 189-195.
- [84] Ni J B, Zeng Z, Ke C H. Sex steroid levels and expression patterns of estrogen receptor gene in the oyster *Crassostrea angulata* during reproductive cycle[J]. *Aquaculture*, 2013, 376-379: 105-116.
- [85] Smolarz K, Zabrzeńska S, Konieczna L, *et al.* Changes in steroid profiles of the blue mussel *Mytilus trossulus* as a function of season, stage of gametogenesis, sex, tissue and mussel bed depth[J]. *General and Comparative Endocrinology*, 2018, 259: 231-239.
- [86] Balbi T, Ciacci C, Canesi L. Estrogenic compounds as exogenous modulators of physiological functions in molluscs: signaling pathways and biological responses[J]. *Comparative Biochemistry and Physiology-Part C: Toxicology & Pharmacology*, 2019, 222: 135-144.
- [87] Wang C D, Croll R P. Effects of sex steroids on *in vitro* gamete release in the sea scallop, *Placopecten magellanicus*[J]. *Invertebrate Reproduction & Development*, 2003, 44(2-3): 89-100.
- [88] Wang C D, Croll R P. Effects of sex steroids on gonadal development and gender determination in the sea scallop, *Placopecten magellanicus*[J]. *Aquaculture*, 2004, 238(1-4): 483-498.
- [89] Wang C D, Croll R P. Effects of sex steroids on spawning in the sea scallop, *Placopecten magellanicus*[J]. *Aquaculture*, 2006, 256(1-4): 423-432.
- [90] Wang C D, Croll R P. Estrogen binding sites in the sea scallop: characterization and possible involvement in reproductive regulation[J]. *Comparative Biochemistry and Physiology-Part B: Biochemistry and Molecular Biology*, 2007, 148(3): 303-313.
- [91] Croll R P, Wang C D. Possible roles of sex steroids in the control of reproduction in bivalve molluscs[J]. *Aquaculture*, 2007, 272(1-4): 76-86.

- [92] Teaniniuraitemoana V, Leprêtre M, Levy P, *et al.* Effect of temperature, food availability, and estradiol injection on gametogenesis and gender in the pearl oyster *Pinctada margaritifera*[J]. *Journal of Experimental Zoology-Part A: Ecological and Integrative Physiology*, 2016, 325(1): 13-24.
- [93] Morales M, Martínez-Paz P, Sánchez-Argüello P, *et al.* Bisphenol A (BPA) modulates the expression of endocrine and stress response genes in the freshwater snail *Physa acuta*[J]. *Ecotoxicology and Environmental Safety*, 2018, 152: 132-138.
- [94] Liu P P, Miao J J, Song Y, *et al.* Effects of 2, 2', 4, 4'-tetrabromodiphenyl ether (BDE-47) on gonadogenesis of the manila clam *Ruditapes philippinarum*[J]. *Aquatic Toxicology*, 2017, 193: 178-186.
- [95] Yang Y Y, Zhou Y Y, Pan L Q, *et al.* Benzo[a]pyrene exposure induced reproductive endocrine-disrupting effects via the steroidogenic pathway and estrogen signaling pathway in female scallop *Chlamys farreri*[J]. *Science of the Total Environment*, 2020, 726: 138585.
- [96] Cai Y F, Pan L Q, Miao J J. Molecular evidence for the existence of an aryl hydrocarbon receptor pathway in scallops *Chlamys farreri*[J]. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, 2016, 196-197: 74-84.
- [97] 曾臻, 倪健斌, 史博, 等. 3 β -HSD基因在福建牡蛎性类固醇激素合成机制中的表达研究[J]. *渔业研究*, 2019, 41(2): 87-95.
- Zeng Z, Ni J B, Shi B, *et al.* Expression of 3 β -hydroxysteroid dehydrogenase gene (3 β -HSD) in steroidogenesis mechanism in the Fujian oyster, *Crassostrea angulata*[J]. *Journal of Fisheries Research*, 2019, 41(2): 87-95 (in Chinese).
- [98] Hathaway R R. Conversion of estradiol-17 β by sperm preparations of sea urchins and oysters[J]. *General and Comparative Endocrinology*, 1965, 5(5): 504-508.
- [99] De Longcamp D, Lubet P, Drosdowsky M. The *in vitro* biosynthesis of steroids by the gonad of the mussel (*Mytilus edulis*)[J]. *General and Comparative Endocrinology*, 1974, 22(1): 116-127.
- [100] Le Curieux-Belfond O, Moslemi S, Mathieu M, *et al.* Androgen metabolism in oyster *Crassostrea gigas*: evidence for 17 β -HSD activities and characterization of an aromatase-like activity inhibited by pharmacological compounds and a marine pollutant[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2001, 78(4): 359-366.
- [101] Zhang G F, Fang X D, Guo X M, *et al.* The oyster genome reveals stress adaptation and complexity of shell formation[J]. *Nature*, 2012, 490(7418): 49-54.
- [102] Zhou J, Zhu X S, Cai Z H. Influences of DMP on the fertilization process and subsequent embryogenesis of abalone (*Haliotis diversicolor supertexta*) by gametes exposure[J]. *PLoS One*, 2011, 6(10): e25951.
- [103] Prisco M, Agnese M, De Marino A, *et al.* Spermatogenic cycle and steroidogenic control of spermatogenesis in *Mytilus galloprovincialis* collected in the Bay of Naples[J]. *The Anatomical Record*, 2017, 300(10): 1881-1894.
- [104] Rosati L, Agnese M, Abagnale L, *et al.* The mussel *Mytilus galloprovincialis* in the Bay of Naples: new insights on oogenic cycle and its hormonal control[J]. *The Anatomical Record*, 2019, 302(6): 1039-1049.
- [105] Lima D, Machado A, Reis-Henriques M A, *et al.* Cloning and expression analysis of the 17 β hydroxysteroid dehydrogenase type 12 (HSD17B12) in the neogastropod *Nucella lapillus*[J]. *The Journal of Steroid Biochemistry and Molecular Biology*, 2013, 134: 8-14.

Review of types and functions of 17 β -HSDs and related research progress in mollusks

ZENG Zhen^{1,2,3}, YU Meishun¹, TAN Qianglai^{1,2*}, SHI Bo^{3,4},
LI Jianbo¹, LI Weijie¹, CAI Guang¹

(1. *Engineering Research Center of Marine Biopharmaceutical Resource of Fujian Province, Xiamen Medical College, Xiamen 361023, China;*

2. *Engineering Research Center of Natural Cosmeceuticals College of Fujian Province, Xiamen Medical College, Xiamen 361023, China;*

3. *State Key Laboratory of Marine Environmental Science, Xiamen University, Xiamen 361102, China;*

4. *Fisheries College of Jimei University, Xiamen 361023, China)*

Abstract: In order to understand the regulation mechanism of 17 β -HSDs on gonadal development and reproductive endocrine of mollusks, this paper has reviewed the types and functions of 17 β -HSDs, classified all the subtypes reported so far, and summarized the cloning, expression, function and mechanism of 17 β -HSDs in mollusks. In spite of some progress made in 17 β -HSDs regulating the reproductive process of mollusks, many underlying problems remain unsolved and further investigations are needed: ① discovering new subtypes of 17 β -HSDs in mollusks; ② analyzing the temporal and spatial characteristics of expression; ③ investigating the structure-activity relationship; ④ clarifying the impact of environmental pollutants and making the corresponding countermeasures; ⑤ guiding the practice and application of aquaculture industry. This review has referred to former research on other species, which offers reference and guidance for further study on the mechanism and application of 17 β -HSDs in regulating gonadal development and reproductive endocrine of mollusks.

Key words: mollusks; 17 β -hydroxysteroid dehydrogenase (17 β -HSDs); sex steroids; reproduction

Corresponding author: TAN Qianglai. E-mail: tanqianglai@xmmc.edu.cn

Funding projects: National Natural Science Foundation of China (31702314); Health Young and Middle-aged Backbone Personnel Training Project of Fujian Provincial Health Commission (2019-ZQNB-21); Program of Department of Education from Fujian Province (JT180661, JAT190849); Foundation for Engineering Research Center of Marine Biopharmaceutical Resource of Fujian Province (XMMC-MBS201901); Foundation for Engineering Research Center of Natural Cosmeceuticals College of Fujian Province (XMMC-NC201901)