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不同物种中*Dmrt1*在性别发育中的功能研究

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摘　要

Dmrt是一个从低等动物到高等动物之间都具有高度保守性且与性别决定和分化密切相关的基因家族。尽管不同物种间性别发育的遗传控制存在差异，但***Dmrt1***已被广泛证实在雄性的性别决定和精巢的性腺分化及维持中行使重要功能。本文重点从***Dmrt***基因家族的分类和***Dmrt1***在不同物种性别发育中的功能研究展开了综述，以期为性别决定基因的分子调控机制和发展人工性别控制育种提供理论依据。

关键词

Dmrt1，性别，基因表达，功能研究

The Function of *Dmrt1* in Sexual Development in Different Species

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Abstract

As a gene family related to sex determination and differentiation, *Dmrt* is highly conserved from lower animals to higher animals. Despite the differences of sex control mechanisms among species, *Dmrt1* has been widely related to male sex determination, testis differentiation and maintenance. This review focused on the classification of *Dmrt* gene family and the functional studies of *Dmrt1* related to gender development in different species, which would probably offer insights into the sex-determination mechanisms and artificial sex-controlled breeding.

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Keywords

***Dmrt1*, Gender, Gene Expression, Functional Research**

1. *Dmrt* 基因家族概述

DMRT (*Double-sex and Mab-3 related transcription factor*)基因具有高度保守的 DM 结构域，其在性别决定和性腺发育的过程中发挥着至关重要的作用[1] [2]。迄今为止，*Dmrt* 基因家族已在哺乳类、鸟类、爬行类和鱼类中均检测到了同源性基因[3]，且大多数基因在性腺中高表达。目前在哺乳动物中，*Dmrt* 基因家族包含 8 个主要亚群，分别为 *Dmrt1~Dmrt8*；在鸡中发现了 3 种 *Dmrt* 家族的基因，分别为 *Dmrt1~Dmrt3*；在爬行类中发现了 *Dmrt1~6* 的家族基因；在大多数鱼类中均可检测到 5 个基因亚群，分别为 *Dmrt1~Dmrt5*，而仅在少部分鱼类中发现了 6 类家族基因，如在亚洲鲈鱼、大口黑鲈、鲶鱼等中发现了 *Dmrt6* 基因[4]。其中，研究最为广泛的 *Dmrt1* 被证实在不同物种中均与雄性性别决定和精巢的发育及维持相关，呈现出一定的进化保守性[5]。

2. *Dmrt1* 基因在无脊椎动物中的性别调控功能

秀丽隐杆线虫是研究最广泛的动物模型之一，其具有 XX/XO 的染色体系统[6]。在基因组预测的 11 个 DM 基因中，*mab-3*、*mab-23* 和 *dmd-3* 三个基因在雄性分化中起着关键作用。研究表明，*mab-3* 抑制与卵黄蛋白产生相关基因的转录，其突变会导致雄性蠕虫中出现卵黄蛋白的合成[7]。交配所需的雄性特异性感觉神经元中基因亦受 *mab-3* 调控，缺失 *mab-3* 的雄性在对雌雄同体的吸引力和交配方面存在缺陷[8]。

3. *Dmrt1* 基因在脊椎动物中的性别调控功能

3.1. 哺乳类

在小鼠中，*Dmrt1* mRNA 可在 10.5 天胚胎的体细胞和两性原始生殖细胞(PGC)的生殖嵴中检测到，随着睾丸开始分化，14.5 天时其在雄性性腺中高度富集[9] [10]。*Dmrt1* 基因在小鼠中并不参与性别决定，但在性腺开始分化后其表达量在卵巢中下降、精巢中上升[11]。在成熟小鼠睾丸的支持细胞中，*Dmrt1* 的缺失会导致 *Sox9* 等雄性偏好基因表达下调、*Foxl2* 等雌性偏好基因异位表达，并诱导支持细胞向卵巢颗粒细胞转化[12]。由此可见小鼠中的 *Dmrt1* 主要是在性腺开始分化后承担促进睾丸的发育和维持的功能。

在人类中，通过 RNA 印迹对 50 个组织样本进行检测，仅在睾丸中发现了 *DMRT1* 的存在[1]。在胎儿发育过程中，可在妊娠第 11 周(GW11)检测到 *DMRT1* 的 mRNA，*DMRT1* 蛋白在 GW10 和 GW20 之间的祖细胞中最丰富，然后大约从 GW24 开始在精原细胞中变得显著，*DMRT1* 也在 GW20 之前的卵母细胞中表达，并在减数分裂时开始下调，在成人睾丸中，*DMRT1* 在支持细胞和精原细胞中均表达[13]。*DMRT1* 位于人类 9 号染色体远端短臂的 9p24.3 区域，该区域的缺失与性腺发育障碍有关，会导致男性出现性腺发育不全[14] [15]、男性不育症[16]和性逆转[14] [17]。

3.2. 鸟类

鸟类是雌性异配雄性同配型(ZW/ZZ)，到目前为止，还没有证据表明雌性特异性 W 染色体上存在卵巢决定基因[18]。研究表明，鸟类的性别决定主要取决于 Z 染色体上的 *Dmrt1* 基因剂量[18] [19]。*Dmrt1* 表达仅限于性腺和缪勒氏管的细胞中，在性别决定后，其在雄性中的表达水平高于雌性[9] [20]。有研究发现 *Dmrt1* 水平的降低会导致遗传型 ZZ 雄性性腺的雌性化[21] [22]，而 *Dmrt1* 的过表达会导致遗传型 ZW 雌性性腺的雄性化[23]。在鸡的胚胎中，*Dmrt1* 在早期雌雄性腺中均表达，但雄性中表现出比雌性更高的表达量。使用 CRISPR-Cas9 得到 *Dmrt1* 突变的雄性 ZZ 鸡中，睾丸发生退化发育成卵巢，并出现典型的颗粒细胞[21]。

3.3. 两栖类

非洲爪蟾的性别决定类型是雌性异配型(ZW/ZZ)，其 W 染色体上有一个 *Dmrt1* 的同源物 *DM-W*，可与常染色体上的 *Dmrt1* 相结合从而阻碍 *Dmrt1* 与其下游基因的相互作用，使性腺向卵巢分化[24]。*Dmrt1* 和 *DM-W* 在蝌蚪的原始性腺和性别决定后期的精巢与卵巢中均有表达，在性别决定早期，*DM-W* 在 ZW 蝌蚪的原始性腺中比 *Dmrt1* 的表达更丰富[25]。*DM-W* 的过表达可诱导 ZZ 蝌蚪向雌性分化，而敲除 *DM-W* 可导致 ZW 蝌蚪的雌性向雄性性别逆转[24] [26]。Abramyan 等[27]通过荧光定量分析发现，在海蟾蜍中 *Dmrt1* 转录本在雄性和雌性的性腺中均表达，在精巢中主要表达于支持细胞中。Shibata 等[28]在 XX/XY 型的粗皮蛙精巢中分离鉴定出了 *Dmrt1* 基因，向 XX 的雌性蝌蚪中注射睾酮，可以使雌性发生性逆转。

3.4. 硬骨鱼类

硬骨鱼类中 *dmrt1* 广泛参与性腺发育并呈现显著的性别二态性表达。青鳉 Y 染色体上 *dmrt1* 基因的同源物 *dmrt1bY* (或 *Dmy*) [29]，被证明是雄性发育的主控因子，类似于哺乳动物中的 *Sry* 基因[30]，*dmrt1* 于青鳉的精巢中特异性表达，外源性雄激素或高温处理会上调 *dmrt1* 的表达，诱导 XX 雌性胚胎发生性逆转[31] [32] [33]。尼罗罗非鱼 *dmrt1* 特异表达于雄性的精巢的支持细胞和体细胞内，*dmrt1* 的缺失会导致 XY 雄鱼的精巢退化，乃至生殖细胞完全丧失[34]。半滑舌鳎具有雌性异配型 ZW/ZZ 的染色体系统，*dmrt1* 位于 Z 染色体上且仅表达于精巢，*dmrt1* 缺失的 ZZ 突变体中雄性偏好基因显著下调，雌性偏好基因显著上调，最终会发育成具有卵巢样睾丸结构的双性鱼[35] [36]。

在斑马鱼、斑点叉尾鮰和大西洋鳕鱼等鱼类中，*dmrt1* 表现出显著的雄性偏好性。斑马鱼的性别主要由常染色体多基因和环境因子互作决定，虽然在精巢和卵巢中均可检测到 *dmrt1* 基因的表达，但其主要富集于精子的发生时期[37]，*dmrt1* 缺失的斑马鱼大部分发育为雌性，少部分发育成不育的雄性并表现出精巢发育不良[38]。*dmrt1* 在斑点叉尾鮰精巢中的表达水平要高于卵巢，经过 17β-雌二醇处理后的 XY 型雄鱼中 *dmrt1* 的表达受到显著性抑制[39]。在大西洋鳕鱼中通过原位杂交技术，发现 *dmrt1* 定位于两性生殖细胞，在未达到性成熟的雄鱼性腺中表达水平最高[40]。在雌雄同体的斜带石斑鱼和雌性先熟的濑鱼中，*dmrt1* 基因的表达量在卵巢向精巢性反转的过程中呈现上升趋势[41] [42]；在雄性先熟的黑鲷中，*dmrt1* 是自然性别逆转的早期分子信号，雌激素会抑制黑鲷精巢中 *dmrt1* 的表达，并致使精巢退化和卵巢发育[43]。

4. 结论

DMRT 基因家族广泛参与了从低等动物到高等动物的性别决定和性腺发育，该家族成员共享的 DM 结构域在不同物种中具有高度保守性，其中 *Dmrt1* 在胚胎发育和性腺的功能维持方面具有重要作用。*Dmrt1* 主要参与雄性的性别决定，在大多数物种的精巢中呈现特异性表达或显著的雄性偏好性，而部分

Dmrt1 的同源物也参与了卵巢的发育，如非洲爪蟾中的 *DM-W*。*Dmrt1* 的缺失在大多数物种中会造成精巢的发育不全乃至出现部分或完全的性逆转现象。对 *Dmrt1* 的研究大多集中在分子特征、表达模式和功能初探方面，关于具体的级联调控机制还需要进行更深入的研究。本文整合了目前国内外关于 *Dmrt1* 基因在无脊椎动物和脊椎动物等不同物种中性别发育中的研究进展，以期为进一步深入研究不同种的性别决定机制和发展人工性别控制单性育种提供了理论指导。

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