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An epigenetic regulatory switch controlling temperature-dependent sex determination in vertebrates

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Most vertebrates present two sexes, and females and males are determined via two diverse strategies including genotypic sex determination (GSD) and environmental sex determination (ESD) (Mei and Gui, 2015; Ma et al., 2016). The most common form of ESD is temperature-dependent sex determination (TSD). Although several master sex-determining genes and their molecular pathways have been elucidated in vertebrates with GSD, the molecular mechanism underlying TSD remains unclear (Bachtrog et al., 2014; Capel, 2017). Recently, the research teams of Drs. Ge and Qian from Zhejiang Wanli University and that of Dr. Capel from Duke University have illustrated this puzzle (Figure 1). Ge et al. have reported that the histone H3 lysine 27 demethylase KDM6B regulates TSD in the red-eared slider turtle *Trachemys scripta elegans* (*T. scripta*) (Ge et al., 2018), thus providing valuable insight into the mechanism underlying TSD.

In the last 5 years, an array of studies on turtle sex determination performed by Ge and Qian have demonstrated that the doublesex and mab3-related transcription factor 1 (*Dmrt1*) gene is a strong candidate for male sex determination in *T. scripta* (Zhang et al., 2016; Ge et al., 2017) and a key regulator of male sexual differentiation in Chinese soft-shelled turtle (*Pelodiscus sinensis*) (Ge et al., 2014; Sun et al., 2015). Recently, Ge et al. have revealed that *Kdm6b* knockdown mutants of *T. scripta* exhibit male-to-female sex reversal in more than 80% of the embryos at 26°C, a temperature at which wild-type offspring develop into males (Ge et al., 2018). The KDM6B protein directly binds to the *Dmrt1* promoter and eliminates H3K27 trimethylation, which activates the transcription of *Dmrt1*. Thus, high expression of *Kdm6b* at male-producing temperature (MPT) activates *Dmrt1* and determines male sex, whereas *Kdm6b* knockdown represses *Dmrt1* and triggers male-to-female sex reversal at MPT. Additionally, *Dmrt1* overexpression is sufficient to rescue the sex reversal induced by the knockdown of *Kdm6b*. These findings indicate that *Kdm6b* is an epigenetic regulatory switch that plays a critical role in male sex determination in *T. scripta* (Figure 2).

Ge and colleagues are the first to identify that the epigenetic regulator *Kdm6b* is responsible for sexual development in *T. scripta* (Ge et al., 2018), although DNA and histone methylation have been previously correlated with TSD and sexual differentiation in painted turtle (*Chrysemys picta*) and *T. scripta* (Matsumoto et al., 2016; Radhakrishnan et al., 2017). Ge and colleagues have also demonstrated that temperature influences the expression of the epigenetic regulator *Kdm6b*, which further regulates the expression of the male determination gene *Dmrt1* (Figure 2) (Ge et al., 2018). However, whether *Kdm6b* responds to temperature directly or via hitherto unidentified upstream temperature-responsive elements remains unknown. Thus, the identification of upstream genes/proteins whose expression/activity is directly

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Figure 1 (Color online) Research groups of Professors Ge and Qian from Zhejiang Wanli University, China and that of Professor Capel from Duke University, USA.

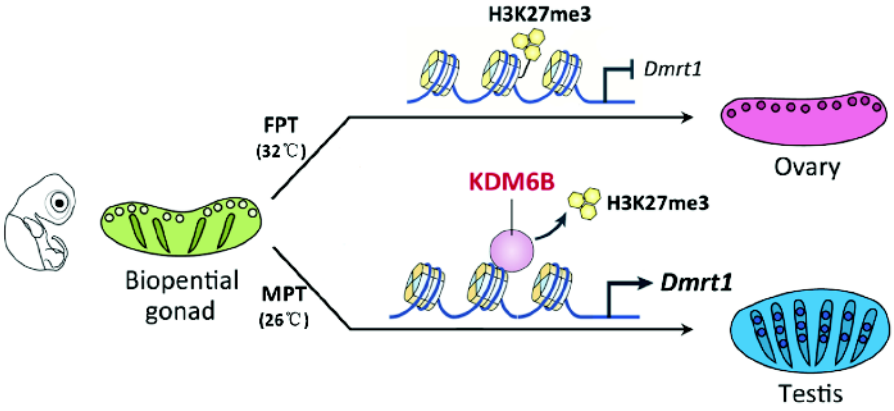

Figure 2 (Color online) Schematic diagram of temperature-dependent sex determination in the red-eared slider turtle *Trachemys scripta elegans*. At female-producing temperature (FPT), the expression of *Kdm6b* is down-regulated. Consequently, *Dmrt1* promoter undergoes H3K27 trimethylation, which suppresses *Dmrt1* expression and leads to female development. At male-producing temperature (MPT), *Kdm6b* expression is up-regulated, and the KDM6B protein demethylates *Dmrt1* promoter, which up-regulates *Dmrt1* expression and leads to male development (This figure is a modification of the original provided by Professors Ge and Qian).

responsive to temperature may help to uncover the molecular mechanism(s) of TSD.

Since the discovery that the ambient temperature during embryogenesis determines the gonadal sex of a lizard species, rainbow agama (*Agama agama*) (Charnier, 1966), TSD has been identified in many fishes (Li et al., 2018), amphibians (Sarre et al., 2011), and reptiles (Holleley et al., 2015). Additionally, the coexistence and transition of diverse sex determination, including GSD and TSD, have been discovered in some species, such as Australian bearded dragon (*Pogona vitticeps*) (Holleley et al., 2015), half-smooth tongue sole (*Cynoglossus semilaevis*) (Chen et al., 2014; Shao et al., 2014), and polyploid gibel carp (*Carassius gibelio*) (Gui and Zhou, 2010; Li et al., 2016; Li et al., 2018). Therefore, sex determination studies focused on these non-model organisms with diverse sex determination strategies will not only advance our understanding of the mechanisms underlying GSD and TSD, but also provide insights into the evolutionary trajectories and consequences of plastic sex determination strategies in vertebrates.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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