<Further Development 6_04>

The Origins of Genitalia

The origins of the cells that give rise to the penis and clitoris have only recently been identified. Moreover, their identity explained such puzzling phenomena such as why snakes have two penises and how the clitoris of hyenas becomes almost as large as the male's penis.

Snake double penises

In amniotes, the beginnings of the external genitalia depend on the cloaca. The cloaca is the embryonic organ that stores and eliminates both solid waste and urine. In birds, reptiles, monotremes, and amphibians, the posterior opening of the cloaca serves as the only opening for the intestinal, urinary, and reproductive urinary. While this cloaca is seen in embryonic mammals, it has no opening to the outside. Instead, it separates into the anus and the urethra, each with its separate opening to the outside world. But it is still important. In all amniotes, including mammals, the cloaca induces the formation of the external genitalia (Tschopp et al. 2014; Herrera and Cohn 2014).

The external genitalia begin as paired swellings of cells, the genital tubercles, on either side of the cloacal membrane. Labeling experiments have shown that lateral plate mesoderm is the source of the genital tubercle cells. These are tail cells in the mouse, tail and limb bud cells in the chick, and limb bud cells in the lizard.

The reason why different groups of mesoderm cells are being recruited for genitalia formation in different groups of amniotes has to do with the location of the cloaca. The cloaca forms in different places in different groups of amniotes. In mice, the cloaca extends caudally past the hindlimbs, so the genital tubercles are posterior to the limbs. In snakes, the genital tubercle is at level of hindlimb buds. In chicks, it extends between the limb bud and tail. And if a cloaca is transplanted into a chick embryo at different sites, the lateral mesoderm cells at that site will be recruited into the genital tubercle (Tschopp et al. 2014). In the chick and mice, the two genital tubercle cell populations fuse ventrally as the closure of the body wall brings the right and left sides of the embryo together (Figure 1). This allows the formation a single genital organ. In snakes, however, the limb bud cells are "re-purposed" as genitalia and remain near the sides.

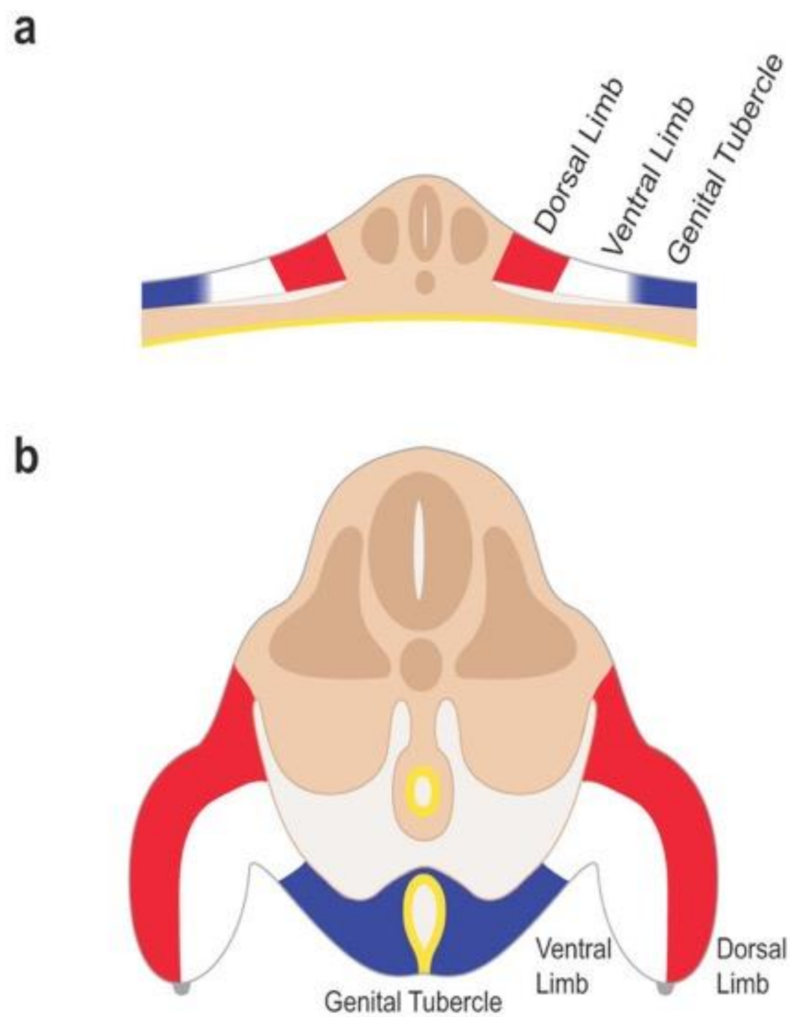

Figure 1 Fate mapping of chick cells using vital dyes showed that the genital tubercle formed from cells involving the ventral limb bud and tail. (After Herrera and Cohn 2014.)

Thus, the cloaca acts as the signaling center for genitalia by secreting sonic hedgehog (Shh) and Fgf8 paracrine factors (Haraguchi et al. 2001). In the tail, this causes an epithelial-to-mesenchymal transition in the lateral mesoderm, and its migration to the ventral region.

So now you know why snakes don't have limbs. They've been recruited to form its two copulatory organs. The two penises of the snake are called hemipenes**.** Both are usually functional, but not at the same time.

The baculum

The similarity between limbs and genitalia is strengthened by molecular findings. Just as there is a series of bones in the limbs, most mammals (but not humans) have bones in their genitalia. The os clitorides (in the female) and the os penis (or baculum, in the male) are retractable bones that give hardness to the copulatory organs. It is characteristic of rodents, carnivores, bats, and primates. It probably serves different functions in different organisms, providing stiffness in dogs, sexual stimulation of partners, and protection of the urethral opening during intercourse (Herdina et al

The development of the rodent baculum is regulated by the posterior members of the HoxD set of transcription factors (Zákány et al. 1997) which appears to be induced by members of the TGF-b1 and BMP families (Origuchi et al. 1998). Indeed, the Hox genes expressed in the baculum appear to be the same as those in the distal portion of the limb. The fingers and the baculum share several enhancers (Lonfat et al. 2014).

It is not known why or how human males lost the baculum. Male gorillas, chimps, and bonobos have this bone. It is probable, given the healing fractures found in walrus bacula (oosiks), that such a bone became a liability when humans took an upright posture. The male spider monkey, which also stands erect, also lacks a baculum. A Biblical scholar and a developmental biologist (Gilbert and Zevit 2001; Zevit 2013) independently came to the conclusion that the writers of the Bible were referring to the baculum, not a rib, when discussing the generation of Eve in *Genesis* 2:21–23.

Cloacal kisses

Male birds differ enormously in their external genitalia. Indeed, one of the biggest differences between chickens and ducks is the sizes of the penises. Chicks don’t really have an external phallus, and this is especially puzzling when compared to the prodigious penises of ducks and geese (Figure 2; McCracken et al. 2001). But chicks are the norm. Less than 5% of male birds have phalluses capable of intromission. Rather, most birds transmit sperm through a “cloacal kiss,” wherein sperm collected in the cloacal opening of the male is transferred to the cloacal opening of the female, who positions herself and extends her vagina.

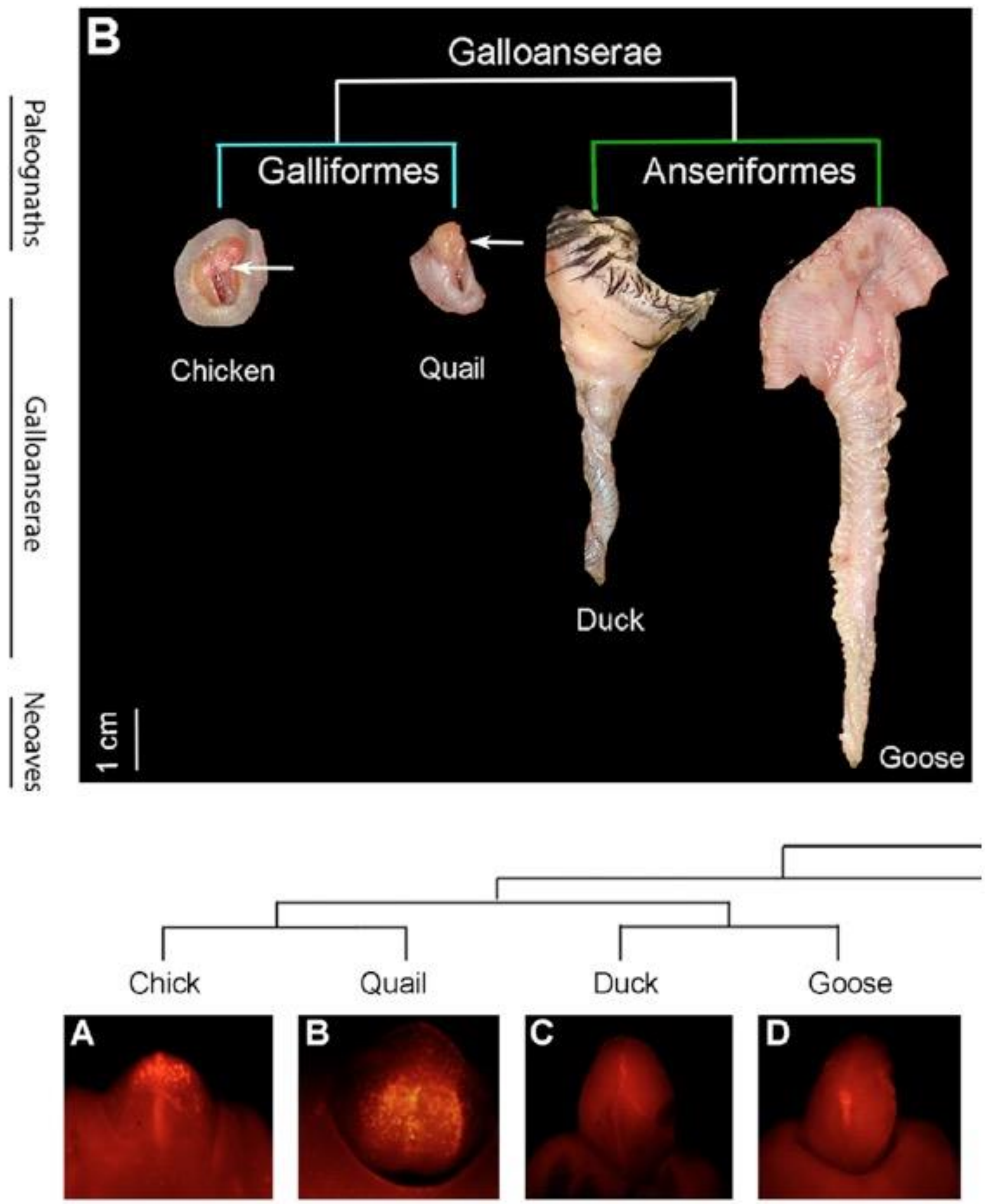

Figure 2 Penis development in birds. Like most birds, chickens and quails have severely reduced penises that are incapable of intromission. Ducks and geese, however, have larger penises. The mechanism for shortening the chick and quail penis is BMP4-induced apoptosis. The bottom figures stain the apoptotic cells red. (After Herrera et al. 2013.)

The agent that is shortening the chick phallus is BMP4 (Herrera et al. 2013). Just like in the limb bud, it induced apoptosis of cells in the genital tubercle. Chicks and ducks initiate their genital tubercle formation similarly, but after then initial extension, the chick genital tubercles stops growing and regresses. BMP4 is found in the chick (and not duck) genital tubercle cells at this stage, and the addition of BMP inhibitors (such as Noggin) to chick genital tubercles prevents apoptosis and allows their extension.

The clitoris of the spotted hyena

Usually, one of the first actions of testosterone on the indifferent (ambisexual) genital tubercle is to specify its identity as a penis (Rodriguez et al. 2012). Subsequently, androgens extend the growth of the genital tubercle. However, things are different in the spotted hyena. In the spotted hyena (*Crocuta crocuta*), the clitoris is almost as long as the penis and extends outside the body. Spotted hyenas are the only mammals in the world that mate and give birth through its clitoris, and female hyenas have no external vaginal opening (Figure 3).

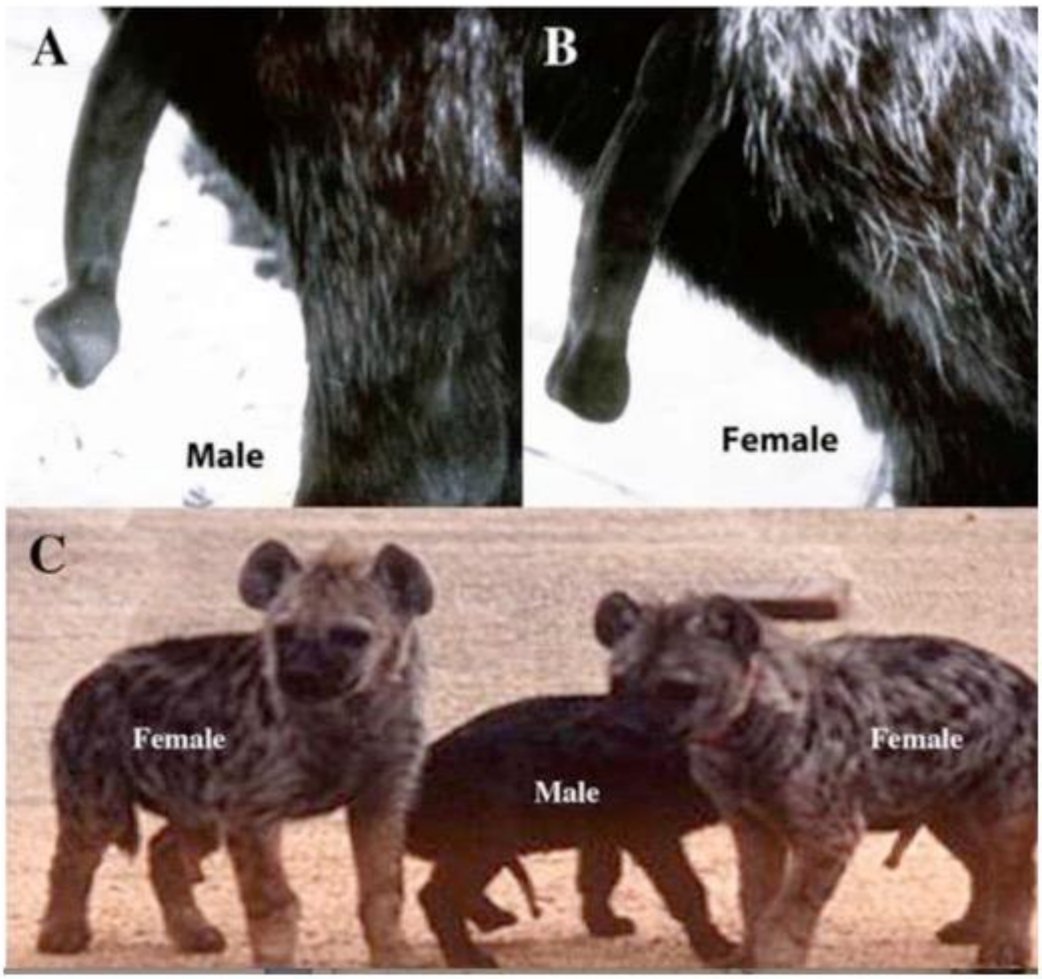

Figure 3 The adult erect hyena penis (A) and clitoris (B). While both are large and extend from the body, they can be recognized by the distinctive shapes at the tip. (C) Three infant spotted hyenas (3-4 months old) in full erection. (From Cunha et al. 2014.)

In this species, the growth of the penis and clitoris is not dependent on testosterone (or any other androgen, so far as anyone can tell), although some anatomical differences at the tip of each are testosterone-mediated, and estrogen is needed for proper development, as well (Cunha et al. 2014).

It seems that the genital tubercle has the potential for significant growth in both sexes. The mechanism for this remains unknown.

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