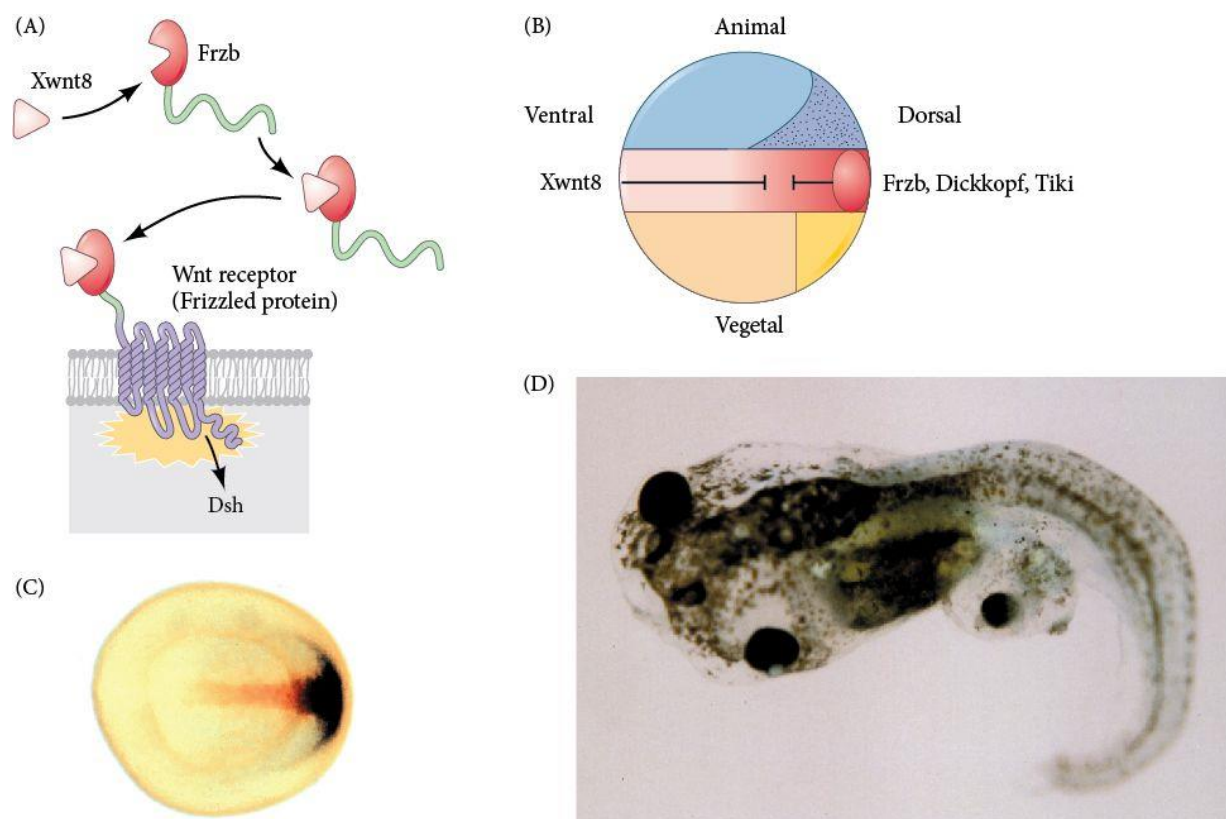


Frzb, Dickkopf, Notum, and Tiki: More Ways to Block Wnts

Shortly after the attributes of Cerberus were demonstrated, two other proteins, Frzb and Dickkopf, were found to be synthesized in the involuting endomesoderm. Frzb (pronounced “frisbee”) is a small, soluble form of Frizzled (the Wnt receptor) that is capable of binding Wnt proteins in solution (Figure 1A, B; Leyns et al. 1997; Wang et al. 1997). Frzb is synthesized predominantly in the endomesoderm cells beneath the prospective brain (Figure 1C). If embryos are made to synthesize excess Frzb, Wnt signaling fails to occur throughout the embryo; such embryos lack ventral posterior structures and become “all head (Figure 1D).” The Dickkopf (German, “thick head,” “stubborn”) protein also appears to interact directly with the Wnt receptors, preventing Wnt signaling (Mao et al. 2001, 2002). Injection of antibodies against Dickkopf causes the resulting embryos to have small, deformed heads with no forebrain (Glinka et al. 1998).



A from T. Bouwmeester et al. 1996. *Nature* 382: 595-601, courtesy of E. M. De Robertis. B and C after L. Leyns et al. 1997. *Cell* 88: 747-756. From L. Leyns et al. 1997. *Cell* 88: 747-756, courtesy of E. M. DeRobertis.

Figure 1 Inhibiting Wnt signaling enables head formation. (A) Frzb protein is secreted by the anterior region of the organizer. It must bind to Xwnt8 before that inducer can bind to its receptor. Frzb resembles the Wnt-binding domain of the Wnt receptor (the Frizzled protein), but Frzb is a soluble molecule. (B) Xwnt8 is made throughout the marginal zone. (C) Double in situ hybridization localizing Frzb (dark stain) and Chordin (reddish stain) messages. The *frzb* mRNA is transcribed

in the head endomesoderm of the organizer, but not in the notochord (where *chordin* is expressed). (D) Injecting *cerberus* mRNA into a single D4 (ventral vegetal) blastomere of a 32-cell *Xenopus* embryo induces head structures as well as a duplicated heart and liver. The secondary eye (a single cyclopic eye) and olfactory placode can be readily seen. *Xwnt8* is capable of ventralizing the mesoderm and of preventing anterior head formation in the ectoderm.

Two other organizer proteins, Tiki and Notum, have recently been found to bind to Wnt proteins during gastrulation. Tiki not only prevents Wnts from binding to their receptors, it cleaves the Wnt to render it nonfunctional. Tiki is synthesized primarily in the anterior regions of the organizer and is crucial for head formation in *Xenopus* (Zhang et al. 2012.) And to make certain that Wnt doesn't stop brain development, the ectoderm itself makes a membrane-tethered Wnt inhibitor, Notum, that acts by removing the lipid moiety that keeps the Wnt proteins from forming inactive dimers with one another (Zhang et al. 2015).

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