Retinoid signaling determines germ cell fate in mice

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In a mouse embryo, germ cells migrate into the developing gonads at approximately 10 – 11 days post coitum (dpc) where they continue to divide mitotically until about 13.5 dpc. At that time, germ cells cease division and, in a female gonad, begin meiosis or, in a male gonad, arrest in G0/G1. Various studies have suggested that entry into meiosis is cell-autonomous and occurs spontaneously unless germ cells are situated in a male gonadal environment. Accordingly, it is postulated that somatic cells of the developing male gonad secrete a meiosis inhibitory factor. Recently it was demonstrated that XX germ cells enter meiosis in an anterior to posterior wave along the length of the female gonad. This finding suggests that, contrary to the well-accepted theory, entry into meiosis is an induced event rather than a spontaneous one. We show that the mesonephros, which lies adjacent to the developing gonad, is a potent source of retinoic acid in both sexes and that the retinoic acid degradation enzyme, CYP26B1, is expressed in somatic cells of the male gonad only. By treatment of gonadal explants, we show that either retinoic acid or an inhibitor of CYP26B1 is able to induce XY germ cells to enter meiosis. Conversely, a retinoic acid receptor antagonist blocks entry of XX germ cells into meiosis. CYP26B1-null XY embryos show strongly up-regulated markers of meiosis in the gonad suggesting that their germ cells are entering meiosis prematurely. These results strongly suggest that retinoic acid, produced by the mesonephros, induces germ cells in the female gonad to enter meiosis but is prevented from doing so in the male gonad because of the actions of CYP26B1. We postulate that the anterior to posterior wave occurs because retinoic acid enters the gonad predominantly through mesonephric tubules that connect the mesonephros with the anterior end of the gonad only.