VIEWS ON THE GENE e (EYELESS)

Robert Cuny
Department of Anatomy
University of Saskatchewan
Saskatoon, Saskatchewan
Canada S7N OWO

Humphrey (1969) described the genetics of the e mutation of the axolotl (Ambystoma mexicanum Shaw). The allele is single locus, autosomal, nonlethal and recessive. Partial penetration occurs in animals heterozygous for e and r, or e, r, and x Phenotypic features include (1) lack of eyes in the adult, (2) sterility, and (3) freckled skin pigmentation. Using transplantation, Van Deusen could show that the sterility is a consequence of a primary failure in the mutant e hypothalamus. Epp and Van Deusen demonstrated further that freckled pigmentation is caused by an overproduction of melanocyte-stimulating hormone, due to insufficient secretion of inhibiting factor by the hypothalamus. Wild type eye implantation corrects pigmentation but not sterility. Eagleson revealed deficiencies in gonadotropin-releasing hormone releasing hormone and PAF+ stainable material in the hypothalamus, whereby the primary defects were chiefly localized in the posterior hypothalamus. The visual functioning of implanted wild type eyes in gene e hosts was demonstrated by Epp, Hibbard, Ornberg, Schwenk and Harris, using optokinetic drums, autoradiography and eletrophysiological recording. Although the optic nerve enters the brain at novel ectopic sites, Harris showed that the nerve endings home in the visual cortex of the tectum in register with the retinal map, independent of the somatosensory map. Gruberg and Harris reported that serotonergic somatosensory nerve endings reach the surface of the mutant e tectum, due to the absence of of the cholinergic visual cortex. The visual cortex was restored by wild type eye implantation. Therefore, the mutant e tectum is not directly targeted by the gene e.

Several tissues participate in eye formation and interact via growth factors. Briggs and Van Deusen asked whether the optic area is correctly stimulated in the neural plate by the underlying prechordal plate mesoderm. Blastula roof transplantation demonstrated that the mutant e mesoderm is fully capable of the stimulation of the optic area in the neural plate. Van Deusen's results placed the mutant e defect with the head ectoderm, and Brun investigated whether the retina-forming neural plate or perhaps the lens-forming head epidermis are directly affected by the gene e. Due to the use of advanced embryonic stages, his results remain conflicting. Cuny and Malacinski cultured neural plate and head epidermis of very early neurulae as sandwiches. The evidence suggests that the gene e focuses upon the developing retina, while the head epidermis could function normally. Van Deusen and Eagleson pointed out that both the retina and the hypothalamus and derived from the same, possibly clonal cell population in the anterior neural plate.

Eye morphogenesis is normal in the mutant e until the early optic vesicle, Rabl stage 1a, at Harrison's whole body stage 29-32. However, cell division slows down thereafter, becames irregular, and the retinal cell mass becomes thus chaotic. Some pigmented retinal cells differentiate. This suggests that the differentiation of at least some retinal cell types is not directly blocked by the gene e. Ulshafer and Hibbard noted that the basal lamina matures very early in the mutant, which might be the cause, or a consequence of the eyeless defect. The rarely seen tiny lenses are normal in shape. The late immigrating head mesenchyme pushes them either close to the retina or close to the epidermis.

The cellular defect in the mutant e retinal cells is not yet known; however, retina cell survival improves upon immersion in a wild type environment. Van Deusen injected cells of the mutant e blastula roof into

albino host blastulae. He obtained patches of pigmented neural retina in the albino eyes. Brun implanted embyronic mutant eyes under the flank epidermis and still observed a high proportion of surviving eyes around hatching time. Implantation of wild type tissues on the contralateral body side improves eye development on the ipsilateral body side, according to Brun.

In the future, it will be important to determine which retinal cell types are a primary target of the gene e. The cell lineage of retinal and hypothalamic rudiments in the mutant is also a promising project. Harris elegantly uses the eyeless axolotls to investigate nerve guidance in the brain. It would be most urgent to isolate the e gene, analyze its structure by sequencing, determine its chromosomal location by in situ hybridization, and to study the role of its transcripts and protein products.