No evidence for a genetic blueprint: The case of the "complex" mammalian photoreceptor

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Despite the intensity of the search for genes causing inherited retinal degenerations over the past 3 decades, of the approximately 200 disease genes identified to date, all appear to be ordinary housekeeping genes specifying proteins playing basic structural and functional roles in the mature photoreceptor cells. No genes or genetic elements have been identified which can be construed as having a specific morphogenic role, directing the development of the cytoarchitecture of any particular retinal cell. The evidence suggests that the cytoarchitecture of the retinal photoreceptors, although enormously complex, arises from the self-organization of the cells constituents without any regulation or direction from an external genetic blueprint.

Key words: Emergence, genetic blueprint, photoreceptor, retina, retinal genetics

The retina is a very complex organ consisting of a number of highly characteristic neurons arranged in several layers forming the typical laminated retinal structure,[1,2] which is almost invariant in all mammals and is very similar in all vertebrates.[3,4] The individual retinal cell types are among some of the most complex of cells in the body. The photoreceptors that make up most of the outermost layer of the retina (outermost being the furthest from the front of the eye) are highly modified for the photoreception and are particularly complex. The rod photoreceptors are elongated cells, some 50 microns long,[1] consisting of several different segments: A columnar "outer segment," about 24 microns long and 2 microns in diameter,[5] made up of a stack of 1300–1500 bilayer lipid discs,[1] containing the photoreceptor pigments; this outer segment is connected via a specialized cilium to the "inner segment" containing among other organelles, ribosomes, mitochondria and Golgi apparatus. The inner segment is in turn connected to a nuclear region containing the nucleus that terminates in a synapse that connects the photoreceptor with another retinal neuron, the bipolar cell.[2]

The belief that complex organic forms including specific cell types like the retinal photoreceptors are specified in genetic programs or blueprints encoded in the genome has been one of the defining axioms of 20th century biology. But as we show here, despite the intensity of the search for genes causing defects in retinal cell form and function, over the past three decades, there is to date little evidence that the cytoarchitectures of these extraordinarily complex cells are assembled under the direction of anything resembling a genetic blue print.

The Genetics of the Photoreceptors

Thirty years ago virtually nothing was known of the genetics of the retina, and none of the genes responsible for any of the various inherited pathologies of the retina in man had been identified. But since 1980 a veritable zoo of more than 200 genes causing human retinal pathologies (Retnet, http://www.sph.uth.tmc.edu/Retnet/) have been identified and with the possible exception of the erythrocyte, the genetics of the photoreceptors have been more intensively studied than any other body cell.[6]

These disease genes cause a vast diversity of abnormalities affecting every aspect of photoreceptor cell form and function.[2,6] Many of these mutations effect photo transduction function and lead to secondary degenerative changes in the forms of the cells. In many cases of retinitis pigmentosa, for example, the degenerative changes in the photoreceptors may lead to a secondary loss of outer segments and a "rounding up" of the cells.[7,8] Other mutations cause primary morphological defects in the photoreceptors, particularly in the cilium and outer segments. For example, mutations in the RDS gene (peripherin) cause disorganized outer segment lamellae.[9] Similarly mutations in the RP1 gene lead to incorrectly oriented outer segment discs that fail to stack properly.[10] Again mutations in the prominin gene cause grossly overgrown and disorientated discs.[11] Mutations in genes specifying proteins associated the connecting cilium such as retinitis pigmentosa GTPase regulator (RPGR)-interacting protein and RPGR also cause grossly oversized discs.[12] Another gene causing retinal degenerative disease Mak (male germ cell associated kinase) regulates retinal photoreceptor ciliary length and sub compartmentalization. Mak is localized both in the connecting cilia and outer-segment axonemes of photoreceptor cells. In the Mak-null retina, photoreceptors exhibit elongated cilia and progressive degeneration.[13]

An Absence of Morphogenes

Remarkably among these 200 or so genes known to cause retinal pathologies very few (if any) have been identified which might be construed to be anything more than ordinary structural or functional components of the mature photoreceptor. There is no genetic evidence that any of the genes expressed in the photoreceptors causing dysmorphologies are morphogenes in Franklin Harold's sense[14,15] that is, genes whose primary function is directing or supervising the deployment of the constituents of the photoreceptors into their complex three-dimensional native cellular architectures. As in the case of the red cell (see accompanying paper),[6] all mutations identified to date, which cause dysmorphologies appear to cause defects in ordinary or "mundane" structural and functional components of the mature photoreceptor!

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Discussion

Given the complexity of these remarkable cells and the fact as mentioned above that the genetics of the photoreceptors have been the subject of intensive study,[6] this is an important finding, which has not been reported before and which provides significant support for the growing consensus among cell biologists that cell forms arise mainly from the self-organization of their constituents rather than by instruction from a detailed blueprint in the genome.[16-19]

We conclude that the native cytoarchitecture of the photoreceptors is essentially epigenetic structures arising from the spontaneous self-organization of the material constituents of the cells themselves, a conclusion consistent with the developing "epigenetic self-organizational paradigm" in cell biology. While in the case of the far simpler red cell some of the emergent biophysical causal factors have now been identified,[20] many additional studies will need to be carried out before the emergent biophysical and biomechanical forces responsible for the morphogenesis of more complex cells are understood.

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