The phagolysosomal system of the pigment epithelium. A key to retinal disease

New concepts of the nature of certain retinal diseases are emerging since the discovery by Young in the late 1960's that the photoreceptor outer segments are continually renewed, and that the pigment epithelium is responsible for removing the terminal rod outer-segment disks. The recent demonstration in the monkey eye that each retinal rod produces 80 to 90 disks per day, that the entire complement of outer-segment disks is replaced every 9 to 13 days, and that each pigment epithelial cell engulfs and destroys about 3,000 disks every day, gives us an awesome new outlook on the biology of the retina.

The pigment epithelial cell must have a highly developed phagocytic-lysosomal system in order to digest these enormous amounts of exogenous material daily for 70 or more years. Unlike the phagocytic cells of the reticuloendothelial system, the pigment epithelium has a low rate of mitosis and remains in situ for a lifetime. The biologic implications of these facts are that a pigment epithelial cell suffering from over-engorgement or indigestion cannot escape with its burden to the liver or spleen, nor can it readily divide the load by undergoing mitosis. Herein may reside the pathogenesis of certain retinopathies in the aging eye.

The mechanisms of phagocytosis and lysoosomal digestion have been studied in some detail in leukocytes and macrophages.

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Engulfment of exogenous material is initiated by interactions between the exogenous particle and recognition sites on the cell surface. Engulfing movements are affected by contractile, actin-like proteins (microfilaments) in the cytoplasm. A larger fiber system, the microtubules, may also be involved in this, or in the movement of lysosomes. Once the particle is enclosed in the phagocytic vacuole (now called a phagosome), primary lysosomes fuse with the vacuole. (Primary lysosomes contain lytic enzymes that were synthesized on ribosomes of the endoplasmic reticulum and transported to the Golgi apparatus where they matured and pinched off into vesicular packages.) Upon delivery of the enzymes, the pH of the phagocytic vacuole falls and digestion of the contents begins. The phagosome is now called a phagolysosome or a secondary lysosome. As digestion of macromolecules proceeds, small molecules diffuse through the membrane into the cell sap and the size of the phagolysosome diminishes, theoretically, to zero. Undigestible or slowly digestible substances may be seen in the cell long after the phagocytic event in structures called residual bodies. These fluorescent pigmented granules, common in heart, brain, and pigment epithelium, are called lipofuscin in the pathology literature. Nonmotile cells may eventually eject some residual bodies by exocytosis or cell defecation. (Some components of drusen arise via this process.)

We do not know whether the pigment epithelium follows this general scheme in the phagocytosis and digestion of rod outer-segment disks, or whether, owing to its origin, position, life-expectancy, nature of the engulfed particles, etc., modifications or specializations have been built-in to certain steps of the process. Pigment epithelial cells will phagocytose carbon particles and latex beads introduced into the interphotoreceptor space, therefore, the phagocytic mechanism is not specific for outer-segment disks.

Very little is known about the lysosomal enzymes of the pigment epithelium. Acid phosphatases and aryl sulfatase have been demonstrated by enzyme histochemistry in various lysosomal particles and in the Golgi complex of human and animal pigment epithelial cells. A more direct approach to the identification and quantitation of lysosomal capabilities is via analyses of homogenates of isolated pigment epithelial cells and of their subcellular fractions. Acid lipase, a lysosomal enzyme that could hydrolyze the abundant phospholipid components of the outer-segment disks, occurs in bovine pigment epithelial cell homogenates with much higher specific activity than in standard liver homogenates.

In contrast, activities of N-acetyl-glucosaminidase, an enzyme that may cleave the sugar chain of rhodopsin, and of acid phosphatase are considerably lower. The proteases utilized in the hydrolysis of effete rhodopsin molecules have not been characterized as yet.

Numerous genetic anomalies are recognized in man wherein deletions of enzymes from the lysosomal complement result in disease, e.g., the mucopolysaccharidoses, gangliosidoses, etc. It can be expected that the lysosomal system of the pigment epithelium is heir to enzyme defects also, and that hitherto unrecognized inadequacies of the ocular digestive system may be the primary event in some retinal pathologies. In some lysosomal storage diseases such as Hunter's or Hurler's syndrome, a patient's fibroblasts can be "cured," in vitro, by addition of the missing enzymes. The defective cells will phagocytose exogenous corrective enzymes and when the phagosome fuses with the defective lysosomes the accumulated indigestible material is hydrolyzed, just as it would have been with normal endogenous enzymes. This suggests a promising approach to correction of defects in the phagolysosomal system.

Phagocytosis of undigestible particles, e.g., uric acid crystals in gout, by leukocytes and macrophages, causes regurgitation of lysosomal enzymes into the extracellular
space thereby initiating tissue destruction and acute inflammation. Similar leakage, if it occurs at any time during phagocytosis by the pigment epithelium, probably results in digestion of the interphotoreceptor matrix and could give rise to focal retinal detachment and other destructive sequelae.

The anti-inflammatory capabilities of the corticosteroids are thought to be due largely to their well-documented stabilizing effect on lysosomal membranes. Recent experiments showing inhibition by catecholamine of the osmotic release of enzymes from lysosomes, and acceleration by cholinergic agents, suggests that the autonomic nervous system may modulate phagocytic and digestive functions of some cells. If specific retinopathies can be traced to the phagolysosomal system of the pigment epithelium, the basic tools are at hand for modifying the activity of this system.

Investigations have been conducted to determine whether some abnormality of the photoreceptor renewal-removal mechanism could account for retinal dystrophies. An autoradiographic study of protein synthesis and movement in the dystrophic Royal College of Surgeons (RCS) rat showed that the rate of production of outer-segment material was normal, but the removal mechanism was impaired. This resulted in an abnormal accumulation of disarranged outer-segment lamellae by three weeks of age, followed by disintegration of the whole photoreceptor layer within one to two months. The pigment epithelium of normal rats begins removing outer-segment disks even before the outer segments reach their adult length, i.e., at about 13 days. In the RCS rats, phagosomes were never seen within the pigment epithelial cell. It was concluded that the dystrophy was due to the failure of the pigment epithelium to remove the effete disks. Further studies by this group indicate that the pigment epithelium of the RCS rat will phagocytose substances other than outer-segment disks, e.g., carbon, latex, and thorium. This implies that the recognition sites at the surface of the outer segment, those that signal "time to destroy," are absent or defective.

The terminal histologic picture in human retinitis pigmentosa resembles that of the RCS rat. This, along with limited physiologic and biochemical data suggests that the animal disease may have a pathogenesis similar to the human disease. Further aspects of the cell biology of the RCS rat retina are, therefore, under investigation in a number of laboratories.

The clinical efficacy of trying to slow down the rod outer-segment renewal rate in patients with retinitis pigmentosa and/or conserve the limited ability of the pigment epithelium to process large quantities of disks is being assessed by occluding one eye for a period of time. This therapeutic approach rests on the premise that the dynamics of the renewal-removal mechanism is affected by the amount of light. In vitamin A-deficient animals daily exposure to light results in a decline in the rhodopsin content of the retina. Normal animals kept in the dark increase the rhodopsin content of their retinas. In animals depleted of vitamin A, a normal electroretinogram and rhodopsin content can be maintained for five to six months if they are kept in the dark. If retinitis pigmentosa really is a disease of disturbed vitamin A-rhodopsin metabolism, "dark rest" of the retina may be efficacious. It is also well established that in normal animal eyes excessive light causes disintegration of outer-segment disks and that the pigment epithelium is subsequently burdened with abnormal quantities of phagocytosed debris; therefore, if the defect in retinitis pigmentosa proves to be primarily in the pigment epithelial cell, reduced levels of light may prolong the functional capabilities of these cells. Transient decrease in the b-wave of the electroretinogram following months of light deprivation indicates that processes occurring proximal to the photoreceptor are affected and must also be considered in the assessment of this therapy.

Retinitis pigmentosa has been cited as an
example of how new knowledge of the function of the pigment epithelium can be applied to clinical investigations of pathologic processes. There are many others to challenge the combined efforts of basic science and clinical investigators.

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