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Cell death in age-related macular degeneration

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The cellular and molecular mechanisms underlying the death of photoreceptors and other retinal cells in age-related macular degeneration (AMD) remain poorly understood. Some of the questions for which answers need to be sought, and which are explicitly or implicitly addressed in this article include: (1) how do patterns of cell death in AMD compare, qualitatively and quantitatively, with "normal" cell death in aging retinas, and with cell death in retinitis pigmentosa (RP) and its animal models; (2) is apoptosis involved in AMD; (3) is there any evidence that rods are necessary for cone survival; (4) if the answer is yes, is there evidence that rods produce one or more survival-promoting factor(s) that act directly on cones; (5) are the effects of rods upon cones exclusively mediated by diffusible factors, or do they also involve contact-mediated interactions; (6) is there any evidence that photoreceptors regulate the survival and/or function of RPE and Müller cells, as well as the interactions between these cells and cones; (7) are trophic factors and their receptors in the macula different from those in other parts of the retina; and (8) are toxic mechanisms involved in the onset and progression of cell death in AMD? Clear cut answers to most of these (and related) questions about cell death in AMD are not yet available. The goal of this article is to summarize discussion that should help in the formulation of suitable hypotheses, amenable to experimental analysis. To provide a platform for such discussion, we present an overview of progress made in recent years in the analysis of other retinal degenerations and of neuronal degenerations in other regions of the CNS. We conclude with an overview of concepts and speculation derived from our current research.

Transgenic Models of Amyotrophic Lateral Sclerosis and Alzheimer's Disease

The human neurodegenerative diseases, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), are adult-onset, chronic, progressive disorders whose clinical features reflect the vulnerability of specific populations of neurons in each disease. In ALS, weakness and atrophy reflect dysfunction/death of motor neurons; in AD, memory loss and dementia are the result of neurofibrillary tangles, amyloid deposits, and death of neurons in cortex and hippocampus. Subsets of cases of familial ALS (FALS) and AD (FAD), often show dominant inheritance: some cases of FALS are linked to mutations in the superoxide dismutase I (SOD l) gene; and some pedigrees with FAD exhibit mutations in genes encoding either the amyloid precursor protein (APP) or the presenilins (PS l and PS2). The biology of these mutant transgene products has been clarified by recent in vitro and in vivo studies. In vitro, some mutant SOD 1 transgene products show normal enzyme activity, yet kill cells, presumably, by the acquisition of neurotoxic properties. In vitro studies have provided new information about the topology and processing of APP and effects of mutations of APP and PS 1 on amyloidogenesis. However, the most exciting advances have come from transgenic strategies that have been used to reproduce features of these human disorders in mice. In these models, investigators have begun to define the character, spatial/temporal evolution, and mechanisms of cellular pathology as well as the biochemical bases for the gain of toxic properties associated with the presence of these mutant transgene products. Transgenic mice with SOD1 mutations develop weakness and muscle atrophy associated with a variety of degenerative changes in motor neurons that result from the acquisition of toxic properties by mutant SOD1. Similarly, transgenic mice that express mutant human FAD-linked genes show behavioral impairments and cellular abnormalities, including senile plaques (i.e., amyloid deposits and dystrophic neurites). The results of these studies indicate that, in mouse models of FALS and FAD, the mutant transgene products lead to a cascade of events that damage subsets of nerve cells. These transgenic models are not only proving of great value for investigations of disease mechanisms, but they are being used to design and test novel therapies that, if effective in model systems, can be rapidly introduced into clinical trials.

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Interdependence of Photoreceptors in Retinal Degenerations

Since 1990, many mutations that cause retinitis pigmentosa (RP), a major model of retinal degeneration, had been identified. In 1993, several groups demonstrated in different mu-

rine models of RP that rod photoreceptors die by apoptosis. Although apoptosis may be the final common pathway of rod degeneration in RP [1], the mechanisms by which mutations may lead to apoptosis remain unknown. In spite of the scientific progress made in the last decade, an effective treatment for RP remains elusive.

Even without full knowledge of the pathogenic mechanisms of the mutations, one might consider apoptosis as a potential target of therapy. For cells in general, it is believed that some of the signals leading to apoptosis may be intimately associated with signals to divide. Therefore, long-term inhibition of rod photoreceptor apoptosis, even if such an intervention can be found, carries the risk of undesired cell proliferation. Thus, the value of this approach to treat RP still needs to be established.

The "sequential model" of RP pathogenesis, which begins with the cell's specific expression of a mutant gene, resulting in the presence of a defective protein (or the lack of a normal functional protein) which in turn leads to apoptosis, only deals with some of the underlying pathogenic mechanisms leading to retinal degeneration. As shown by the results from experiments with chimeric mice [2,3], cell-to-cell interactions play a critical role in retinal degeneration caused by a mutation. These results illustrated nonautonomy of gene action and clearly demonstrated the concept that in RP, the mutations act as if they trigger some retinal processes that ultimately lead to degeneration of rod and cone photoreceptor as well as other retinal cells [4]. Therefore, a new conceptual model of RP pathogenesis is needed to provide a framework to address these unknown retinal processes, which include the mechanisms leading from a rod-specific mutation to cone photoreceptor death. Questions derived from the expanded conceptual framework, regarding the potential interdependence of retinal cells, are particularly relevant to therapeutic research.

To provide an ideal animal model for the implementation of this strategy, a transgenic pig model of RP was created [5-7]. Transgenic pigs that express a mutated rhodopsin gene (Pro347Leu) illustrate some important features of the broader concept. Like RP patients with the same mutation, which genetically is a rod-specific defect, these pigs have early and severe rod loss; however, many cones survive the initial phase of photoreceptor death; nevertheless, these cones continue to degenerate. The persistence of functional cones in the transgenic pigs over an extended period, more than a year, suggests that the later phase of cone degeneration may be independent of the direct effects of the initial disease-inducing mutation, and thus implicates a more direct role for other retinal mechanisms. Since there are many RP-inducing mutations that via potentially different mechanisms cause photoreceptor death, the mechanisms causing degeneration of the residual cones, therefore, may make a common target for therapy. The hypothesis that cones, perhaps more than rods, should be the focus of therapeutic intervention has been suggested by scientists; the Pro347Leu transgenic pigs, on the other hand, have illustrated it.

In addition to the Pro347Leu pigs, a line of Pro347Ser transgenic pigs has been created [8]. Compared to the Pro347Leu pigs, the Pro347Ser pigs have a less severe phenotype. In a 52 week old animal, 20% of the rods survived and the cones remained relatively spared. The milder phenotype in Pro347Ser pigs may be due to the specific mutation. Alternatively, the survival of almost all the cones may be due to the presence of the rods. These transgenic pigs provide an opportunity to test hypotheses regarding the gradual loss of cones in RP.

Trophic Factors Influencing Cone Survival

Several lines of evidence indicate that rod-cone interactions are very important in cone survival. In the retinal degeneration (*rd*) mouse mutant in which the genetic cause of the pathology has been localized to rod photoreceptor cGMP phosphodiesterase, primary rod degeneration is followed by a second wave of cone death [9]. In transgenic mice in which lethal transgenes are targeted to rod photoreceptors, delayed cone death follows that of the rods [10]. In AMD, it has been shown that initial losses occur in the perifoveal rods prior to cone degeneration [11]. A simple hypothesis that can be formulated to explain this secondary cone death is that rods supply a "trophic factor" either directly or indirectly necessary for cone survival. We have conducted two different types of experiment to address this possibility. The first exploits the laminated structure of the retina and the existence of techniques permitting clean separation of component retinal cell layers by planar vibratome sectioning. Fragments of normal mouse outer nuclear layers (composed of ~97% rods) were transplanted into the subretinal space of recipient *rd* mice eyes at a time at which host rods have virtually disappeared but ~50% cones are still present (5 weeks). Host cones, and rods in both host and transplanted retinas, were visualized using the cone-specific lectin peanut agglutinin and rod-specific anti-opsin antibodies respectively. Quantification of host cones in the region surrounding the optic nerve head revealed highly statistically significant increases (~30%) in their numbers compared to unoperated or sham-operated controls 2 weeks after surgery [12]. Such data indicate that rod-rich grafts promote host cone survival, even at a distance from the graft site. To distinguish between diffusible and contact-mediated influences, a second series of studies were undertaken using a co-culture system in which target 5 week old *rd* intact retina were maintained in chemically defined medium for one week. The adjoining compartment, separated by a membrane allowing passage of diffusible molecules but preventing contact, contained either mixed retinal cell cultures prepared from young normal or *rd* retinas (both containing rods), or explants of adult normal (with rods) or *rd*(without rods) retinas. Photoreceptors were visualized using the immunocytochemical approaches described above, and in addition with anti-arrestin antibody. Cones were quantified by stereological techniques adapted from neurological anatomical studies, which permitted reducing the wide standard deviations in cone numbers recorded using other techniques (up to 2000%) to acceptable levels (~6%). Only in co-cultures in which rods were present in the adjoining culture chamber was there a statistically significant increase in *rd* cone numbers (prevention of ~50% loss normally occurring between 5 and 6 weeks) compared to *rd* retinas cultured alone [13]. These data support the existence

of diffusible factors released by normal rod-containing retinas necessary for continued cone survival.

The use of neurotrophic factors as pharmacological agents for limiting or preventing retinal degeneration is an attractive possibility [14], but neurotrophic factor biology is complex and general principles are difficult to formulate. For example, a given growth factor can either stimulate or inhibit photoreceptor differentiation or survival depending on the species being studied [15]. Clearly if such molecules are to be used in clinical treatments, more information is required on humans and appropriate animal models. We have shown that retinal photoreceptors and other neurons isolated from fully adult postmortem human retinas or pigs (an interesting model of human retina) can survive, regrow neurites and display correct ion- and voltage-gated channel activity when maintained in standard long term monolayer culture conditions [16,17]. Such models are currently being used to analyze cell-cell interactions and to screen known neurotrophic factors for photoreceptor survival-promoting activity, and could in addition provide a donor-independent source of transplantable material.

Photoreceptor Dysfunction and Death in Aging and Age-related Maculopathy

The human macula contains a small cone dominated fovea surrounded by a rod dominated parafovea. Each condition affecting photoreceptors has a characteristic rate of rod and cone degeneration. Photoreceptor status is the most direct bioassay of the functional significance of pathologic changes in the RPE/ Bruch's membrane complex. Recent anatomical and psychophysical studies have provided insight not only into how photoreceptors are affected in aging and ARM but also into possible mechanisms [11,18-23].

Aging— Anatomy: In eyes with grossly normal maculae, the number of cones is stable through the ninth decade, but the spatial density of rods in the parafovea is decreased by 30%. Mosaic integrity is maintained despite loss, however, because surviving rod inner segments broaden to fill vacated space.

Aging—Psychophysics: Older adults with excellent macular health exhibit a scotopic sensitivity loss of 0.5 log units. Scotopic sensitivity loss is not greater in the parafovea where anatomic rod loss is maximal. This finding suggests that other mechanisms, such as slowed rhodopsin regeneration,may contribute to decrease sensitivity. In fact, the rate of dark adaptation slows over the lifespan, especially the rod-mediated component of the function.

ARM—Anatomy: Eyes with large drusen (>125 μm) or severe RPE changes have detectable photoreceptor degeneration. In eyes with large drusen and thick basal deposits, the number of foveal cones is stable. The density of both rods and cones decreases in the parafovea relative to age-matched normals, but rod loss is worse.

ARM—Psychophysics: Both scotopic and photopic sensitivity are decreased in ARM patients compared to control patients. The majority of ARM patients exhibit more scotopic sensitivity loss than photopic sensitivity loss. Even in ARM patients whose scotopic sensitivity is unaffected, the kinetics of dark adaptation are markedly slowed. ARM patients expressed more difficulty with nighttime driving compared with controls, and their reported difficulty varied proportionally to their scotopic sensitivity loss.

Data from our multidisciplinary studies are consistent with the following conclusions: (1) Rods are affected earlier than cones in both aging, and ARM. (2) Dark adaptometry is a more sensitive test of rod dysfunction than scotopic sensitivity. (3) The qualitative similarity of dark adaptometry in aging and ARM suggests a commonality of mechanism. Slowing of the rod adaptation curve implies slowed translocation of 11-cis-retinal through the RPE/ Bruch's membrane complex. The accumulation of Bruch's membrane debris, thought to impair transport across this barrier, is a candidate mechanism that could explain both aging and ARM changes. (4) Functionally significant rod dysfunction occurs well before noticeable anatomical degeneration and cell death. Intervention early in disease progression may retard or prevent photoreceptor death.

Programmed Cell Death and Neurotrophic Factors in Retinal Pathology: a Nostalgic Re-evaluation of the Good Old (Simpler) Times

The involvement of neurotrophic factors in the regulation of developmental programmed cell death in the retina and other neural tissues has been recognized for many years [24]. Extrapolation from these developmental studies led, over a decade ago, to the suggestion that trophic factors could also act as therapeutic agents for retinal degenerations. After some initial skepticism, enthusiasm for this concept increased dramatically in the early 1990s; this was due to the discovery in several laboratories that abnormal cell death in retinal degenerations occurs through mechanisms similar to those involved in programmed developmental neuronal death [1,25], and that photoreceptor death in retinal degeneration animal models could be prevented, or at least retarded, by intraocular administration of neurotrophic factors, similar to those that act on developing cells. While much of this enthusiasm is clearly justified, the evaluation of possible therapeutic uses of trophic factors in patients should take into account some cautionary notes derived from a substantial body of new information, showing that the regulation of neuronal survival in the retina (as in other neural organs) is much more complex than once thought. The concept that factors are highly cell type-specific, for example, which was for many years a central tenet of the neurotrophic hypothesis, is now being challenged by studies showing that such monospecific factors are the exception, rather than the rule [26-34]. The pleiotropic nature of most factors is usually very broad, and their classification as "neurotrophic", "growth-promoting", "cytokines", and the like, frequently reflects only the sources and/or activities through which they were discovered. This has a counterpart, on the other hand, in the fact that most neuronal cells are capable of responding to more than one factor. An additional, recently discovered, source of concern is that some factors (e.g., the neurotrophins) can induce the survival of some cells and the death of others, with the difference depending on the type of receptors expressed by each cell.

In the case of the retina, literally dozens of different factors have been identified [35-37]; the factors and their recep-

tors are distributed in topographically specific patterns, and their expression is dynamic and can change during development as well as in response to pathological conditions. As in other neural organs and tissues, many of these factors can act within the retina on various neuronal and non-neuronal cell types, and the cells in turn have receptors for, and can respond to several different factors. It would appear, therefore, that the survival and maintenance of retinal cells may be regulated by a homeostatic network of factors, which could be altered in still unpredictable fashion by intraocular factor injections. Therefore, while neurotrophic factors and related molecular agents obviously remain strong candidates as possible pharmacological agents for the treatment of retinal degeneration, additional information appears necessary to increase the efficacy and safety of these putative therapeutic strategies

Some concepts and speculation

While there are significant and obvious differences between AMD and CNS degenerations such as Alzheimer's disease (AD), there are also important similarities between them which suggest that some of the principles emerging from research in one field could potentially be relevant to the other. While most cases of macular degeneration and AD have a late onset in life and lack clear patterns of inheritance, for example, there are also familial diseases in which similar (if not necessarily identical) degenerations are triggered earlier in life, have Mendelian patterns of inheritance, and are caused by genetic mutations that have already been identified. A considerable volume of information has been generated in the study of familial forms of AD and amyotrophic lateral sclerosis (ALS); in vivo and in vitro studies of transgenic mice expressing mutated forms of superoxide dismutase (for ALS), or of amyloid precursor protein or the presenilins (for AD) have led to much progress in understanding mechanisms through which mutations lead to characteristic pathological changes in the familial forms of the corresponding diseases. The similarities between those abnormalities and the pathology observed in patients with the late onset, non-familial forms of the diseases, moreover, represents a substantial step forward towards the formulation of testable hypotheses about their possible pathogenesis. By analogy, it would appear reasonable to propose that a similar strategy should be aggressively followed in the case of AMD, by creating transgenic animals expressing mutations associated with familial forms of macular degeneration because, even if the mutations are not involved in AMD, analysis of the transgenic animals could produce significant insights into the mechanisms leading to the complex pathological changes associated with this disease.

Growing evidence shows that mutations expressed in one particular retinal cell type can affect not only cells of that type, but also other retinal cells in which the mutations are not expressed. Clear evidence for such "non-cell autonomous" effects are rod mutations causing human retinitis pigmentosa and similar disorders in experimental animals. While the secondary degeneration of cones as a result of rod-specific mutations has attracted much attention, changes in other cells also occur in those cases; studies from Fulton Wong's [2] and Gabriel Travis' [3] laboratories have shown that even wild type rods degenerate when they share the same microenvironment with rods that express a mutation, and non-cell autonomous effects of rod mutations have also been described in retinal pigment epithelium, in glial cells of Müller, and in vascular cells. The mechanisms underlying these non-cell autonomous mutation effects remain unknown; they could in principle involve either trophic or toxic interactions, which in turn could be mediated either by diffusible factors or by contact-mediated cell interactions. Evidence [12,13] that suggests very strongly that rods may be a source of survival-promoting ("trophic") factors for cone photoreceptors; this is a most promising area of research, which should include not only investigation of the identity of such hypothetical factors but also their mechanisms of action, their effects on other retinal cells, and their changes in abnormal retinas. The possible role of apoptosis-inducing mechanisms was not discussed at the symposium due to time constraints, but it appears obvious that they also deserve to be studied.

The notion that rod photoreceptors are necessary for the survival and well being of cones (and perhaps other retinal cells) appears very relevant for the interpretation of observations, which show that there is a significant loss of rod photoreceptor cells, without concomitant cone cell loss, during "normal aging", while rod losses appear to be more extensive and are accompanied by cone dropout in patients affected by age-related maculopathy. It could be hypothesized that there is a threshold number of rod photoreceptors needed to support cones, and that factors that precipitate AMD could do so by exacerbating rod loss in the macular region of the retina until they reach numbers below that threshold. This could happen as a consequence of mutations in rod proteins (such as those described in familial forms of macular degeneration) or as a consequence of abnormalities in other cell types (such as the RPE).

Related to the preceding considerations is the notion that AMD and other macular degenerations may represent "cell communication disorders", in which an initial lesion affecting one cell type leads to abnormal modifications of the retinal microenvironment, which in turn triggers changes and the eventual degeneration of other cells. Although it would be tempting to view such microenvironmental alterations in terms of the loss of individual factors, the situation is likely to be much more complicated because, there is a growing literature [35,36,38] indicating the presence of a very large number of members of several different growth factors in the retina, and retinal cells express receptors for several of them. The original tenet of the neurotrophic hypothesis, namely, that each cell requires one specific factor, and that each factor was specific for one or at most a very few cell types, is now being extensively revised; factors appear to be much more pleiotropic and promiscuous than once thought, and there are also many interactions between members of different families of growth factors. It is therefore likely that there is a complex "growth factor homeostasis" in the retina, and that its alterations could lead to the many changes observed in AMD and other retinal degenerations. This concept, moreover, raises a concern regarding therapeutic approaches based on the intraocular administration of individual factors because, even if

they are beneficial for one cell type in the short-term, they may have undesired consequences through the disruption of the homeostatic balance within the retina. Clearly, much research is needed to elucidate mechanisms of cell interactions in the retina.

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