The cell cycle, diabetes, and the retina

With the exception of lens and corneal epithelia, cell division in adult mammalian ocular tissues occurs infrequently. Yet, most cells are thought to retain the potential for leaving their dormant Go state to re-enter the active cell cycle (Fig. 1). It has long been known that such reactivation of cells is accomplished by malignant transformation that may follow exposure of cells to certain viruses, chemicals, or radiation, and it has been inferred that the primary process might involve chemical modification of nuclear DNA, the dislodging of gene repressor molecules, or the directed synthesis of adventitious nuclear DNA.

More recently, it has become apparent that in normal cells the cell cycle can be activated or shut down by agents acting at the surface membrane. Surface contact between adjacent normal cells in culture produces inhibition of further replication, whereas malignant cells continue to proliferate. One of several clues to the cause for this behavior is the observation that the binding of the protein, concanavalin A, to mannose end-groups of the hydrophilic cell surface polysaccharide molecules that project out of the hydrophobic cell membrane can restore the property of contact inhibition to malignant cells in culture.

Perhaps cell surface phenomena also determine the future of endothelial cells of the retinal vasculature when the eye is exposed to trauma, and in the proliferative retinopathies that occur in sickle cell disease, diabetes, and other disorders. The normal turnover of retinal capillary endothelial cells as estimated by tritiated thymidine uptake appears to be very infrequent when compared to uptake by the microvasculature of other tissues. Tritiated thymidine studies suggest that when an endothelial cell dies, a neighboring endothelial cell may be released from contact inhibition, allowing replacement of the dead cell by an orderly process in which the daughter cells are again subject to contact inhibition and enter the Go state.

An inborn cellular defect has been postulated to occur in diabetes in which cells of various tissues are abnormally susceptible to injury of the "wear and tear" variety in which cell death and replacement occurs with greater than normal frequency. Earlier or exaggerated age-related changes would thus be anticipated to occur in diabetic tissues, and such changes have been described. An accelerated rate of cell death and cell replacement in diabetic muscle capillaries occurs, with daughter endothelial cells apparently synthesizing a new basal lamina that, by addition of another layer to the pre-existing lamina, increases the overall thickness of the basement membrane. Similar changes have been found in capillaries of the retina. Accelerated cell death of intramural pericytes and endothelial cells may be followed by replacement of only endothelial cells. The new cells generally would be confined to "vacant" sites remaining after the death of cells of the same type along the "scaffolding" provided by the internal surface of the basement membrane tube.

How can the daughter cells of an endothelial cell that had been triggered to re-enter the active cell cycle escape the normal "shutdown" of passage into the Go state under the twin controls of contact inhibition and impoundment by basement
membrane? The stimulus, if any, by circulating insulin or glucose has not been demonstrated. Possibly, rupture or injury of pre-existing basement membrane could provide a channel through which endothelial cells could proliferate. Repeated cell death and replacement could, in time, lead to sufficient narrowing of the lumen of a capillary to impede passage of blood causing ischemia on the venular side with subsequent inadequate cell replacement, leakiness, or hemorrhage. Neovascularization in the retina occurs from venules near sites of hemorrhage or ischemia. It may be that prostaglandin release from ischemic or otherwise traumatized cells or from leukocytes may increase the permeability of neighboring endothelial cells, making them more susceptible to serum components that activate nutrient uptake mechanisms which sustain growth and cell division.

Many difficulties and inconsistencies have been encountered in the study of the retinal vasculature in experimental diabetes. There is some evidence that endothelial cell proliferation is not limited to hereditary diabetes. Some confusion exists concerning the magnitude of changes that have been observed compared to those found in human diabetes. Recently, KK-strain genetically diabetic mice have been reported to show some retinopathic changes that may make this strain extremely useful for the laboratory study of retinopathy. It now should be possible to determine whether in streptozotocin-induced and hereditary diabetes similar localized cellular changes beginning with accelerated cell turnover occur in the vasculature of the retina and progress in a definable sequence of events that includes thickening of basement membrane, ischemia, cell death with inadequate replacement, increased vessel permeability and, ultimately, proliferation of endothelial cells leading to neovascularization.

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REFERENCES
