How do we solve the PRK haze puzzle?

Dr. Wilson and colleagues are investigating what made these two groups different. The working hypothesis is that patients who are steroid responsive, the predominant cellular type is from bone marrow-derived cells rather than keratocytes. It has been shown in several tissues now outside of the cornea that the predominant cell that leads to myofibroblast cell formation is the bone marrow-derived cell.

Over time, myofibroblast normally disappear and the haze disappears. Once the myofibroblast disappears, keratocytes move in and reabsorb organised collagen and glycosaminoglycan and restore transparency, he explained.

The appearance of haze after PRK means there are myofibroblasts present in the cornea.

The myofibroblasts themselves are opaque and they produce very high levels of disorganised collagens and other substances that do not have the regular arrangement that is found in the normal cornea.

The researchers developed a rabbit model for studying the effects of PRK and LASIK on the cornea. In one study, alpha smooth muscle actin staining showed that only a couple of myofibroblast cells could be detected beneath the corneal endothelium one week after surgery. By one month, there were a lot more of these cells beneath the endothelium.

One important finding was a correlation between the amount of surface irregularity and the degree of haze development. The researchers also noticed a direct correlation between the number of myofibroblast cells and the amount of surface irregularity they induced on the cornea. Use of alpha-smooth muscle actin staining to identify myofibroblasts showed the density of those cells in the anterior stroma corresponded to the severity of haze.

Dr. Wilson said it was always of interest to him why when you did a virtually identical procedure you would get a much higher rate of haze in a -9.0 dioptre PRK as compared to a -4.5 dioptre PRK when everything was similar, except for the ablation depth.

"One thing that struck us was that in -9.0 dioptre PRK you were also much more likely to have surface irregularities, such as central islands and peninsulas, with a much higher incidence than with the lower PRK corrections."

He also used a procedure developed by Paolo Vinciguerra to eliminate surface irregularities, which involves putting a thin layer of 10 per cent Healon on the surface of the cornea and putting the laser in PRK mode continuously ablating that surface. Using this technique, the peaks stick up above the Healon and the laser beam only hits the peaks and does not hit the valleys. The result is that even large amounts of irregularity can be made perfectly smooth.

Additional investigations looking at the corneas in more detail to find some of the factors associated with the haze revealed defects in the basement membrane of the epithelium above the alpha smooth muscle actin-positive myofibroblast cells. They are always located beneath the epithelium, which suggested to us early on that there was a communication going on between these cells and the overlying epithelium. We had found was that there were always breaks in the basement membrane overlying these myofibroblast cells. We think that is the key factor in the generation of myofibroblast cells. If you have a structural or functional defect in the basement membrane, with surface irregularity leading to imperfect reformation of the basement membrane, cytokines, like TGF beta, penetrate into the stroma and modulate myofibroblast development from progenitor cells. Over time, those basement membranes repair themselves and the movement of TGF beta to the stroma is halted and the myofibroblast cells can no longer survive and they die by apoptosis.

Dr. Wilson said it was possible to predict, based on this concept of surface irregularity and basement membrane abnormalities, which procedures are most likely to yield significant haze.

"For example, there is a marked reduction in haze when you go deeper and spare any damage to the overlying basement membrane," he said.

Clinical advice

Dr. Wilson advised that all patients with post-PRK haze should have a trial of high potency corticosteroid and if they respond within a week, they can be maintained with topical cyclosporine to give sufficient time for the basement membrane to reacquire its structural and functional integrity.

Topical cyclosporine may also delay the onset of haze beyond the normal two to three months when it is normally seen. Almost always the haze will come at two or three months in a patient, unless they have been taking cyclosporine, said Dr. Wilson.

"But what is going to happen in 20 and 30 years if these cells do not repopulate the stroma? Are we going to see late complications in some of these patients?"

"Haze tends to persist in patients who develop ‘breakthrough haze’ despite mitomycin C treatment and this is likely due to diminished keratocytes in the anterior stroma. Low dose mitomycin C is usually effective but it is not clear to us whether we are really doing anything with that lower concentration because, of course, the incidence of haze is very low when mitomycin C is not used."

Dr. Wilson also noted some concerns about any concentration of mitomycin C in the cornea.

"What is going to happen long-term with these corneas? We have corneas that were treated with mitomycin 10 years ago. But what is going to happen in 20 and 30 years if these cells do not repopulate the stroma? Are we going to see late complications in some of these patients? We haven’t seen it yet, so we don’t know. We have discovered though is that we did get a number of breakthrough patients in the lower concentration of mitomycin C, and based on that we have gone back to using 0.02 per cent mitomycin C for 30 seconds."

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