Editorial

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# New strategy to restore ocular surface health

The ocular surface, consisting of both the cornea and conjunctiva, is the only wetted body surface that is directly exposed to the outside environment. This mother-nature design was developed through evolution and is essential to maintain ocular surface health so that one may enjoy clear vision without suffering from discomfort due to dryness in the open-eye state. In this Issue, Mead *et al.*,[1] points out that the neuroanatomic integration of the ocular surface epithelia with the external adnexae, i.e., eyelids, lacrimal glands, and meibomian glands, is the operating mechanism to ensure ocular surface health. These diverse components are integrated into one unit by the first branch of the trigeminal nerve, which triggers tearing (compositional) and blinking (hydrodynamic) reflexes to maintain a stable preocular tear film. The concept of neuroanatomic integration explains why corneal pathologies are overlapped in two seemingly different diseases, i.e., neurotrophic keratitis and dry eye disease, once we realize that there is a progressive loss of subbasal corneal nerve density with increasing severity of the latter. For the rest of the body, taking diabetic foot ulcers as an example,[2] ischemia is the primary cause of nonhealing ulcers. As the cornea is avascular and already setup for ischemia, its source of oxygen depends on a stable precorneal tear film when the eye is open. To further compensate for this avascular "ischemic" state, the cornea is endowed with the most highly innervated tissue in the body to drive the aforementioned neuroanatomic integration. Therefore, the neuroanatomic integration also explains why neurotrophic keratitis causes the worst form of dry eye and is the prime cause of persistent epithelial defect and nonhealing ulcers for the cornea.

Also summarized by Mead *et al.*,[1] transplantation of cryopreserved human amniotic membrane has become one novel strategy to promote wound healing for patients suffering from neurotrophic keratitis. Insertion of PROKERA® is now a convenient way of performing amniotic membrane transplantation in the clinic not only to promote healing in patients with neurotrophic keratitis and ulcers but also to restore corneal surface integrity in patients with moderate to severe dry eye disease. Chronic inflammation is a well-known, common pathological denominator for both neurotrophic keratitis and dry eye diseases; not only has cryopreserved amniotic membrane been shown to reduce inflammation, but it most excitingly has been shown to promote corneal nerve regeneration.[3]

Since our first reintroduction of amniotic membrane transplantation in ophthalmology in 1995,[4] a myriad of plausible mechanisms had been proposed to explain how amniotic membrane transplantation works by 2004.[5] Nearly one decade from that time, our laboratory has been devoted to searching for the molecular candidate responsible for the amniotic membrane's therapeutic actions. From water-soluble amniotic membrane extract, we have purified heavy chain (HC)-hyaluronic acid (HA)/pentraxin 3 (PTX3) consisting of high molecular weight HA covalently linked with HC1 from inter-α-trypsin inhibitor ("-" denotes covalent linkage) and further complexed with PTX3 ("/" denotes



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noncovalent linkage).[6,7] As summarized by Tighe *et al.*,[8] HC-HA/PTX3 is a unique matrix abundantly present in the birth tissue, i.e., amniotic membrane and umbilical cord. As a single agent, HC-HA/PTX3 orchestrates a number of biological actions in several cell types. Its actions toward neutrophils, macrophages, and lymphocytes translate into a broad-spectrum anti-inflammatory action that extends from innate to adaptive immune responses. HC-HA/PTX3 also exerts anti-scarring action to prevent myofibroblast differentiation. Furthermore, HC-HA/PTX3 supports limbal niche cells to maintain quiescence of limbal epithelial stem cells. These actions collectively support why transplantation of amniotic membrane augments the success of *in vivo*[9-11] and *ex vivo*[12-14] expansion of limbal epithelial stem cells to treat corneal blindness caused by limbal stem cell deficiency. Further research is underway to explore how HC-HA/PTX3 might aid in nerve regeneration. Collectively, these actions render HC-HA/PTX3 as the prime candidate in the birth tissue to deliver regenerative healing.[15] These regenerative properties of HC-HA/PTX3 in the birth tissue have been demonstrated not only in ophthalmology as summarized by Mead *et al.*,[1] but also beyond ophthalmology in diabetic foot ulcers,[16] spina bifida,[17] surgical reconstruction of extremities,[18] and radical prostatectomy.[19] Thus, one may imagine that regenerative treatment through the use of the birth tissue may one day become a new biologic strategy not only to restore ocular surface health but also to fulfill unmet clinical needs in many degenerative diseases that prevail beyond the ocular surface.

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