Bull Yamaguchi Med Sch 43(3-4) : 1996

Epidermal Growth Factor and Transforming Growth Factor α Induce Cell Proliferation in Mammalian Inner Ear Epithelia

Hiroshi Yamashita

Department of Otolaryngology, Yamaguchi University School of Medicine, Ube, Yamaguchi 755, Japan
(Received August 26, 1996)

Key words: EGF, TGF-α, Hair cell regeneration, Cell proliferation, Inner ear, Utricle

It has been suggested that mature mammals have a limited capacity for hair cell regeneration in the vestibular sensory epithelia. After aminoglycoside-induced hair cell death, supporting cells within the vestibular sensory epithelia proliferate (1, 2). Small cells with ultrastructural features that are characteristic of newly formed hair cells are observed (3).

Epidermal growth factor (EGF) is a monomer of 53-amino acid polypeptide, first isolated in submaxillary gland of mice (4). EGF is known to affect epithelial and mesenchymal cell proliferation, migration and differentiation (5, 6). EGF and transforming growth factor (TGF)-α are needed for developing retinal neuronal progenitor cells (7, 8) and stimulate proliferation of multipotent cells isolated from the adult mouse brain (9).

Several lines of evidence suggest an involvement of EGF and TGF-α in the inner ear. TGF-α mRNA has been shown to be present at high levels in the otic vesicle of the mouse fetus (10). EGF receptors have been detected on supporting cells of the organ of Corti in the neonatal rat (11).

Yamashita and Oesterle (12) reported that EGF and TGF-α have a mitogenic effect on cultured vestibular sensory epithelia from mice. Yamashita et al. (13) also reported that EGF, TGF-α and EGF receptors have been detected in the vestibular epithelia in the human fetal inner ear, especially at early stages.

These studies suggest that EGF and TGF-α have a mitogenic effect on the mammalian vestibular sensory epithelia and are probably related to healing or regeneration of the drug-damaged vestibular end organs, However, it is not clear that new cells stimulated by EGF and TGF-α have a function as same as mature hair cells. We have to determine whether these factors or other growth factors can recover the function of the mammalian inner ear in vivo.

References

1) Rubel, E.W., Dew, L.A., and Roberson, D. W. : Mammalian vestibular hair cell regeneration. *Science*, **267** : 701-703, 1994.
2) Warchol, M.E., Lambert, P.R., Goldstein, B.J., Forge, A., and Corwin, J.T. : Regenerative proliferation in inner ear sensory epithelia from adult guinea pigs humans. *Science*, **259** : 1619-1622, 1993.
3) Forge, A., Li, L., Conwin, J.T., and Nevill, G. : Ultrastructual evidence for hair cell regeneration in the mammalian inner ear. *Science*, **259** : 1616-1619, 1993.
4) Cohen, S. : Isolation of a mouse submaxil-

lary gland protein accelerating incisor eruption and eyelid opening in the new born animal. *J. Biol. Chem.*, **237** : 1555-1562,. 1962.
5) Rheinwald, J., and Green, H. : Epidermal growth factor and the multiplication of cultured human epidermal keratinocytes. *Nature*, **265** : 421-424, 1977.
6) Carpenter, G., and Cohen, S. : Human epidermal growth factor and the proliferation of human fibroblasts. *J. Cell. Physiol.*, **88** : 227-238, 1976.
7) Anchan, R.M., Reh, T.A., Angello, J., Balliet, A., and Walker, M. : EGF and TGF-α stimulate retinals neuroepithelial cell proliferation in vitro. *Neuron*, **6** : 923-936, 1991.
8) Lillien, L., and Cepko, C. : Control of proliferation in the retina: temporal changes in responsiveness to FGF and TGF-alpha. *Development*, **115** : 253-266, 1992.
9) Reynolds, B.A., and Weiss, S. : Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science*, **255** : 1707-1710, 1992.
10) Wilcox, J.N., and Derynck, R. : Developmental expression of transforming growth factors alpha and beta in mouse fetus. *Mol. Cell. Biol.*, **8** : 3415-3422, 1988.
11) Lefebvre, P.P., Staecker, H., Malgrange, B., Moonen, G., and Van De Water, T.R.: Transforming growth factor alpha acts with retionic acid to stimulate the regeneration of mammalian auditory hair cells. *Assoc. Res. Otolaryngology Abstr.*, **17** : 115, 1994.
12) Yamashita, H., and Oesterle, E.C. : Induction of hair cell proliferation in mammalian inner ear sensory epithelia by transforming growth factor-alpha and epidermal growth factor. *Proc. Natl. Acad. Sci. USA*, **92** : 3152-3155. 1995.
13) Yamashita, H., Takahashi, M., and Bagger-Sjöbäck, D. : Expression of epideraml growth factor, epidermal growth factor receptor and transforming growth factor -alpha in the human fetal inner ear. *Eur. Arch. Otorhinolaryngol.*, **253** : 494-497, 1996.