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Plasminogen heals chronic tympanic membrane perforations

Most acute tympanic membrane (TM) perforations heal spontaneously, but 10-20% remains open as a chronic or permanent TM perforation (CTMP). Why the healing of CTMPs is arrested is still an enigma. Chronic perforations may lead to an impaired hearing ability and recurrent middle ear infections with draining ears. Traditionally, CTMPs are closed surgically, which is a costly and time-consuming procedure. Therefore, it should be a great advantage if one could develop simpler therapeutic strategies. Previous studies by us have shown that plasminogen (plg) is a proinflammatory regulator that accelerates cutaneous wound healing in mice. Interestingly, we have also shown that healing of TM perforations in plg-deficient mice (plg^{-/-}) is completely arrested and that these mice develop CTMPs due to the lack of plg. In fact the perforations in plg deficient mice are so far the only true CTMP model. We have shown that CTMPs are caused by an arrested migration of keratinocytes, an abnormal recruitment and activation of inflammatory cells and a massive deposition of fibrin. In the initial TM perforation experiments plg^{-/-} mice were treated with intravenous plg and their CTMPs healed. More recent experiments with daily local injections of plg into the soft tissue surrounding the TM and topical application restored the ability to heal TM perforations in a dose-dependent manner. Treatment by plg was also tested in a CTMP model in rats. The CTMPs were caused by local application of hydrocortisone on acute TMPs. Plg, either applied by local injections or topically, also healed the CTMPs in rats. Plg was also tested on acute TMPs in wild-type mice and it was shown that local injections of plg accelerated the healing rate and quality of the healed TM. We have shown that local injection of plg into the soft tissue surrounding the TM or topically applied restored the healing ability of CTMPs in both mice and rats. Our data suggest that plg is a promising drug candidate for the treatment of CTMPs in humans, which are rational for the clinical studies on CTMPs in humans already in progress.

Biography

Sten Hellstrom is a Senior Professor at Karolinska Institute, Sweden. He is also working as a Senior Consultant in Department of Audiology and Neurotology, Karolinska University Hospital. He is Specialist in Otorhinolaryngology (ORL) and started his clinical career in Umeå, the most northern university town of Sweden. Prior to moving to Stockholm in 2005, he was the Head of the ORL Department of the Northern University Hospital combined with a professorship in ORL at Umeå University. He has published more than 300 papers in well renowned journals and been the main supervisor of 17 research students receiving their PhDs. He has organized several international symposia on interactions between the middle ear and inner ear and also on otitis media.

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