



Letter to the Editor

Re: Udo Nagele, Sabine Maurer, Gerard Feil, et al. In Vitro Investigations of Tissue-Engineered Multilayered Urothelium Established from Bladder Washings. Eur Urol 2008;54:1414–22

I have read the interesting paper, “In Vitro Investigations of Tissue-Engineered Multilayered Urothelium Established from Bladder Washings” [1]. I also agree with Campodonico, who noticed two questionable points related to this paper: A quite high rate of bladder washings did not result in successful cultures, and older patients produced fewer cultures [2]. These findings probably reflect some weak points of the experimental concept.

These important topics are closely connected with the mitotic age of the cultured cells and the histologic structure of the stem cell niche. Shibata and Tavaré have shown that somatic cells with greater mitotic ages (total numbers of divisions since the zygote) should accumulate greater numbers of replication errors and methylated genes [3]. All cells within an individual have identical chronological ages (years since birth), but their mitotic ages may differ. Different division dynamics can be observed in different tissues. The urinary tract epithelium represents mitotic tissue with continuous genealogy. In this case [1], the mitotic age should increase with chronological age. This means that the proliferative potential of cells from older individuals is lower, according to the Hayflick limit.

A matter of concern is the low proportion of successful cultures observed in this study [1]. It seems that this problem is related to the structure and physiology of the stem cell niche of the donor tissue. There are a number of systems in which asymmetry in the division process has been observed. Asymmetric cell division has also been demonstrated for mammalian epithelium [4]. There is a high probability that asymmetric division predominates among urothelial stem cells. Asymmetric stem cell division generates one stem and

one differentiated daughter cell; however, the proliferative potential of both cells is already reduced. The proliferative potential of the differentiated daughter cell will decrease with increasing number of mitotic cycles and will probably be the lowest in the superficial urothelial cell layer. In contrast, urothelial p63-positive stem (progenitor) cells are located within the basal cell layer, which is strictly connected to the basement membrane [5]. Despite the type of division (asymmetric, clonal succession or symmetric), the progenitor cells will remain in deep layers of epithelium due to the histologic structure of the urothelial stem cell niche. With this in mind, the chance of obtaining mitotically “young” cells with high proliferative potential from bladder washings is low. From bladder washings, we can at least obtain amplifying cells, the mitotic age of which will be even greater after finishing the period of in vitro culture characterised by intensive proliferation.

In conclusion, it is possible to explain the low success rate of establishing urothelial cell cultures in this particular case [1]. More important questions have to be posed: Should we need these cells for tissue engineering? Do these cells maintain proliferative capacity in vivo? Will these cells regenerate the urinary tract properly? Finally, the authors concluded that these cultures have no potential to achieve terminal differentiation. Maybe it is more reasonable to search for “younger” cells by exploring deeper layers of urothelium?

Conflicts of interest: The author has nothing to disclose.

References

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