



## Words of Wisdom

### Re: Hedgehog/Wnt Feedback Supports Regenerative Proliferation of Epithelial Stem Cells in Bladder

Shin K, Lee J, Guo N, et al

Nature 2011;472:110–4

#### Experts' summary:

The regeneration of multilayered urinary bladder epithelium that consists of umbrella cells, intermediate cells, and basal cells that shift from a state of near quiescence to being highly proliferative in response to injury [1] was the focus of the in vitro and in vivo investigations of Shin et al. In contrast to bladder epithelia, the epithelia of other organs, such as the intestine, regenerate constantly and without an injury-response stimulus. The proliferative response to simulated bacterial infection or chemical injury of the murine bladder was induced and the suspected regulatory signaling between the basal cells of the urothelium and the underlying stromal cells was examined in vitro. Hereby, it was impressively shown that within the basal-cell population, a multipotent stem cell exists that is capable of regenerating all cell types within the urothelium.

Not only was the putative urothelial stem cell identified via the expression of secreted sonic hedgehog (Shh) protein, Wnt signaling was confirmed to affect the cell's proliferative behavior. Due to injury, Shh expression was upregulated in basal cells while increasing stromal expression of Wnt protein signals. The induced signal feedback circuited and the associated increased cell proliferation appeared to be required for restoration of the urothelial function. In addition, the regenerative potential of the urothelial stem cells was demonstrated when single Shh-expressing cells formed cyst-like organoids in Matrigel cultures.

#### Experts' comments:

The evidence of an existing bladder stem cell implicates the exciting possibility of epithelial regeneration. It was previously suggested that basal cells may function as stem cells in many other epithelia besides the bladder [2]; however, a bladder stem cell *niche*, as it is known for the hematopoietic [3] or the cardiovascular system [4], remains undiscovered. Although we were not able to identify this particular niche in our own analysis, using previously described stem and

progenitor cell markers using adult bladder tissue sections, the data of the presented study demonstrate the existence of a bladder stem cell. Whether there is a three-dimensional niche structure within bladder tissue still needs to be elucidated. One could speculate about the possibility of finding the putative urothelial stem cell spatially close to the basement membrane based on the findings of studies focusing on other stem and progenitor cell niches. Extracellular matrix proteins like laminins, elastin, and different types of collagen (type I, III, IV, V, VI, and VII) [5] were previously determined to play major roles in the epidermal or cardiovascular niche microenvironment [3,4]. Shin et al showed similar results analyzing crucial factors that act through the Wnt signaling pathway, such as  $\beta$ -catenin and Axin2.

With special regard to a potential clinical application in reconstructive urology, such as bladder augmentation or urethral surgery and its corresponding tissue engineering processes, answering the question of how to isolate urothelial stem cells will be of particular importance. The isolation of multipotent cells from bladder washings or through conventional biopsy techniques is currently a challenging task. Since we are able to produce multilayered human urothelial mucosa constructs demonstrating characteristics of various cell types within the urothelium [6], one might speculate that multipotent cells are present in the harvested cells. Further investigations will be required to determine the distribution and usefulness of these cells within the bladder epithelium and use this knowledge to improve urothelial engineering.

**Conflicts of interest:** The authors have nothing to disclose.

#### References

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## Re: Alkaline Citrate Reduces Stone Recurrence and Regrowth After Shockwave Lithotripsy and Percutaneous Nephrolithotomy

Lojanapiwat B, Tanthanuch M, Pripathanont C, et al

Int Braz J Urol 2011;37:611–6

### Expert's summary:

This study is a randomized comparison of patients with residual stone material in the kidney after shockwave lithotripsy (SWL) and percutaneous nephrolithotomy (PNL) who were treated with alkaline citrate (ALK) or left untreated. After a relatively short follow-up period (12 mo), there were significant differences in terms of stone-free kidneys, regrowth of residuals, and new stone formation. Of initially stone-free patients treated with ALK, 7.7% had formed new stones after 1 yr compared with 42.3% of those without such treatment. In patients with residual fragments, more patients in the ALK-treated group became stone free, and growth of residual fragments was encountered in 7.7% of the treated group and 54.5% of the control group. The conclusion from this study was that treatment with ALK gives positive effects in patients both with and without residual fragments after active stone removal.

### Expert's comments:

Although it has been shown previously that ALK is efficient in counteracting new calcium stone formation [1] as well as regrowth of residual fragments [2,3], this article is a valuable reminder of the usefulness of medical treatment of patients with calcium stone disease. At a time when there has been a considerable technical development of ureteroscopes and stone-disintegrating devices, the enthusiasm to use these instruments has placed recurrence prevention in the shadows, and this field is seriously neglected today.

It is recognized that asymptomatic residual fragments might be present in the kidney after SWL; however, it needs to be emphasized that residual fragments are also common after retrograde intrarenal surgery and occur even after PNL. Moreover, it is also notable that in cases of obviously complete clearance of calcium stones, recurrent stone formation is considerable, with an average risk of new stone formation in as many as 5% after 1 yr and 30% after 5 yr.

In the reported study, sodium potassium citrate was used as the only agent, and it is possible that this form of treatment was particularly useful for fragment clearance [4]; however, I personally am in favor of a selective recurrence prevention based on biochemical findings. The sodium content might result in increased excretion of calcium that is not entirely positive, and the follow-up period is too short for general conclusions. The message of this report, however, is clear: Considering use of medical agents to facilitate fragment passage and to counteract new stone formation and growth of residual fragments should be part of the urologic care of patients with calcium stone disease. This is particularly important for those patients who have a previous history of stone formation and for those who have asymptomatic residual fragments. Both of these groups also should have an individualized follow-up program [5].

**Conflicts of interest:** The author has nothing to disclose.

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## Re: Baseline Prostate-Specific Antigen Testing at a Young Age

Loeb S, Carter HB, Catalona WJ, Moul JW, Schroder FH

Eur Urol 2012;61:1–7

### Expert's summary:

This paper by Loeb et al was followed by comments from editors and reviewers and these were responded to by the authors. The text is presented as the first article of the first issue in the start of the new year.