The DNA Damage Response of Gastrointestinal Cells in the Bladder Microenvironment

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Background: Augmentation cystoplasties are performed in children with complex urogenital abnormalities. The gastrointestinal tissues utilized in an augmented bladder are at increased risk for cancer, although the mechanism is unknown. We have recently shown that the hyperosmolal bladder microenvironment may attenuate the DNA damage response in gastrointestinal, but not bladder, cancer cell lines. However, whether this observation will hold true in non-cancer cell lines remains to be seen. We hypothesize that gastrointestinal and bladder cells may activate DNA damage responses differently in the hyperosmolal urinary microenvironment which could, in part, explain the tissue-specific differences in susceptibility to cancer in the augmented bladder.

Objective: To determine if the DNA damage response, DNA repair, and cell cycle arrest differ between normal mouse gastrointestinal and bladder epithelial cells gradually adapted to a hyperosmolal microenvironment.

Design/Methods: Conditionally immortalized mouse colon (YAMC), small intestine (MSIE) and bladder (ULTI) epithelial cells were gradually adapted to either isoosmolal or hyperosmolal conditions. Cells were then treated with either Etoposide, a DNA damaging agent, or DMSO. Cell lysate were collected and activation of the DNA damage response (ATM, γH2AX and RPA32 expression), cell cycle arrest (p53 and p21 expression), and apoptosis (cleavage of caspase 3 and PARP) were evaluated by western blot analysis. Flow cytometry was also performed using propidium iodide to measure DNA content and cell cycle progression.

Results: Under control conditions, both colon and bladder cells in culture are able to recognize DNA damage, halt cell cycle progression, and attempt DNA repair. However, under hyperosmolal conditions of NaCl or urea, these responses are attenuated greatly in colon cells. Bladder cell lines showed an increased resistance to the effects of hyperosmolal conditions, and maintained modest ability to recognize and repair DNA damage. Furthermore, bladder cells showed a much greater capacity to halt their cell cycle at the G1/S checkpoint in the face of DNA damage and hyperosmolality when compared to their gastrointestinal counterparts.

Conclusions: By singling out high osmolality as the culprit for increased cancer risk of gastrointestinal tissue as it exist in the augmented bladder, a clinical solution becomes fairly simple. Hydration therapy involving regularly scheduled water consumption or judicious use of diuretics can decrease urine osmolality in these patients, and thereby relieve the osmotic stress placed on gastrointestinal tissues. By favoring isoosmotic urine production, gastrointestinal tissue in the bladder microenvironment will be better suited to recognize and repair DNA damage, thereby decreasing the possibility of developing malignancy.