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Urological Pathology

Hedgehog Signaling Links Bladder Regeneration And Oncogenesis

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With an estimated 57,000 new cases in 2003, bladder cancer is the sixth most common cancer in the United States, and is highly linked to environmental exposure to agents that injure bladder epithelium. We have shown that signalling by the Hedgehog (Hh) pathway links toxin exposure, injury, repair and carcinogenesis in the lung, a foregut derived organ, and may have a similar role in other gut-derived organs, including the esophagus, stomach, and biliary tract. Here we show that Hh pathway activity drives urothelial proliferation in the hindgut-derived bladder in response to mucosal injury and is also required for proliferation in urothelial cancers. Bladder injury with cyclophosphamide resulted in elevated transcription of the Hh pathway targets Patched (PTCH) and GLI within 8 hours of administration, returning to baseline within the next 16 hours. PTCH and GLI expression was accompanied by increased levels of c-myc, and cyclins D and E, known mediators of proliferation in benign and malignant cells. PTCH and GLI expression was also elevated in 5 of 10 urothelial carcinoma cell lines, as was expression of a Hh-responsive luciferase reporter. Hh reporter activity could be completely abolished by treatment with the Hh pathway antagonist cyclopamine. Hh pathway blockade dramatically suppressed growth in urothelial cancer cell lines, but only in those cell lines demonstrating elevated Hh pathway, indicating that these growth suppressive effects act specifically through Hh pathway blockade. These results indicate that bladder cancer may derive from a urothelial progenitor cell that requires Hh pathway activity for growth. They further indicate that Hh pathway blockade may be useful in the treatment of bladder cancer.