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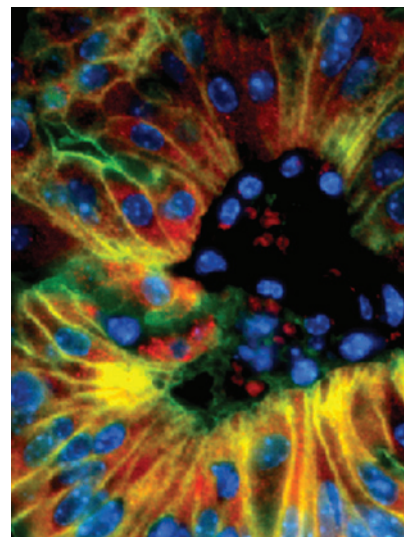
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**New Directions for Biologic Targets
in Urothelial Carcinoma – Letter**Andrea Necchi, Luigi Mariani,
Nadia Zaffaroni, Patrizia Giannatempo, and
Roberto Salvioni**ABOUT THE COVER**

Cyclooxygenase-2 (COX-2) is upregulated in pancreatic ductal adenocarcinomas (PDAC). However, COX-2 inhibition has not shown significant improvements in the survival of patients with metastatic PDAC. The cell-intrinsic role of COX-2 in PDAC progression was tested using both loss-of-function and gain-of-function approaches. *Cox-2* deletion significantly delays the development of PDAC in mice. However, all animals ultimately succumbed to PDACs, suggesting that tumors can compensate for COX-2 loss through other mechanisms. Using coimmunofluorescence, it was found that membrane-associated GRP78 expression was associated with poor prognosis in a number of human cancers and was recently identified as a critical factor in protecting cells from cell death, and also colocalized with P-AKT expression in tumors with COX-2 deletion. Together, these results suggest that, while anti-COX-2 therapy may delay the development and progression of PDAC, mechanisms known to increase chemoresistance through AKT activation must also be overcome. For details, see article by Hill and colleagues on page 2127.



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