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THERAPEUTIC ULTRASOUND-MEDIATED DELIVERY OF THE GENE ENCODING FOR THE TUMOR SUPPRESSOR, SEF, INTO PROSTATE TUMORS SUPPRESSED TUMOR GROWTH AND REVEALED SEF POTENT ANTIANGIOGENIC ACTIVITY

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Carcinomas account for over 80% of all human cancer types with no effective therapies. The tumor suppressor Sef [similar expression to fibroblast growth factors (FGF)] is expressed in all the human epithelial tissues and is down-regulated in all the carcinoma types that have been examined so far in a manner that correlates with tumor aggressiveness. We examined the therapeutic potential of restoring the expression of the hSef-b isoform in a prostate carcinoma model. In our *in vitro* studies, hSef-b inhibited the proliferation of TRAMP C2 cells and attenuated the activation of ERK/MAPK as well as the master transcription factor NF-κB in response to FGF and IL-1/TNF, respectively. Both FGF and NF-κB are strongly implicated in prostate carcinoma progression. Next, the hSef-b, gene was delivered using therapeutic ultrasound (TUS) to pre-established prostate tumors *in vivo*. Tumors were injected with a bicistronic vector co-expressing hSef-b with eGFP to serve as a reporter for transfection rates, and treated with TUS. Transfection efficiency of plasmid co-expressing hSef-b/eGFP into TRAMP C2 tumors following a single TUS application was 14.7±2.5%. Repeated TUS treatments with hSef-b plasmid, significantly suppressed prostate tumor growth (60%) through inhibition of cell proliferation (60%), and also reduced blood vessel density (56%). In addition, the levels of the promitogenic and proangiogenic factor, FGF2, were significantly reduced following repeated TUS treatments with hSef-b plasmid. Collectively, our results strongly suggest that hSef-b acts in a cell autonomous as well as in a paracrine manner and further revealed the efficacy of non-viral, TUS-based hSef-b gene delivery approach for the treatment of prostate cancer tumors, and possibly other carcinomas where Sef is downregulated. Moreover, using this approach, we discovered that hSef-b is also furnished with the capacity to inhibit tumor angiogenesis.

Biography

Dina Ron has completed her PhD from Ben-Gurion University and Postdoctoral studies from the National Cancer Institute, NIH, USA. She is a Lab Chief in the Biology Department, the Israel Institute of Technology. She has published more than 60 papers in Refereed professional journals and served as an Editorial Board Member of the *Journal of Biological Chemistry*.

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