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Letter to the Editor

Cancer Research

Innervation of the Tumor Microenvironment–Letter

Mark R. Goldstein and Luca Mascitelli

The intriguing article by Allen and colleagues recently published in *Cancer Research* (1) further elucidates how the catecholamine norepinephrine is produced in the tumor microenvironment and leads to cancer progression and metastasis (2). The authors demonstrated, in mice, that catecholamine-stimulated adrenergic signaling through the β-3 adrenergic receptor (β3-AR) on tumor cells resulted in the production of brain-derived neurotrophic factor (BDNF) in the tumor microenvironment, which then led to the stimulation of tumor innervation. The newly developed nerve endings released tumor growth-promoting norepinephrine and a higher sustained local norepinephrine concentration. These findings have profound implications, because a β3-AR agonist is already widely used in clinical practice (3).

Mirabegron (Myrbetriq) is a β3-AR agonist approved by the FDA for clinical use in 2012 for the treatment of overactive bladder (OAB) in men and women (3). Premarket studies of mirabegron demonstrated an imbalance of cancers in subjects randomized to mirabegron; the cancers included, but were not limited to prostate cancer, bladder cancer, metastatic colon cancer, lung cancer, and melanoma (3). The FDA expressed some concern and mandated a postmarket study to access the potential risk of mirabegron-associated new cancers (3). Recently, a 12-month study involving mirabegron and solifenacin (VESIcare, a well-known cholinergic receptor antagonist used in the treatment of OAB), taken together or separately, was reported (4). Likewise, it demonstrated an imbalance of cancers in subjects randomized to mirabegron or a mirabegron/solifenacin combination; the cancers included basal and squamous cell carcinomas of the skin, bladder cancer, breast cancer, melanoma, Bowen disease, and metastatic uterine cancer (4).

Importantly, β3-ARs have been shown to be overexpressed in various cancers compared with matching normal tissues (5). These cancers include breast cancer, lung cancer, ovarian cancer, uterine cancer, thyroid cancer, urothelial cancer, melanoma, colon cancer, esophageal cancer, stomach cancer, prostate cancer, lymphoma, and liver cancer (5).

In conclusion, Allen and colleagues expose a biologically plausible mechanism by which β3-AR agonists might promote cancers. Mirabegron is now a widely used β3-AR agonist for the treatment of OAB, a problem commonly seen in the geriatric population. It is older individuals that are more likely to harbor clinically unapparent cancers, and therefore might be more susceptible to the promotion of these preexisting cancers by β3-AR agonists. Finally, it is imperative that there is ongoing strict postmarket surveillance of mirabegron, particularly in the geriatric population and those with remote or prevalent cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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