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Letter

Triggering Neurotransmitters Secretion from Single Cells by X-ray Nanobeam Irradiation

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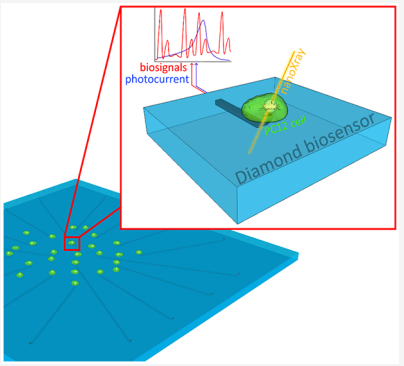
ABSTRACT: The employment of ionizing radiation is a powerful tool in cancer therapy, but beyond targeted effects, many studies have highlighted the relevance of its off-target consequences. An exhaustive understanding of the mechanisms underlying these effects is still missing, and no real-time data about signals released by cells during irradiation are presently available. We employed a synchrotron X-ray nanobeam to perform the first real-time simultaneous measurement of both X-ray irradiation and in vitro neurotransmitter release from individual adrenal phaeochromocytoma (PC12) cells plated over a diamond-based multielectrode array. We have demonstrated that, in specific conditions, X-rays can alter cell activity by promoting dopamine exocytosis, and such an effect is potentially very attractive for a more effective treatment of tumors.



KEYWORDS: *X-ray synchrotron nanoirradiation, dopamine exocytosis, diamond microelectrode arrays, photocurrent detection, radiobiology*

Dopamine (DA) is an important monoamine neurotransmitter involved both in central nervous system regulation of cognition, behavior, mood, addiction, reward,[1−5] and in multiple functional modulations of peripheral tissues and organs. The possible role of DA and its receptors in affecting the growth of some malignant tumors was hypothesized for the first time about 20 years after observing its large decrease in cancer tissues compared to normal ones.[6−8] Nowadays, it has been proved that DA inhibits angiogenesis by affecting vascular permeability factor (VPF) and vascular endothelial growth factor (VEGF)-induced endothelial cell proliferation[9] and that it reduces mesenchymal stem cell (MSC) and endothelial progenitor cell (EPC) migration.[10] Increasing evidence indicates that DA plays an important role not only in mediating cross-talk between central nervous and immune systems[11,12] but also at a peripheral level by acting on tumor-associated immunologic alterations.[13] Indeed, DA is synthesized, with rare exceptions, in most types of immune cells[14] and released to the extracellular environment after specific stimulation.[15] Due to the increasing interest in the use of immunotherapy as an efficient tool to boost the occurrence of the abscopal effect[16,17] and because of the DA interference with the immune system, a study of dopaminergic cell response to X-ray irradiation is necessary, especially in view of the potential synergy that it could have along with immunotherapy for malignant tumor treatment.

In this study, we have employed the PC12 immortalized cell line, which synthesizes DA and releases it upon membrane depolarization in a Ca^{2+}-dependent way. The cellular exocytotic activity has been monitored by means of a device consisting of a single-crystal diamond substrate equipped with a multielectrode array of graphitic microchannels (μG-D-MEA). This device was fabricated out of high-quality artificial diamond substrate by means of a lithographic technique based on the use of MeV ions, which was optimized in previous studies (see Supporting Information for details). Its suitability to the fabrication of integrated cellular sensors for *in vitro* measurements has already been demonstrated in a series of previous works.[18−20] As shown in Figure 1, each fabricated subsuperficial conductive microchannel is characterized by two emerging end-points, one in correspondence of the biological sample under investigation (i.e., the cells plated in the central region of the device) and the other at the input of the acquisition electronic chain (i.e., the readout contacts at the peripheral region).

Diamond biocompatibility allows plating cells directly over the surface of the sensor without altering the cellular activity over long-term measurements, as demonstrated in previous

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