MITOCHONDRIAL DYSFUNCTION, ASSOCIATED WITH CALCIUM OVERLOAD AND ROS PRODUCTION, IS INVOLVED IN THE PRODEATH ACTIVITY OF TOCOTRIENOLS IN PROSTATE CANCER CELLS

Fontana F. (1), Raimondi M. (1), Marzagalli M. (1), Audano M. (1), Sartori P. (2), Procacci P. (2), Mitro N. (1), Limonta P. (1)

(1) Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milano (Italy)
(2) Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milano (Italy)

Castration resistant prostate cancer (CRPC) is an aggressive tumor with still limited therapeutic outcomes due to the development of resistance to standard treatments. Unraveling the molecular mechanisms at the basis of the prodeath activity of novel anticancer compounds is necessary to increase the treatment strategies for this pathology.

We previously demonstrated that, in human CRPC cell lines (PC3 and DU145), delta-tocotrienol (d-TT, a vitamin E derivative) exerts a proapoptotic activity by triggering the ER stress-autophagy axis. In these cells, d-TT also induces paraptosis, a non-canonical cell death mechanism characterized by cytoplasmic vacuolation resulting from mitochondrial/ER swelling and requiring protein synthesis. In the present study, we investigated the effects of this compound on mitochondrial metabolism and functions. We observed that d-TT reduces the expression levels of OXPHOS proteins (complex I, II and III) and inhibits mitochondrial respiration, leading to decreased oxygen consumption, ATP depletion and AMPK activation. d-TT treatment resulted in mitochondrial Ca2+ homeostasis alteration and increased ROS production, accompanied by mitochondrial fission (as evidenced by MitoTracker staining and by the cleavage of L-OPA1) and degradation (as indicated by the activation of the mitophagic flux). Interestingly, both mitochondrial Ca2+ flux and redox state alterations were demonstrated to be significantly involved in d-TT-induced cell death pathways.

Taken together, these data demonstrate that d-TT specifically alters mitochondrial morphology and functions in CRPC, inducing Ca2+ overload- and ROS production, to trigger mitophagy/autophagy and cell death mechanisms, such as apoptosis and paraptosis.

(Supported by PRIN 2015, n. 2015B7M39T_004; MIUR Progetto di Eccellenza, DiSFeB, Università degli Studi di Milano).