Metformin and cancer

Doses, mechanisms and the dandelion and hormetic phenomena

Begoña Martin-Castillo, Alejandro Vazquez-Martin, Cristina Oliveras-Ferraros and Javier A. Menendez*
Catalan Institute of Oncology (ICO); and Girona Biomedical Research Institute (IdIBGi); Girona, Catalonia Spain

In the early 1970s, Professor Vladimir Dilman originally developed the idea that antidiabetic biguanides may be promising as geroprotectors and anticancer drugs ("metabolic rehabilitation"). In the early 2000s, Anisimov's experiments revealed that chronic treatment of female transgenic HER2-/*neu* mice with metformin significantly reduced the incidence and size of mammary adenocarcinomas and increased the mean latency of the tumors. Epidemiological studies have confirmed that metformin, but not other anti-diabetic drugs, significantly reduces cancer incidence and improves cancer patients' survival in type 2 diabetics. At present, pioneer work by Dilman & Anisimov at the Petrov Institute of Oncology (St. Petersburg, Russia) is rapidly evolving due to ever-growing preclinical studies using human tumor-derived cultured cancer cells and animal models. We herein critically review how the antidiabetic drug metformin is getting reset to metabolically fight cancer. Our current perception is that metformin may constitute a novel "hybrid anti-cancer pill" physically combining both the long-lasting effects of antibodies—by persistently lowering levels of blood insulin and glucose—and the immediate potency of a cancer cell-targeting molecular agent—by suppressing the pivotal AMPK/mTOR/S6K1 axis and several protein kinases at once, including tyrosine kinase receptors such as HER1 and HER2. In this scenario, we discuss the relevance of metformin doses in pre-clinical models regarding metformin's mechanisms of action in clinical settings. We examine recent landmark studies demonstrating metformin's ability to specifically target the cancer-initiating stem cells from which tumor cells develop, thereby preventing cancer relapse when used in combination with cytotoxic chemotherapy (dandelion hypothesis). We present the notion that, by acting as an efficient caloric restriction mimetic, metformin enhanced intrinsic capacity of mitotically competent cells to self-maintenance and repair (hormesis) might trigger counterintuitive detrimental effects. Ongoing chemopreventive, neoadjuvant and adjuvant trials should definitely establish whether metformin's ability to kill the "dandelion root" beneath the "cancer soil" likely exceeds metformin-related dangers of hormesis.

Key words: metformin, cancer, AMPK, stem cells, hormesis

Submitted: 11/22/09

Accepted: 12/21/09

Previously published online: www.landesbioscience.com/journals/cc/article/10994

*Correspondence to: Javier A. Menendez; Email: jmenendez@iconcologia.net

We all know there are benefits to improving cancer patients' lifestyles through better diet and more exercise. Besides effects on *quality* of life, healthy lifestyle interventions' effects on cancer patients might be also viewed in terms of *quantity* of life. This assumption becomes apparent when considering that essential hallmarks of cancer disease (e.g., uncontrolled proliferation) are intertwined with an altered tumor cell-intrinsic metabolism, either as a consequence or as cause.[1] In this scenario, the implementation of caloric/dietary restriction (i.e., under-nutrition without malnutrition) should be expected to directly regulate several factors intimately implicated in the molecular biology of cancer itself. Yet, we should be conscious that implementation of lifestyle interventions aimed to significantly disrupt signalling pathways and/or energy factories that account for metabolic reprogramming of