Editorial

New Tale of Metformin in Cardio-Oncology

Wang Xin

Faculty of Biology, Medicine and Health, University of Manchester, Oxford Road, M139PT Manchester, UK.
Correspondence: xin.wang@manchester.ac.uk

Metformin (1,1-dimethylbiguanide hydrochloride) has been a first-line treatment for people with type 2 diabetes mellitus for over 60 years, as recommended by most current guidelines. Its origins can be traced back to *Galega officinalis*, a traditional herbal medicine used in medieval Europe for treating conditions such as worm infection, epilepsy, fever, and polyuria (a symptom of diabetes) [1,2]. This herb was found to be rich in guanidine, which was discovered in 1918 to lower blood glucose in animals. Guanidine derivatives were synthesized, but some (not including metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the availability of insulin [3,4].

In the 1940s, while searching for antimalarial agents, metformin was rediscovered and was found to be useful in treating influenza [5]. The breakthrough in using metformin to lower blood glucose came in 1957, when Dr. Jean Sterne translated its potential into a therapeutic reality [6]. However, metformin received limited attention as it was less effective than other biguanides, which were withdrawn in the late 1970s due to lactic acidosis [7,8]. This withdrawal led to limited clinical use of metformin.

In the 1980s, new information revealed the ability of metformin to reduce hepatic gluconeogenesis and increase glucose utilization without causing weight gain or increasing the risk of hypoglycaemia [9,10]. This information allowed metformin to survive through the biguanide cull. After intense scrutiny, metformin was introduced into the USA in 1995 [11]. The long-term cardiovascular benefits of metformin were reported through the UK Prospective Diabetes Study (UKPDS), led by Professors Turner and Holman, providing a new rationale to adopt metformin as an initial therapy to manage hyperglycaemia in type 2 diabetes in 1998 [12].

Besides its credence in treating type 2 diabetes, metformin also shows promise for the treatment of type 1 diabetes, diabetes in pregnancy, polycystic ovary syndrome (PCOS), ageing and cancer [13-19]. Its pleiotropic effects attract an avalanche of experimental and clinical studies; however, we still do not fully understand the precise mechanism of action. Several hypotheses have been proposed to suggest that the protective action of metformin is complex and multidirectional, which include reduction of oxidative stress, improvement of mitochondrial function, activation of AMP-activated protein kinase (AMPK), and modulation of autophagy/mitophagy [20,21].

In the current issue, Van and Liang et al present intriguing data revealing a unique property of metformin in faring against cardiotoxicity induced by doxorubicin [22]. Doxorubicin is a widely used and highly effective chemotherapeutic agent for the treatment of a broad spectrum of cancers. However, doxorubicin chemotherapy is associated with severe cardiotoxic effects that culminate in irreversible congestive heart failure. Due to the dose-dependent risk, the lifetime cumulative dose of doxorubicin should be limited under 450 mg/m^2 in a patient [23-25]. A common approach for managing doxorubicin cardiotoxicity is to use a cardioprotective agent during chemotherapy. However, current adjuvant regimens show marginal beneficial effects. Thus, intense research has been conducted to identify new strategies that can reduce doxorubicin cardiotoxicity but without compromising its antitumor activity. In this respect, metformin came under limelight. Van and Liang demonstrated that metformin diminishes doxorubicin-induced cardiomyocyte death likely through a mechanism involving inhibition of autophagy and mitophagy, which is contrasting to a prevailing notion of its ability to enhance autophagy and mitophagy. Autophagy is a self-digesting mechanism responsible for the removal of long-lived proteins and damaged organelles by the lysosome. Mitophagy is the process to degrade injured or dysfunctional mitochondria through the autophagy-lysosome pathway. Autophagy/mitophagy is a dynamic cellular process that can be either protective or detrimental. Combined, the study by Van and Liang raises an interesting point that metformin can modulate autophagy/mitophagy, not simply enhancing or inhibiting, but depending on the dose and duration of

doxorubicin treatment. Next obvious study will be to investigate whether metformin would be able to facilitate mitochondrial biogenesis in the doxorubicin context, which is a counterbalancing cellular event to mitophagy. This assumption is inferred from well-noted evidence that metformin is an AMPK activator and AMPK activation impacts on improving mitochondrial biogenesis. In addition to its ability to confer protection against doxorubicin-induced cardiotoxicity but without compromising doxorubicin antitumor activity, metformin per se also possesses antitumor property. Taken together, these presents a fine chance that metformin could work to reap benefits of its pleiotropic effects in cardio-oncology applications as an adjuvant agent for chemotherapies.

In summary, the clinical use of metformin has experienced a rocky journey over several centuries, starting from its herbal origins in Europe, to the synthesis and discovery of the glucose-lowering activity, and ultimately reaching the top spot among glucose-lowering agents. Metformin does not seem to have a single target mechanism, but rather exerting multiple effects that are individually modest whereas collectively substantial. The value of such a safe, effective, inexpensive, and versatile medication is duly appraised, and we eagerly await more evidence to support its use in diseases other than diabetes.

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