

A second look at the ancient drug: new insights into metformin

Metformin, a biguanide derived from *Galega officinalis* (French lilac), has been used for the treatment of type 2 diabetes (T2D) for over half century. It is now the most widely prescribed anti-diabetic drug and recommended as the first line oral therapy for T2D. Metformin is generally considered as a very safe drug with favorable cost-efficacy-ratio. With regard to the safety concern of its use in gestational diabetes, Bertoldo *et al.* provided us an excellent summary of the current knowledge on the role of metformin in pregnant women as well as in fetal development.

In addition to its use in T2D, metformin has also been prescribed for polycystic ovary syndrome (PCOS). In this issue, Neil P. Johnson reviewed the best available evidence for the use of metformin in women with PCOS and discussed its position among other options used to treat various problems faced by women with PCOS.

In recent years, metformin has gained a lot of attention for its potential application in the prevention and treatment of cancer. The idea of cancer preventive and therapeutic effect of metformin originates from a series of observational studies in populations with or without metformin consumption. Compared to its definitive performance in diabetic patients, the exact mechanism(s) of action and the direct molecular target(s) of metformin are less conclusive. In this special issue, Kasznicki *et al.* provided us an overview of proposed mechanism(s) of action of metformin in cancer prevention and therapy, along with preclinical and clinical data suggesting its favorable effect against cancer in different populations. The role of metformin on selective modulation of microRNAs to reprogram altered metabolism of a cancer cell toward that of untransformed cell was extensively reviewed by Pulito *et al.* Considering the crucial role of microRNAs

in cancer stem cells (CSCs) or stem cell-like cancer cells, which are believed to be difficult to eradicate by various treatments, Bao *et al.* further discussed the potential role of metformin in modulating CSC-associated microRNAs as part of the novel mechanism of action of metformin in the development and progression of breast and pancreatic cancers. Aside from the anti-tumor effect of metformin, Dr. Vladimir N. Anisimov presented a critical review regarding the capacity of metformin to prevent spontaneous and induced tumorigenesis based on published data derived from animal studies in an attempt to address the question “do metformin a real anticarcinogen”.

Despite the popularity of metformin in the field of cancer research, it is not negligible that concerns have been raised towards various observational studies indicating that metformin use may reduce the incidence and/or mortality of different types of cancer. In order to help us uncover the veil of mysterious biases occurred during these cohort studies, which have been mostly criticized, Yang and Chan reviewed and discussed in detail the methodologies employed in metformin-related observational studies. Another paradox that metformin is facing is whether it acts against or towards cognitive impairment and Alzheimer disease in patients with T2D. In two separate editorials, European scientists Ilker Tasci and Paula I. Moreira presented their own opinion towards this controversy.

Herein, I would like to acknowledge each and every one who has devoted their time and efforts to this special issue. We believe this issue has included most up-to-date information regarding the conventional use of metformin as well as the potential expansion of its applications. Hopefully our readers will enjoy and benefit from reading this special issue.

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