Editorial

Metformin: a promising candidate for chemoprevention of colorectal tumor and its future

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Type 2 diabetes mellitus (DM) has been associated with increased risk of colorectal cancer (CRC). DM and CRC are significant health problems worldwide and have common risk factors, including obesity. In addition, they are sharing possible pathophysiological mechanisms such as hyperglycemia, hyperinsulinemia, insulin resistance, and chronic inflammation (1).

Metformin is a classic biguanide drug that has been widely used as first-line therapy for type 2 DM. Metformin inhibits hepatic gluconeogenesis and reduces insulin resistance in peripheral tissue, thus decreasing the levels of circulating glucose and increasing insulin sensitivity. It is known as a safe and economical drug which has been used for more than 50 years. Metformin has a variety of metabolic mechanisms and clinical benefits beyond the control of diabetes, and shows the possibility of potential new uses for some disorders, such as obesity, polycystic ovary syndrome, thyroid dysfunction, and some cancers (2).

As for the cancer prevention, Evans *et al.* (3) in a pilot cohort study reported that metformin was associated with a reduced risk of several cancers. Then, large cohort studies and systematic analyses supported the cancer-protective effect of metformin in diabetes patients (4), showing that patients with diabetes taking metformin had a lower incidence of cancer and better outcomes than those not taking the drug (5). Although there have been some controversial report, many observational studies and meta-analyses have shown that metformin is also associated with lower incidence of CRC and lower risk of CRC mortality (6). Therefore, metformin has recently gained much attention because of its possible anti-tumor effects. In addition, there were some studies on the relationship between metformin use and colorectal adenoma, the precursor of CRC, showing that metformin had a protective beneficial effect in the development of colorectal adenoma in colonoscopic surveillance of diabetic CRC patients (7,8).

CRC can be sporadic or hereditary, and has definite measurable premalignant lesions, and metachronous cancer risk is high. Therefore, CRC is a good candidate for chemoprevention trials, and many clinical trials using prevalence of adenoma, premalignant lesion of CRC, have been performed for identification and validation of candidate chemopreventive drugs. Well-known chemopreventive drugs against CRC, such as aspirin, nonsteroidal anti-inflammatory drugs, and cyclooxygenase 2 selective inhibitors, are still in many clinical trials in various clinical settings (9). However, their use for chemoprevention is limited in only very high risk populations such as patients with familial adenomatous polyposis because of their cardiovascular side effects or bleeding risk.

In view of ideal conditions of chemopreventive agents, such as safety, good compliance, cost, and well-defined mechanism, new drugs are needed and metformin meets these criteria. Despite the promising results in retrospective or cohort studies, there were no results from well-controlled, prospective clinical studies using metformin for CRC and its precancerous lesions. In addition, the effect of metformin on nondiabetic patients should also be assessed because the direct anti-tumor effect of metformin is also well known and it has no glucose-lowering effect in

nondiabetic patients. In this situation, before large scale trial with long duration, alternative clinical trial using surrogate endpoint over a shorter duration would be efficient to test the chemopreventive effect of metformin.

Then, Higurashi *et al*. (10) finally performed a placebo-controlled, randomized, multicenter trial to see the difference of polyp recurrence rate between metformin use and placebo group, and provided the first direct evidence for the chemopreventive efficacy of metformin. In a double blinded, randomized trial of 151 patients who underwent removal of colorectal polyps, use of metformin (250 mg per day) significantly reduced the prevalence of total polyps [RR =0.67 (95% CI, 0.47–0.97)] and adenomas [RR =0.60 (95% CI, 0.39–0.92)] after 1 year, compared with placebo group, and this beneficial effect was associated with an effect of metformin on insulin resistance. In addition, there was no significant difference in the incidence of adverse events between the two groups, all of which were grade 1.

These results are very valuable for several reasons. First, this study is the first evidence of chemopreventive effect of metformin through a placebo controlled randomized trial using an established surrogate endpoint for cancer. Although the recurrence of colorectal polyps, premalignant lesions, was used as surrogate endpoint, in many chemoprevention trials of CRC, the incidence of polyps or cancer have been used as the endpoint of study. Second, these results show the effectiveness and safety of low dose metformin. The effectiveness of low dose is very important in chemopreventive drugs because of the tolerable side effects and drug compliance. Third, the results elucidate the anti-neoplastic effect of metformin in non-diabetic patients, suggesting that the lower cancer risk in diabetes patients taking metformin is due to direct effect of metformin against colon carcinogenesis as well as improved diabetes control. Finally, this report demonstrates that metformin more effectively reduce the risk of polyp recurrence in patients with a greater reduction of insulin resistance, suggesting the usefulness of insulin resistance as a biomarker to predict its anti-neoplastic effect.

As for the mechanism of action, many reports have shown that various molecular mechanisms were involved in anti-neoplastic effect of metformin: indirect effect via an insulin-dependent pathway, and direct anti-tumor effect via the AMP activated protein kinase (AMPK)-dependent and -independent pathway (11). As a first-line anti-diabetic agent, metformin regulates insulin/insulin-like growth factor (IGF)-related pathways in indirect effect of tumorigenesis inhibition by diabetic control, because glucose and insulin fuel the growth of neoplastic cells via IGF. Experimental data also support a direct effect of metformin in suppressing specific pathways that promote cell proliferation, motility, invasion, and migration, via the AMPK/mammalian target of the rapamycin (mTOR) pathway. Activated AMPK inhibits the mTOR-mediated synthesis of key proteins responsible for malignant transformation and cancer cell growth, which is thought to be a main mediator of the potential anticancer mechanism of this drug. In addition, AMPK-independent molecular pathways were also involved in anti-inflammation activity, cell cycle arrest, and cancer stem cell inhibition. Preclinical studies using mouse models also supported these findings, showing that metformin suppressed colonic epithelial proliferation and tumor in an azoxymethane-induced BALB/c mouse model and an ApcMin/+ mouse tumor model (12,13). In addition, metformin reversed the effects of the high-energy diet on tumor growth in a mouse xenograft model (14).

In the view of these various molecular mechanisms of metformin, Higurashi *et al*. showed that the effect of metformin on polyp recurrence was dependent on the reduction of insulin resistance that means suppression of insulin/IGF-related pathway, and the response of insulin resistance could be the biomarker to predict the anti-tumor response of metformin. Therefore, we need more research on predicting markers related with other mechanisms of metformin response, including direct anti-tumor effect of metformin which were mentioned above. For example, the response to metformin is known to exhibit significant interindividual variations (15). This variation is related to body mass index, metabolic status, disease status, and pharmacogenetics of transporter, which are equally applicable both in diabetes and in other diseases including cancer. Previous studies showed that the location and expression levels of membrane transporters, such as organic cation transporters (OCTs) and multidrug toxin extrusion proteins, contributed to the interindividual variability of the metformin effect among different organs (15). In addition, these transporters show significantly different expression levels between normal and tumor tissues, which are associated with various genetic and non-genetic variations, such as single-nucleotide polymorphism and epigenetic and environmental factors. In future clinical studies, these factors also should be considered.

Despite of the first well designed trial showing chemopreventive effect of metformin, this study has several limitations. Because a single low dose of metformin was used

just for 1 year, they could not show dose-response results and this study was underpowered to detect rare adverse events of long term use. In addition, they performed repeat follow-up colonoscopy after only 1 year without clearing colonoscopy. Therefore, some of the polyps found on the 1-year colonoscopy might have included lesions missed at the baseline colonoscopy rather than recurrent lesions. Finally, this study was done in a small region of Japan, and the sample size was small. To generalize these results, it is necessary to perform long-term clinical trials with larger populations involving many nations and ethnic groups.

Furthermore, this chemopreventive role of metformin can extend into adjuvant setting of CRC. Despite some controversial reports, several retrospective and cohort studies showed that metformin use in CRC patients with diabetes is associated with lower mortality compared with patients not taking metformin, suggesting the possibility of an adjuvant role of metformin (16). In addition, there have been some experimental data, showing that metformin can suppress cancer stem cells which are known to be resistant to conventional chemotherapy and the cause of cancer recurrence and metastasis (17). These cancer stem cell killing effects of metformin support the possibility of using metformin as an adjunctive agent combined with conventional chemotherapy.

As for the role of adjuvant treatment of chemopreventive drug in CRC, we already know that use of aspirin, a well-known chemopreventive agent, after diagnosis of CRC shows the survival benefit in retrospective or cohort studies (18), and PIK3CA mutations influence the effect of aspirin in the adjuvant setting of CRC (18). Currently, the study using aspirin as a adjunctive agent in adjuvant setting of CRC is under clinical trial. Like aspirin, metformin might be also considered as an adjunctive agent in adjuvant setting of CRC with a useful biomarker that may guide adjuvant therapy.

In summary, Higurashi *et al.* (10) provided the first direct evidence for the chemopreventive efficacy of metformin through well-designed prospective clinical trial. As a next step, long-term, large-scale, well-designed, and randomized controlled trials are needed to confirm this potential benefit of metformin as a chemopreventive drug for both the diabetic and nondiabetic population. In addition, studies in combination with other established agents like aspirin would be possible to enhance chemopreventive effect and decrease adverse events. Moreover, metformin could also be the basis for development of modified drugs possessing better anti-tumor activity.

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Footnote

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