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Editorial

Methylmalonic acid's potential as a prognostic indicator for cancer-related mortality

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Methylmalonic acid (MMA) is a byproduct of the propionate metabolism, and its circulatory concentrations remain low under normal physiologic conditions. MMA is produced through the propionate metabolic pathway, wherein branched-chain amino acids (leucine, isoleucine, and valine), fatty acids, and cholesterol undergo catabolism, yielding propionyl-CoA within the mitochondria. Propionyl-CoA is subsequently transformed enzymatically into D-methylmalonyl-CoA via the action of propionyl-CoA carboxylase, and then the conversion of the D-isomer to the L-isomer is catalyzed by methylmalonyl-CoA epimerase. Following these steps, L-methylmalonyl-CoA is converted into succinyl-CoA. The enzyme responsible for this conversion is methylmalonyl-CoA mutase, which operates in a manner contingent on the presence of vitamin B-12. This conversion allows succinyl-CoA to enter the tricarboxylic acid cycle [1].

In certain pathologic circumstances, such as cases of vitamin B-12 deficiency [2,3] and in conditions of renal dysfunction [4,5], circulatory MMA concentrations are elevated. Notably, numerous studies have revealed that circulating MMA concentrations tend to increase with age [6–9], putting forward the idea that MMA might be an important component of aging and age-related diseases [1]. Consistent with this notion, higher MMA concentrations have been shown to be associated with an increased risk for all-cause mortality in diabetic patients [10] as well as in patients with cardiovascular disease [8,11]. Strikingly, even when probed in the general population, through the LifeLines Cohort Study, elevated MMA concentrations in circulation are associated with all-cause mortality, independently of vitamin B-12, renal function, or sex [12].

An important and often overlooked age-related disease is cancer [13]. For instance, the median age in years at diagnosis is 62 for breast cancer, 71 for lung cancer, and 67 for colorectal cancer. Strikingly, accumulation of MMA concentrations in circulation has been shown to be the mechanistic link between the circulatory reprogramming that occurs with old age and the progression of breast and lung tumors into metastatic disease [9]. Importantly, these findings have recently been extended to colorectal cancer, suggesting that increased concentrations of MMA in circulation might be a general inducer of tumor progression and poor prognosis [14]. Further highlighting the importance of MMA as a facilitator of tumor progression into metastatic disease, non–age-related aggressive tumors, such as triple negative breast cancer, can hijack MMA production through cancer cell autonomous deregulation of propionate metabolism, thereby empowering their acquisition of prometastatic traits [15]. Recent studies point to additional important effects of MMA in tumorigenesis through its ability of also regulating the tumor microenvironment and its interactions with cancer cells. For instance, MMA has been shown to lead to activation of fibroblasts toward a cancer-associated fibroblast phenotype, which contributes to tumor progression [16]. Additionally, Tejero et al. [17] has put forward MMA as an immunomodulatory metabolite whose accumulation in circulation drives $CD8^+$ T cell exhaustion and suppresses antitumor immunity. Together, these studies put forward MMA as a major regulator of tumorigenesis and support a model where elevated concentrations of MMA, on one hand, act directly on cancer cells, endowing them with the proaggressive properties necessary to metastasize and, on the other hand, act on the different components of the tumor ecosystem to facilitate tumor progression.

Importantly, these mechanistic studies raise the question of whether MMA concentrations can be used as a biomarker to predict patient prognosis. Previously, high MMA concentrations at diagnosis were shown to predict clinical frailty and to correlate with poor overall survival in patients with breast cancer [18], suggesting a potential role for MMA as a biomarker of cancer-associated mortality. Published in this issue of *The American Journal of Clinical Nutrition*, an important article by Liu et al. [19], took advantage of the National Health and Nutrition Examination Survey data of cancer survivors over a 10-year follow-up period to interrogate the potential of MMA as a predictor of mortality. Strikingly, this study demonstrates that high concentrations

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Abbreviation: MMA, methylmalonic acid.

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of MMA in the serum significantly correlated with increase in long-term mortality risk in cancer survivors, independently of vitamin B-12 concentrations. Moreover, gene expression evaluation of propionate metabolism–related enzymes in the 33 cancer types available through The Cancer Genome Atlas supported the link between MMA and poor prognosis as a clear link between MMA-related gene risk score and survival probability in at least 14 different cancer types [19]. Together, this article cements MMA concentrations in circulation as a general driver of tumor progression putting forward the idea of using MMA concentrations as an easily translatable biomarker of prognosis and cancer-associated mortality even in cancer survivors and supports the need for more mechanistic studies to comprehensively understand the contribution of MMA for tumor progression. Moreover, considering the vitamin B-12 independent nature of MMA's association with cancer-driven mortality, these studies lay the ground for future work studying which factors contribute to MMA elevation in circulation and their manipulation as potential interventions that may curtail cancer-associated mortality.

Author contributions

The sole author was responsible for all aspects of this manuscript.

Conflict of interest

The author reports no conflicts of interests.

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