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Commentary

Kynurenine pathway enzyme KMO in cancer progression: A tip of the Iceberg

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The kynurenine pathway (KP) represents a major route of tryptophan (Trp) metabolism in mammals and is known to generate a wide range of bioactive metabolites. Due to the growing interest in the functional effects of the KP pathway on the body, several key KP enzymes have been studied for their pivotal roles in human disorders such as neurodegeneration, schizophrenia, depression, autoimmunity, and cancer [1].

The rate-limiting step of KP is the conversion of Trp-to N-formylkynurenine by indoleamine 2,3-dioxygenease (IDO) and tryptophan-2,3-dioxygenase (TDO), leading to an increase in kynurenine. Kynurenine can then be converted to diverse bioactive metabolites by a series of KP enzymes. Among them, kynurenine 3-monooxygenase (KMO) functions as a pivotal enzyme in the main branch of the enzymatic cascade because it generates several toxic metabolites, including 3-hydroxykynurenine and quinolinic acid, which are responsible for neurodegenerative and inflammatory disorders [2,3].

In 2005, the cancer-promoting role of KP pathway enzymes was first reported by Prendergast and colleagues [4]. These researchers showed that IDO promoted tumor formation by inhibiting T cell-dependent immunity via its enzymatic function. Then, in 2011, Platten and colleagues first reported the strong expression of TDO in several types of cancer, including B-cell lymphoma, Ewing sarcoma, bladder cancer, cervical cancer, colorectal cancer, lung cancer and ovarian cancer [5]. This group found that TDO was responsible for the constitutive release of kynurenine from cancer cells. TDO-derived kynurenine was confirmed to promote cancer progression in both paracrine and autocrine manners. In the former pathway, kynurenin from cancer cells binds to the aryl hydrocarbon receptor (AHR) on T cells and suppresses T cell proliferation and oncolytic activities, attenuating anticancer immunity [6]. The latter pathway involves kynurenine from cancer cells binding to AHR on themselves and increasing cancer cell survival and motility. After these studies, the role of IDO/TDO and its therapeutic implications have been intensely investigated in various types of cancer, particularly as a promising strategy for cancer immunotherapy [7,8]. However, the molecular and biological function of KMO in cancer has rarely been investigated. In this article in *EBioMedicine*, Liu and colleagues investigated KMO as a functional biomarker in breast cancer progression and elucidated its molecular mechanism [9].

In this article, Liu and colleagues convincingly showed the clinical value of KMO expression in breast cancer patients, particularly in triple negative breast cancer (TNBC), which lacks specific targeted drugs. Moreover, these researchers first revealed a novel enzymatic activity independent function of KMO in TNBC. In summary, they found 1) a positive correlation between the increased expression of KMO in breast cancer and TNBC and metastasis and recurrence, 2) the contribution of KMO expression to the malignant phenotype of TNBC cells, particularly cancer stem cell (CSC) properties, and 3) KMO-induced β-catenin stabilization, which leads to increased expression of pluripotent genes such as Nanog, Oct4, and Sox2. Interestingly, enzymatic inhibition of KMO could not destabilize β-catenin protein and could not attenuate the malignant phenotype of TNBC cells, while the overexpression of enzymatically inactive KMO could stabilize the β-catenin protein levels and increase the malignant phenotype of TNBC cells. Mechanistically, Liu and colleagues first documented the binding of KMO to the complex of β-catenin and glycogen synthase kinase-3 β (GSK3β). KMO was confirmed to reduce the kinase activity of GSK3β, resulting in a decrease in phosphorylated β-catenin, which is susceptible to ubiquitination and degradation. Collectively, this is the first report that emphasizes the nonenzymatic function of KMO in TNBC cells, which drives β-catenin stabilization and pluripotent gene expression, indicating the importance of further studies on how KMO suppresses the GSK3β kinase activity against β-catenin.

Taken together, the involvement of KP enzymes in cancer progression has attracted researcher interest in their diagnostic or therapeutic potential for cancer treatment. Although KMO has rarely been explored in cancer relative to other key KP enzymes, such as IDO and TDO, this article provided a new direction of KMO research by proposing a novel mechanism by which KMO promotes breast cancer malignancy. Given that other KP pathway enzymes facilitate tumorigenesis through their bioactive metabolites, further investigations to determine whether KMO-mediated metabolic alteration would affect the tumorigenic process are needed to fully understand the biological function of KMO.

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J-SN and S-YP equally contributed to the literature search and wrote this commentary together.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] Platten M, Nollen EAA, Röhrig UF, Fallarino F, Opitz CA. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. Nat Rev Drug Discov 2019;18(5):379–401.

[2] Zwilling C, Huang S-Y, Sathyasaikumar KV, Notarangelo FM, Guidetti P, Wu H-Q, et al. Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. Cell 2011;145(6):863–74.

[3] Zhang S, Sakuma M, Deora GS, Levy CW, Klausing A, Breda C, et al. A brain-permeable inhibitor of the neurodegenerative disease target kynurenine 3-monooxygenase prevents accumulation of neurotoxic metabolites. Commun Biol 2019;2:271.

[4] Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med 2005;11(3):312–9.

[5] Opitz CA1, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature 2011;478(7368):197–203.

[6] Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010;185(6):3190–8.

[7] Prendergast GC, Malachowski WP, DuHadaway JB, Muller AJ. Discovery of IDO1 inhibitors: from bench to bedside. Cancer Res 2017;77(24):6795–811.

[8] Schramme F, Crosignani S, Frederix K, Hoffmann D, Pilotte L, Stroobant V, et al. Inhibition of Tryptophan-dioxygenase activity increases the antitumor efficacy of immune checkpoint inhibitors. Cancer Immunol Res 2020;8(1):32–45.

[9] Huang TT, Tseng LM, Chen JL, Chu PY, Lee CH, Huang CT, et al. Kynurenine 3-monooxygenase upregulates pluripotent genes through β-catenin and promotes triple-negative breast cancer progression. EBioMedicine. DOI: https://doi.org/10.1016/j.ebiom.2020.102717