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Review

PLOD2 in cancer research

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ABSTRACT

Collagen is not only the most abundant protein providing the scaffold for assembly of the extracellular matrix (ECM), but also considered to be the "highway" for cancer cell migration and invasion depending on the different collagen organizations. The accumulation of stabilized collagen is enhanced by different covalent collagen cross-links, lysyl hydroxylases 2 (encoded by the *PLOD2* gene) is the key enzyme mediating the formation of the stabilized collagen cross-link. Interestingly, *PLOD2* is overexpressed in different cancers and closely related to a poor prognosis. To the best of our knowledge, only the mechanisms of *PLOD2* regulated by HIF-1α, TGF-β and microRNA-26a/b have been elaborated. In addition, several pharmacologic inhibitors of *PLOD2* have been confirmed to have an anti-metastasis effect. However, there have been no reviews about *PLOD2* in cancer research published thus far. In brief, this review about *PLOD2* will describe the function, regulatory mechanism, and the inhibitors of *PLOD2* in cancer, suggesting the credible clinical evaluation of a prognostic signature in pathological examination and the possible development of therapeutic strategies targeting *PLOD2* in the future.

Contents

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1. Background

Mounting evidence currently suggests that the progression of tumour is determined not only by tumour cells, but also by the tumour microenvironment (TME), while previous studies regarding tumour metastasis have primarily focused on the adhesion and migration ability of cancer cells themselves. Moreover, as the chief component of the TME, the extracellular matrix (ECM), plays a significant role in tumour progression, including differentiation, proliferation, migration, adhesion and survival, especially in tumour metastasis [1–3]. Meanwhile, collagen is not only considered to be the most abundant protein providing the scaffold for ECM assembly but is also considered to be the "highway" for cancer cell migration and invasion [4,5]. Collagen is no longer thought to provide a barrier for migration and invasion but is now considered to promote metastasis based on different collagen organizations [6].

Evidence from multiple types of human cancers suggests that the accumulation of stabilized collagen is enhanced by different covalent collagen cross-links [7,8]. As previously reported, lysyl hydroxylases 2 (LH2, encoded by the *PLOD2* gene) is the key enzyme mediating the formation of stabilized collagen cross-links [9]. *PLOD2* is one member of the *PLOD* family (*PLOD1*, *PLOD2*, and *PLOD3*). Only *PLOD2* plays the key role in formation of stabilized collagen cross-links by hydroxylation of lysyl residues [10]. Gain- and loss-of-function studies showed that LH2 hydroxylated telopeptidyl lysine residues on collagen, shifted the tumour stroma toward higher levels of hydroxylysine aldehyde–derived collagen cross-links (HLCCs), lower levels of lysine aldehyde–derived cross-links (LCCs), increased tumour stiffness, and enhanced tumour cell invasion and metastasis [4,5].

PLOD2 was first reported about the activity of LH2 in the liver with hepatic injury, in 1974 [11]. In 1996, *PLOD2* was first reported in breast cancer research by Smith [12]. In recent years, an increasing number of articles on *PLOD2* in cancer research have been published and cited (Fig. 1A and B). Thus far, there have been no reviews on *PLOD2* in cancer research. In this article, we will describe the function and mechanisms of *PLOD2* in different cancers and explore the potential pharmacologic inhibitors of *PLOD2* for their anti-metastatic effect, demonstrating the credible clinical evaluation of a prognostic signature in the pathological examination and suggesting the possible future development of therapeutic strategies targeting the TME.

2. *PLOD2* in different cancers

According to the Cancer Cell Line Encyclopedia (CCLE) project, *PLOD2* has been reported in many different cancers as shown in Fig. 2A. Furthermore, the expression of *PLOD2* in various cancers is strikingly different. Further database analysis demonstrates that *PLOD2* expression is higher in adenocarcinoma tissues than in normal tissues via the Oncomine™ database in several cancers such as lung, breast, liver, pancreas and so on (Fig. 3A–D). In fact, sarcomas [7], bladder cancer [13], renal cell carcinoma [14], glioblastoma [15], cervical cancer [16], oral carcinoma [17], bone metastasis [18] and other cancers also significantly overexpressed *PLOD2*, as previously reported. The overexpression of *PLOD2* is closely related to poor prognosis based on Kaplan-Meier plotter, as shown in Fig. 3G and H. Otherwise, when the *PLOD2* expression is not different in gastric adenocarcinoma tissues versus normal tissues, it consistently has no relation with prognosis in gastric cancer (Fig. 3F and I). In brief, *PLOD2* may be a biomarker for poor prognosis in several cancers.

2.1. Hepatocellular carcinoma

PLOD2 was first confirmed as a novel prognostic factor in hepatocellular carcinoma (HCC), in 2011 [19]. When compared with the low-expression group, the disease-free survival time in the high *PLOD2* expression group of HCC patients is significantly shorter. *PLOD2* expression is significantly correlated with tumour size and macroscopic intrahepatic metastasis among all the clinico-pathological factors. In univariate analysis, six prognostic factors (macroscopic intrahepatic metastasis, tumour multiplicity, microscopic portal invasion, histological grade, macroscopic intrahepatic metastasis, and *PLOD2* expression) are significant for disease-free survival. In brief, *PLOD2* is identified as a significant, independent factor of poor prognosis. Furthermore, the study also preliminarily shows that *PLOD2* expression could be regulated by hypoxia, but the mechanism of regulation is still unknown.

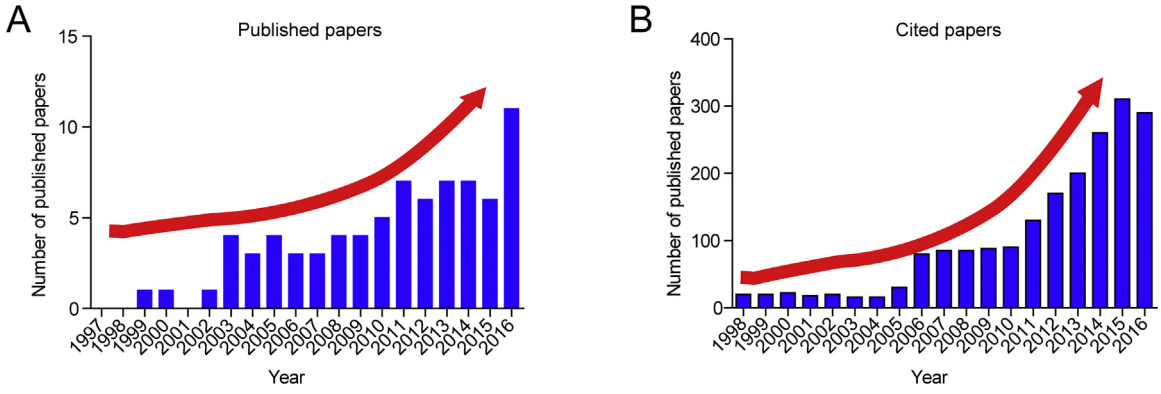

Fig. 1. Published articles on *PLOD2* in cancer research. (A). The number of published papers about *PLOD2* in cancer research. (B). The number of cited papers about *PLOD2* on cancer research. The number is based on Web of Science™ Core Collection. Topic = ((TOPIC: (*PLOD2*) AND TOPIC: (Cancer)) OR (TOPIC: (Lysyl hydroxylase 2) AND TOPIC: (Cancer))). (http://apps.webofknowledge.com/).