ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Review: Association of Myeloid derived growth factor (MYDGF) with Cancer.

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ABSTRACT

Overexpression of growth factors are an indicator of poor prognosis for several kind of malignancies like stomach, glioma, liver and colon cancer. Growth factors secreted from several cell types usually serve to maintain cellular homeostasis. Sudden mutation in their associated genes directs them to be overexpressed or hyperactive resulting excessive cell proliferation. Myeloid derived growth factor has emerged as a freshly identified growth factor in recent studies. It is primarily secreted from bone marrow derived monocytes and macrophages having conceivable cardio protective role. Additionally recent studies also found its association with cancer particularly in hepatocellular carcinoma. Therefore, we have summarized all the studies available in limited numbers for MYDGF including some clinical data from patient database in order to support its possible association with several cancer types.

Keywords: Myeloid derived growth factor (MYDGF), Cancer, Inflammation, Hepatocellular carcinoma (HCC)

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ISSN: 0975-8585

INTRODUCTION

Growth factors are secreted by various cell types, including macrophages, and functions in cell proliferation, differentiation, apoptosis, survival, migration and cellular homeostasis by binding to its receptor. Multiple signaling pathways lie downstream of their receptor. Any mutation of their respective genes, that causes its product to be overexpressed or hyperactive, results in excessive cell proliferation leading to cancer [1]. Amplification of growth factors like vascular endothelial growth factors (VEFR), epidermal growth factor (EGF), transforming growth factor-α (TGF-α) etc. are an indicator of poor prognosis for several kinds of malignancies such as breast, colon, liver and gastric cancer [2]. Along with the established growth factors playing pivotal role in cancer, newly identified growth factors also require researchers attention so that they be can serve as prognostic marker and therapeutic target. Therefore, we have summarized the recent findings of a freshly identified Myeloid derived growth factor (MYDGF) and its possible association with cancer.

Myeloid derived growth factor (MYDGF) is a secreted protein encoded by an open reading frame on chromosome 19 (C19orf10) [3]. The mouse homolog of C19orf10 was originally cloned from a bone marrow derived stromal cell line and was named as SF20 or interleukin 25 (IL-25) since it was thought to be a factor for lymphoid cell proliferation [4]. However, this claim was subsequently retracted due to the inability to reproduce the biological effects [5]. Subsequent proteomic studies found that this protein is secreted from murine fibroblasts during adipogenesis [6], from human synoviocytes [7] and from cultured murine bone marrow derived macrophages [8]. SAGE analysis also revealed MYDGF to be over expressed in hepatocarcinoma cells (HCC) associating MYDGF with cancer phenomenon for the very first time [9].

Korf-Klingebiel et al. designated and demonstrated MYDGF (HUGO Gene Nomenclature Committee approved) as a paracrine-acting protein having potent cardiac myocyte-protective and angiogenic activities. Results evolved from their reports made a strong background for connection between MYDGF and cancer. Firstly, they reported that MYDGF is secreted from bone marrow derived monocytes and macrophages especially from the chemokine receptor CXCR4+ population and was able to increase human coronary artery endothelial cells (HCAECs) proliferations and their capacity to form closed tubes which represents an angiogenic property of MYDGF [3]. It is well documented that tumor microenvironment also occupy tumor associated macrophages (TAMs) which secrete an extensive list of pro-angiogenic growth factors including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor etc. for cancer invasion and metastasis [10]. Therefore, MYDGF might also be a macrophage secreted growth factor having a hidden role in cancer progression. Secondly, Korf-Klingebiel et al. also provided very critical evidence for MYDGF in protecting cardiac tissues from reperfusion following ischemic threat. MYDGF-treated animal's cardiac tissues displayed significant reduced scar size and increased contractile function relative to untreated controls [3]. These results suggest that MYDGF may play an important role in response to hypoxia which is again a common feature of many solid tumor microenvironment. Therefore, we have summarized all the studies available in limited numbers for MYDGF including clinical data from TCGA database in order to support its possible association with cancer.

MYDGF in Inflammation

Inflammation is a decisive component of cancer progression. Cancers usually arise from sites of infection, chronic irritation and inflammation. It is clear enough that tumour microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, nurturing proliferation, survival and migration [11].

Inflammatory microenvironment is often associated with increased MYDGF expression. Weiler et al. found significant amount of MYDGF into the synovial fluid of inflammatory disease like rheumatoid arthritis and osteoarthritis patients (7–184 mgml1) by Proteomic analysis of fibroblast-like synoviocytes (FLSs) [7]. Again, Bailey et al. had reported that granulocyte macrophage colony-stimulating factor differentiated murine bone marrow derived macrophages (GM-BMDM) display markedly elevated levels of MYDGF. Macrophages produced under these conditions display inflammatory M1 macrophage like properties characterized by the production of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-12, and IL-23 [8]. Proteomic characterization of human proinflammatory M1 macrophages in response to *Candida albicans* also expressed increased MYDGF level [12]. These result revealed strong association of MYDGF being induced under inflammatory conditions.

Obesity, one of the major risk factor behind cancer is characterized by excess of body fat mass, which is mostly stored in adipose tissue. Adipocyte-specific or -enriched secreted proteins, are termed as adipokines. Adipokines such as leptin, adiponectin, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α) and their respective signaling pathways have drawn much research attention in the field of oncology and cancer therapeutics. They are believed to contribute in enhanced inflammatory signaling, angiogenesis, cellular proliferation and ultimately, carcinogenesis. Proinflammatory cytokines such as IL-6, TNFα are also adipokines that are widely involved in tumourigenesis [13]. By profiling proteins secreted from preadipocytes (mouse 3T3-L1 cells) by means of 2 dimensional electrophoresis and mass spectrometry, Wang et al. identified MYDGF as an adipokine which was secreted from murine fibroblasts during adipocyte differentiation leading to the suggestion that it is involved in adipogenesis [6]. Therefore MYDGF may also play a role in forming dysfunctional adipose tissue which ultimately may results in cancer.

MYDGF in Cancer

The very first time researchers found potent connection of MYDGF with cancer was in HCC. Sunagozaka et al. demonstrated that gene expression analysis indicated overexpressed MYDGF in approximately two-thirds of HCC tissues compared to the adjacent noncancerous liver tissues. Its expression levels were significantly higher in tumor epithelial cells than in stromal cells. They also revealed that this secretory protein has a positive correlation with one of the established HCC markers alfa-feto protein (AFP). Over expressed MYDGF was able to regulate HCC cell proliferation through Akt/mitogen-activated protein kinase (Akt/MAPK) pathways. Sunagozaka et al suggested that MYDGF might be one of the growth factors and potential molecular targets activated in HCC [9].

MYDGF may have an migratory influence in HCC. Proteomic analysis of Epigenin treated huh-7 cells showed 1.5 fold decreased expression of both vimentin and c19orf10 mRNA level in a same manner. Further, RT-PCR results confirmed that treatment with Epigenin resulted apoptosis in HCC cells with decreased vimentin and c19orf10 expression. Epigenin treatment is potentially related to anti-angiogenesis and anti-migration and vimentin is a key to angiogenesis and migration [14]. Since there was similar decreased pattern both vimentin and c19orf10 share after apigenin treatment, it can be hypothesized MYDGF also having migration and angiogenesis property in HCC. Hollow fiber bioreactor (HFB) system revealed increased secretion of MYDGF protein in cholangiocarcinoma which is a bile duct cancer. Since one of the cause behind this cancer is liver fluke (*Opisthorchis viverrini*), there is a possible association of diseased or infected liver having increased expression of MYDGF too [15].

In vitro observations can be rationalized to some extend by studying patient database studies available online in order to obtain clinical relevance. The Cancer Genome Atlas (TCGA) research database provides a large scale of numerous parameters for cancers. Online availability of these data allows to comprehend non-clinical data with information gathered from patients in order to effectively translate results from the bench into practical clinical application. We have tried to correlate MYDGF's association with cancer where the following results are solely analyzed and provided by TCGA database (http://cancergenome.nih.gov/). Clinical data also supports MYDGF being over expressed in HCC patients. TCGA liver cancer RNAseq (IlluminaHiSeq; N=373) data set claims 27 (7%) out of 373 sequenced samples alerted MYDGF expression (Figure 1a) where its mRNA level is higher in altered HCC tissues compared to the unaltered group (p-Value<.001) (Figure 1b) [16,17]. Clinical specimens from the human protein atlas (www.proteinatlas.org) revealed MYDGF having positive strong expression (>75%) in HCC, and negative weak expression in normal liver (Figure 2a). Consistently, Patients expressing high MYDGF level shows shorter overall survival (Kaplan-Meier analyses in TCGA database) than patients with no alteration (Log rank p-value=0.346) (Figure 2b) suggesting a potential use of MYDGF as a favorable prognostic marker in HCC patients [16,17].These database results are strong enough to hypothesize strong clinical relevance of MYDGF in HCC. Other than HCC, MYDGF was also found to be over expressed in Oral Squamous Cell Carcinoma (OSCC) [18], large cell lung cancer cell lines [19]. Though biological activity of such potential protein is yet to be elucidated.

ISSN: 0975-8585

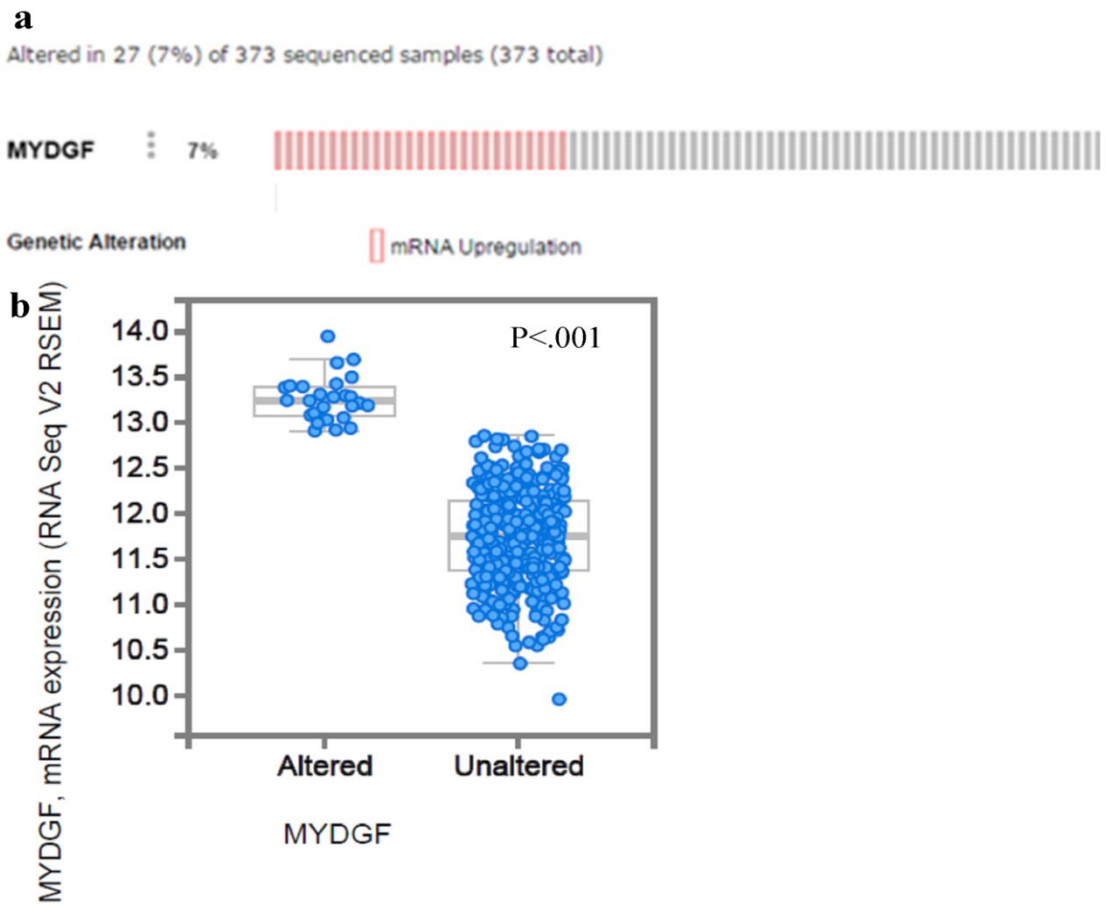

Figure 1:Increased MYDGF mRNA expression in HCC patients. (a) TCGA liver cancer RNAseq (IlluminaHiSeq; N = 373) data set shows 27 (7%) out of 373 sequenced samples alerted MYDGF expression. (b) MYDGF mRNA level is higher in altered HCC tissues compared to unaltered group (p-Value<.001).

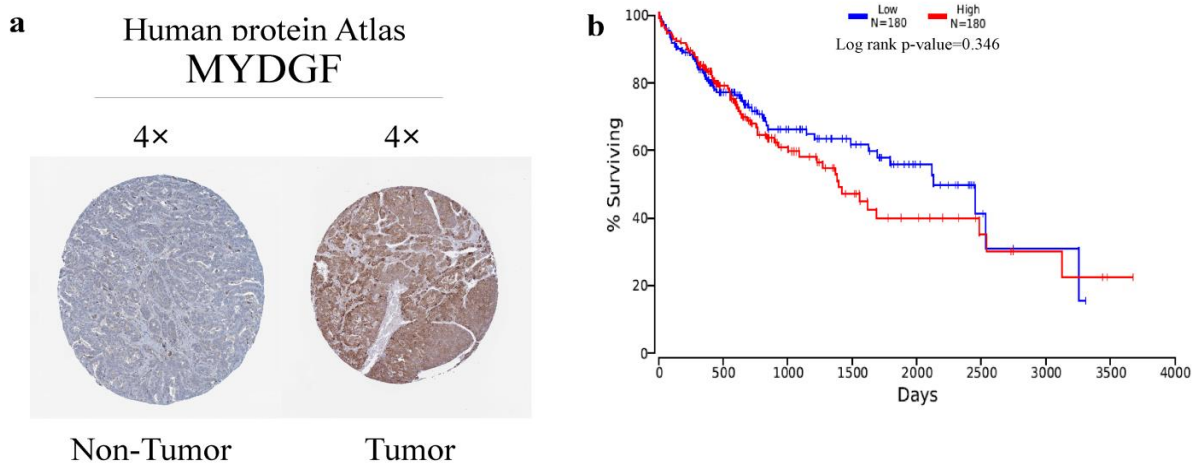

Figure 2:(a) MYDGF expression in normal liver tissue and hepatocellular carcinoma specimens. Images were taken from the Human Protein Atlas (http://www.proteinatlas.org). (b) (Kaplan-Meier-TCGA database represents overall survival percentage among patients with high (N=180) and low (N=180) MYDGF expressing level. (Log rank p-value=0.346).

ISSN: 0975-8585

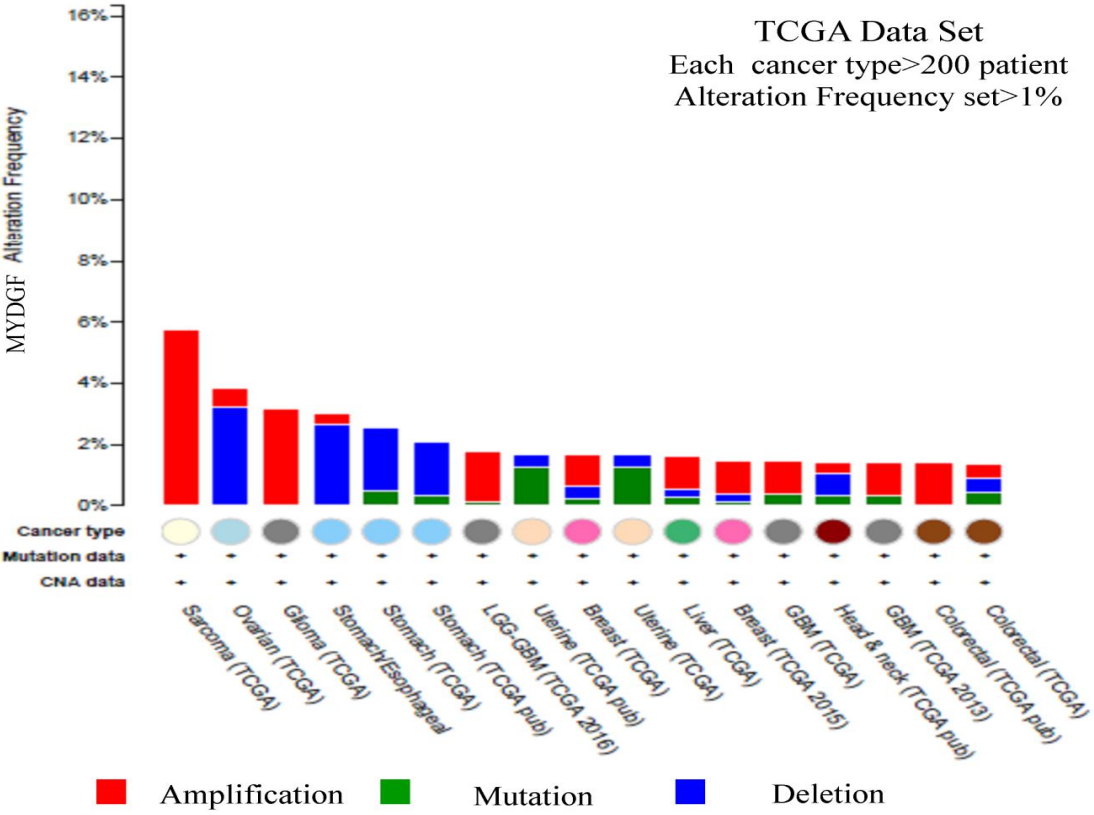

Figure 3: MYDGF amplification frequency in different types of cancer from TCGA dataset (Each cancer type>200 patients)

Table 1: MYDGF's Amplification, Mutation, Deletion and mRNA expression on different cancer (TCGA dataset)

Serial no.	Study Abbreviation	Total Cases	Cases Altered %	Amplific-ation %	Mutation %	Deletion %	mRNA Up-regulation %
1	Sarcoma (TCGA)	243	5.8	5.8	Null	Null	7
2	Ovarian (TCGA)	311	3.90	0.6	Null	3.2	Null
3	Glioma (TCGA)	283	3.20	3.2	Null	Null	6
4	Stomach/Esophageal	265	3	0.4	Null	2.6	Null
5	Stomach (TCGA)	393	2.50	Null	0.5	2	4
6	Stomach (TCGA pub)	287	2.10	Null	0.3	1.7	3
7	LGG-GBM (TCGA2016)	794	1.80	1.6	Null	0.1	Null
8	Uterine (TCGA pub)	240	1.70	Null	1.3	0.4	0
9	Breast (TCGA)	963	1.70	1	0.2	0.4	4
10	Uterine (TCGA)	242	1.70	Null	1.2	0.4	2
11	Liver (TCGA)	373	1.60	1.1	0.3	0.3	7
12	Breast (TCGA 2015)	816	1.50	1.1	0.1	0.2	2.4
13	GBM (TCGA)	273	1.50	1.1	0.4	Null	7
14	Head & neck (TCGA pub)	279	1.40	0.4	0.4	0.7	4
15	GBM (TCGA 2013)	281	1.40	1.1	0.4	Null	5
16	Colorectal (TCGA pub)	212	1.40	1.4	Null	Null	5
17	Colorectal (TCGA)	220	1.40	0.5	0.5	0.5	0.5

***Study names abbreviations according to the table serial number**.1. Sarcoma (TCGA, Provisional), 2.Ovarian Serous Cystadenocarcinoma (TCGA, Provisional), 3.Brain Lower Grade Glioma (TCGA, Provisional), 4.TCGA data for Esophagus-Stomach Cancers (TCGA, Nature 2017), 5.Stomach Adenocarcinoma (TCGA, Provisional), 6.Stomach Adenocarcinoma (TCGA, Nature 2014), 7.Merged Cohort of LGG and GBM (TCGA, Cell 2016), 8.Uterine Corpus Endometrial Carcinoma (TCGA, Nature 2013), 9.Breast Invasive Carcinoma (TCGA, Provisional), 10.Uterine Corpus Endometrial Carcinoma (TCGA, Provisional), 11.Liver Hepatocellular Carcinoma (TCGA, Provisional), 12.Breast Invasive Carcinoma (TCGA, Cell 2015), 13.Glioblastoma Multiforme (TCGA, Provisional), 14.Head and Neck Squamous Cell Carcinoma (TCGA, Nature 2015), 15.Glioblastoma (TCGA, Cell 2013), 16.Colorectal Adenocarcinoma (TCGA, Nature 2012), 17.Colorectal Adenocarcinoma (TCGA, Provisional).

TCGA database also shows significant alterations in MYDGF level in many other cancer (Figure3) (Table1.). Sarcoma(7%), Liver Hepatocellular Carcinoma(7%) Glioblastoma Multiforme(7%), Brain Lower Grade Glioma(6%), Glioblastoma(5%), Colorectal Adenocarcinoma (5%), Stomach Adenocarcinoma(4%), Breast Invasive Carcinoma(4%) and Head and Neck Squamous Cell Carcinoma(4%) are among the cancer types showing significant increase in MYDGF mRNA expression indicating a possible role of MYDGF in these cancers (Table 1).

Secretomic analysis by different researchers also found elevated MYDGF in corneal fibroblast [20], human vitreous humor [21], human umbilical vein endothelial cells (HUVECs) [22], mouse primary Astrocytes [23], human gingival fibroblasts (hGFs) [24]. Thus, MYDGF may have pleiotropic effects on various lineages of normal organs in various developmental stages, and the clarification of its distribution and biological properties in the whole body may provide more detailed information about the function of MYDGF.

CONCLUSION

Molecular targeting therapy for hyperactive growth factors has rapidly emerged for many malignancies. Recent researches on Myeloid derived growth factor (MYDGF) only represent its amplification or overexpression on different cancer lineages as well as some normal organs with few biological role. Again, we have presented the possible association of MYDGF with cancer employing TCGA database. Since TCGA database is a public cancer registry data, so the mechanisms underlying the associations between the MYDGF gene expression and prognosis need to be further studied. Therefore, before establishing its targeted therapy further studies should be conducted to exemplify its precise roles, associated receptors and downstream signaling pathways mediating its effect on cancer.

ACKNOWLEDGMENTS

The authors thank Dr. Yang Yong (China Pharmaceutical University, Nanjing 211198, China) for his considerable inputs and helpful discussions.

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