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ORIGINAL ARTICLE

IGIACP1 predicts the prognosis in multiple myeloma patients

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Abstract

Objective The aim of this study was to investigate the prognostic relevance of acid phosphatase 1 (ACP1) expression in myeloma patients by using Gene Expression Omnibus (GEO) datasets.

Methods A comprehensive search was performed in the GEO database in order to find appropriate datasets. The expression level of ACP1 was extracted from the dataset involving both newly diagnosed and relapsed myeloma patients, and a comparison was made. Clinical follow-up data and ACP1 expression were extracted, and survival analysis of overall survival was performed to compare the high- (top quartile) and low-expression (bottom quartile) groups. Analyses using Kaplan-Meier estimation, log-rank test, and restricted mean survival time (RMST) comparison were performed.

Results The GSE 6477 dataset was used to make a comparison of the ACP1 expression levels among patients with newly diagnosed and relapsed myeloma. The ACP1 expression level was significantly higher in the relapsed group than in the newly diagnosed group [mean difference = -262.9, 95% confidence interval (CI) = (-420.2, -105.5), P = 0.002]. The GSE 2658 dataset was used for investigating the prognostic relevance of ACP1 expression in myeloma. The ACP1 high-expression group had a significantly worse prognosis [low vs high: hazard ratio = 0.54, 95% CI = (0.31, 0.95); χ^2 = 5.02, log rank P = 0.0314]. The median survival was 55.9 months in the high-expression group and was not reached in the low-expression group. The restricted mean time loss (95% CI) was 11.03 (12.97, 23.11) and 18.04 (12.97, 23.11) for the low- and high-expression groups, respectively. The ratio of RMST (95% CI) between the two groups (high vs low) was 0.87 (0.77, 0.99; P = 0.03).

Conclusion Our study, for the first time, showed that ACP1 predicts the prognosis in multiple myeloma patients. Further studies are needed to determine the potential mechanism by which ACP1 is associated with clinical outcomes and should focus on the differential roles of low-molecular-weight protein tyrosine phosphatase (LMWPTP) isoforms.

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Acid phosphatase 1 (*ACP1*) is a gene located at human chromosome 2p25, the product of which is a protein belonging to the phosphotyrosine protein phosphatase family [1]. The main function of the protein encoded by *ACP1*, ACP1, is hydrolyzing protein tyrosine phosphate to protein tyrosine and orthophosphate [2]. This protein, an 18-kDa enzyme and commonly known as low-molecular-weight protein tyrosine phosphatase (LMWPTP), is a polymorphic protein considered to be associated with certain common diseases such as allergy [3-4], cardiovascular diseases [5–9], and obesity [5, 10], but its role in cancer development and progression remains controversial [11]. Little is known about its potential role in prognosis prediction for patients with cancer or hematological malignancies.

Multiple myeloma (MM) is a common hematologic malignant disease, and its pathogenesis and evolution have not yet been fully understood and involve

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Table 1 Basic information of included GEO datasets

GEO accession	Experiment type	Sample size	Platform	Annotation	Contributor
GSE 6477	Expression profiling by array	162	GPL 96	HG-U133A	Rafael Fonseca
GSE 2658	Expression profiling by array	559	GPL570	HG-U133_Plus_2	Shaughnessy Jr. John

multiple biological pathways [12–13]. Although advances in therapeutic agents have largely improved the outcome of MM patients, it is still an incurable disease, and relapse is hard to prevent [14]. Therefore, risk classification and prognosis prediction are important for personalized management of MM.

Owing to recent achievements in human genomic studies and established bioinformatics databases where publicly available gene, molecular, and clinical data are provided, secondary biomedical and translational researches using high-throughput information are made possible, which complement primary studies [15]. In this study, based on mRNA expression and clinical data extracted from relevant datasets downloaded from the Gene Expression Omnibus (GEO), we made a comparison of the ACP1 expression level between newly diagnosed MM and relapsed MM samples and investigated the prognostic relevance of ACP1 expression in myeloma patients in order to provide clues of the potential role of ACP1 in MM and form the basis for further fundamental and translational studies.

Materials and methods

Search for relevant GEO datasets

We used "MM" as the key word to search for potentially relevant datasets in the GEO database. For comparing the ACP1 expression level in newly diagnosed MM and relapsed MM samples, a dataset with adequate sample size that included the two subtypes was required. For prognosis analysis, a dataset with adequate sample size, pre-treatment expression data, and detailed information on time-to-event prognosis data were required. If multiple datasets with identical patient cohorts were identified, the one with the most comprehensive data was included. The included datasets were downloaded from the GEO, and corresponding annotation files were also downloaded from relevant sources.

Comparing ACP1 expression level between newly diagnosed and relapsed MM

The expression level of ACP1 was extracted from the whole dataset for patients with newly diagnosed and relapsed MM. The independent samples *t*-test was performed to test the difference, and the mean difference of the ACP1 expression between the two groups was calculated, as well as the corresponding 95% confidence intervals (95% CIs). $\alpha = 0.05$ was set if the 95% CI did not cover 0, and a *P* value less than 0.05 was considered to indicate a significant difference. The R software version 3.2.3 was used for all the above-mentioned statistical analyses.

Prognosis analysis

Clinical follow-up data were extracted from the downloaded dataset. Cases with incomplete data were excluded from subsequent analyses. Patients with ACP1 expression level higher than the top quartile and those with levels lower than the bottom quartile were defined as the high- and low-expression group, respectively. Overall survival (OS), i.e., the time from observation start to disease-related death, was set as the outcome measure. Kaplan-Meier (KM) estimates of survival probability by time and median OS were calculated for each group, and corresponding KM curves were plotted. The log-rank test was used to compare the prognosis of the two groups. Hazard ratio (HR) and 95% CI were calculated. In addition, we also compared the restricted mean survival time (RMST) of the low-expression and high-expression groups.

Results

GEO datasets included

After a comprehensive query for relevant datasets in the GEO databases, we included two datasets that met the inclusion criteria. The basic characteristics of these datasets were shown in Table 1. The GSE 6477 dataset was used to make a comparison of the ACP1 expression level among patients with newly diagnosed and relapsed MM. The GSE 2658, GSE 4204, and GSE 24080 datasets were initially identified as potentially relevant to our prognosis analysis. However, owing to identical patient cohorts used for creating these datasets, only the GSE 2658 dataset was used for prognosis analysis.

Differential ACP1 expression in newly diagnosed and relapsed MM

The GSE 6477 dataset was used to make a comparison of the ACP1 expression level among patients with newly diagnosed and relapsed MM. According to the results, the ACP1 expression level was significantly higher in the relapsed group than in the newly diagnosed group [mean difference = -262.9, 95% CI = (-420.2, -105.5, P = 0.002)].

Prognostic relevance of ACP1 expression in MM patients

The GSE 2658 dataset was used for investigating the prognostic relevance of ACP1 expression in MM patients. The KM curve was shown in Fig. 1. According to the results, the ACP1 high-expression group had a significantly worse prognosis compared with the low-expression group [low vs high, OS: HR = 0.54, 95% CI = (0.31, 0.95); χ^2 = 5.02, df = 1, log rank P = 0.0314]. The median survival of the high-expression group was 55.9 months, and that of the low-expression group was not reached at the end of the follow-up (> 66.7 months). Additional analysis concerning RMST revealed consistent results. The restricted mean time loss (95% CI) was 11.03 (12.97, 23.11) and 18.04 (12.97, 23.11) for the low- and high-expression group, respectively. The ratio of RMST (95% CI) between the two groups (high vs low) was 0.87 (0.77, 0.99; P = 0.03), indicating that the survival time in the high-expression group was 13% shorter than that of the low-expression group at the population-average level.

Discussion

ACP1, a gene encoding a polymorphic protein whose function is to hydrolyze, which are polymorphic proteins whose function is to hydrolyze protein tyrosine phosphate, has been demonstrated to be correlated with the pathogenesis of common diseases, including allergies [3–4], cardiovascular diseases [5–9], and diabetes [7, 16–17]. Several previously published studies have also revealed a potential role of this gene in malignant neoplasms [18–22]. Recently, a study using animal models has suggested a positive role of ACP1 in tumorigenesis [18]. Hypermethylation of ACP1 was found in hepatocellular carcinoma [23], and gain of the telomeric region 2p25.3 harboring the *ACP1* gene was found to be common in patients with chronic lymphocytic leukemia by array comparative genomic hybridization analysis [24]. To the best of our knowledge, the findings in the present study are the first to show that ACP1 was differentially expressed in newly diagnosed and relapsed myeloma patients and could be used to predict prognosis in MM patients.

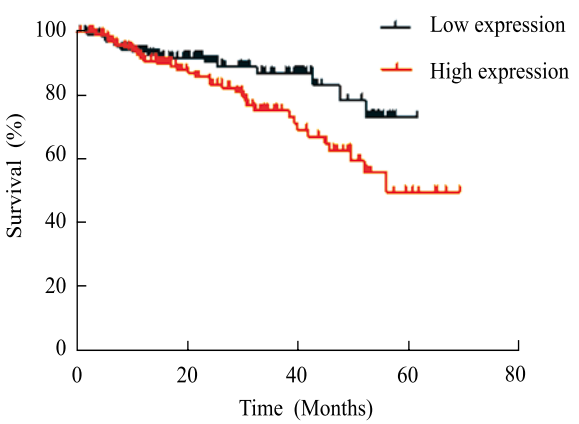

Fig. 1 KM curve comparing the OS of ACP1 low expression and high expression group. Significant difference in favor of the low expression group was noted (log rank P = 0.0314; HR = 0.54, 95%CI = [0.31, 0.95]

The exact role of ACP1 in cancers is still controversial.11 Both anti-oncogenic and oncogenic effects were reported to be associated with ACP1 and LMWPTP [20, 25–32]. LMWPTP may exert anti-oncogenic effects by interacting with platelet-derived growth factor receptor, focal adhesion kinase, and signal transducer and activator of transcription, mainly through the inhibition of growth, metastasis, and survival pathways [25, 29–31, 33] .However, LMWPTP may also be associated with oncogenic effects, which involve the interactions with p190RhoGAP, Ephrin A2 receptor, β-catenin, and JAK, mainly through enhancing cell adhesion, migration, metastasis, and survival pathways [20, 26–28, 32].

This inconsistency may be better understood by considering the genetic polymorphisms. Genetic polymorphism studies can help illuminate the role of a certain gene in human pathophysiology. The *ACP1* gene has three alleles, A, B, and C, and thus, six genotypes [34–35]. Five proteins are encoded by this gene, among which two proteins harbor the main activity, i.e., ACP1_001 (NM_004300.3) and ACP1_002 (NM_007099.3), known as the fast and slow isoform, respectively. It has been reported that the fast isoform of ACP1 is associated with increased risk of cancer in humans, including cervical carcinoma and breast cancer[21]. However, results of another study indicated that in colon cancer patients, the oncogenic effects of the fast isoform could be suppressed by the anti-oncogenic effects exerted by the slow isoform [22] .Furthermore, according to the study by Malentacchi *et al* [19], an increase of ACP1 mRNA expression is observed in most common cancers, irrespective of which isoform is involved.

In summary, our study for the first time demonstrated that ACP1 predicts the prognosis in MM patients. However, the underlying mechanism still needs to be elucidated. Considering the controversial results considering this association, further studies should pay attention to the potential mechanism by which ACP1 is

linked to clinical outcomes and focus on the differential roles of LMWPTP isoforms.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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