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Expression of the aldo-ketoreductases AKR1B1 and AKR1B10 in human cancers

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The American Cancer Society estimates that there will be more than 1.5 million new cases of cancer in 2011, underscoring the need for identification of new therapeutic targets and development of novel cancer therapies. Previous studies have implicated the human aldo-ketoreductases AKR1B1 and AKR1B10 in cancer, and therefore we examined *AKR1B1* and *AKR1B10* expression across all major human cancer types using the Oncomine cancer gene expression database (Compendia Biosciences, www.oncomine.com). Using this database, we found that expression of *AKR1B1* and *AKR1B10* varies greatly by cancer type and tissue of origin, including agreement with previous reports that *AKR1B10* is significantly over-expressed in cancers of the lungs and liver. *AKR1B1* is more broadly over-expressed in human cancers than *AKR1B10*, albeit at a generally lower magnitude. *AKR1B1* over-expression was found to be associated with shortened patient survival in acute myelogenous leukemias and multiple myelomas. High *AKR1B10* expression tends to predict less aggressive clinical course generally, notably within lung cancers, where it tends to be highly over-expressed compared to normal tissue. These findings suggest that AKR1B1 inhibitors in particular hold great potential as novel cancer therapeutics.

Keywords: AKR1B1, AKR1B10, HSIR, aldose reductase, cancer, leukemia, meta-analysis

INTRODUCTION

Cancer is the second leading cause of death in the U.S. behind heart disease, and the American Cancer Society estimates that there will be more than 1.5 million new cases of cancer in 2011. While improvements in detection, treatment, and prevention have led to decreases in cancer deaths and incidence for many cancer types in the U.S., the incidence rate for some cancers such as hepatocellular carcinoma is still rising. However, as the U.S. population ages, cancer incidence may reach a plateau or even rebound. Therefore, identification of new therapeutic targets and development of novel cancer therapies is still a pressing need. Previous studies have shown that the human aldo-ketoreductase AKR1B10 is over-expressed in cancers of the liver and lungs (Fukumoto et al., 2005; Woenckhaus et al., 2006; Heringlake et al., 2010; Kang et al., 2011; Schmitz et al., 2011) while AKR1B10 and the related enzyme AKR1B1 are both linked to drug resistance in cancer-derived cell lines (Dan et al., 2003; Plebuch et al., 2007; Matsunaga et al., 2011; Zhong et al., 2011). Several published studies have also pointed to role for AKR1B1 in colon carcinogenesis (Tammali et al., 2009, 2011a,b; Ramana et al., 2010). As well-characterized inhibitors for these enzymes are already in use or development, they would seem to be attractive targets for cancer therapeutic development. However, these studies have been conducted largely in model systems, and thus there is very little known about the involvement of AKR1B10 in cancer outside of the lungs and liver, and while *AKR1B1* expression has been reported to be elevated in human cancers, this study was limited by a small number of available patient samples (Saraswat et al., 2006). Since AKR1B1 has been shown to be involved in many cellular processes relevant to cancer such as EMT (Zablocki et al., 2011), inflammation (Yadav et al., 2007, 2009, 2011), and angiogenesis (Tammali et al., 2011b,c), and AKR1B10 is known to have relevance to human cancers, we examined *AKR1B1* and *AKR1B10* expression across all major human cancer types using the Oncomine cancer gene expression database (Compendia Biosciences, www.oncomine.com).

Using this database, we found that expression of *AKR1B1* and *AKR1B10* varies greatly by cancer type and tissue of origin, including agreement with previous reports that AKR1B10 is significantly over-expressed in cancers of the lungs and liver (Fukumoto et al., 2005; Woenckhaus et al., 2006; Heringlake et al., 2010; Kang et al., 2011; Schmitz et al., 2011). While under-expression of AKRs in human cancers is less common than over-expression, *AKR1B1* appears to be generally under-expressed in prostate cancers compared to normal tissue while *AKR1B10* expression is reduced in colon tumors. *AKR1B1* over-expression was associated with shortened patient survival in acute myelogenous leukemias and multiple myelomas. High *AKR1B10* expression tends to predict less aggressive clinical course generally, notably within lung cancers, where it tends to be highly over-expressed compared to normal tissue. Neither *AKR1B1* nor *AKR1B10* appears to have notable associations with disease recurrence, and their associations with the presence of metastases are inconsistent.

These findings suggest that AKR1B1 in particular may be a promising drug target, due to its broad over-expression in solid tumors and leukemias. Previous drug development attempts centered on AKR1B1 inhibition in non-cancer disease states were halted due to unacceptable toxicity; however, the reported toxicities were milder than other chemotherapeutics currently in use. Newer AKR1B1 inhibitors such as those derived from natural products (Suryanarayana et al., 2004, 2007; Saraswat et al.,

2008) may have lower toxicity than earlier compounds, and therefore hold great potential as novel therapeutics for cancers where *AKR1B1* tends to be over-expressed.

MATERIALS AND METHODS

Meta-analysis of *AKR1B1* and *AKR1B10* gene expression in human cancers and normal tissues as well as related statistical analysis were conducted using the Oncomine gene expression database (www.oncomine.com, Compendia biosciences, Ann Arbor, MI, USA). Where appropriate, raw data was downloaded from Oncomine and scrutinized to ensure consistent comparisons and definitions such as "high grade" were used across different studies. For example, in prostate tumors "high gleason score" is defined by the highest grade tumors within the study being considered, which for some studies is GS7 and in others GS10. *P*-values were determined by Student's *t*-test and those less than 0.05 were considered significant. Gene rank represents the ordered numerical rank of that gene's *p*-value against all other genes for that comparison – i.e., a gene with a rank of 5 has a more significant difference in expression level for the two conditions examined than for all but four other genes. In data presented considering over-expression versus under-expression in a given cancer type, the most significant *p*-value and gene rank are presented even in cases where neither were significant as defined by $p < 0.05$. Only studies based on human clinical samples were included in our analyses. Where an "overall *p*-value" is listed, the *p*-value generated by simultaneously considering all available data within Oncomine for the given comparison is displayed, i.e., the overall *p*-value for the cancer versus normal comparisons listed in **Table 1** includes all studies for which gene expression for cancerous and corresponding normal tissue was available within Oncomine. Median gene ranks displayed are similarly inclusive of all available data in Oncomine. All graphics displayed in figures are Oncomine.svg file output modified by Adobe Illustrator.

RESULTS

To determine whether the aldo-ketoreductases *AKR1B1* and *AKR1B10* were differentially expressed between cancerous and normal tissues, we broadly examined microarray data from patient samples contained within the Oncomine database. Results from cancer types where a statistically significant difference in AKR expression between the cancerous and corresponding normal tissue exists are summarized in **Table 1**. The cancers where gene expression for AKRs was compared to the corresponding normal tissue, but no overall significant difference was found were certain brain tumors (oligodendrogliomas, mixed gliomas), ductal and lobular breast cancers, acute myeloid leukemias, myelomas, and ovarian cancers (not shown). Data for cancers where only one study was available for analysis is also not shown. *AKR1B1* expression is significantly elevated compared to the corresponding normal tissue in bladder, brain (astrocytomas and glioblastomas), cervical, esophageal, head and neck, kidney, leukemias (T-cell acute, B-cell acute, and chronic), lymphomas, and melanomas (**Table 1**; **Figure 1A**). The fold change in gene expression versus the normal tissue is summarized by study in **Table 1**, with *AKR1B1* expression ranging from ∼1.2- to 5-fold the normal tissue in the majority of cancers where it is significantly over-expressed. The most significant differences between *AKR1B1* expression in cancerous and normal tissue are seen in leukemias (**Table 1**; **Figure 1A**). *AKR1B1* expression is significantly lower than the corresponding normal tissue in prostate cancers (**Table 1**). As previously reported, *AKR1B10* is over-expressed in liver and lung tumors (**Table 1**; Fukumoto et al., 2005; Woenckhaus et al., 2006; Heringlake et al., 2010; Kang et al., 2011; Schmitz et al., 2011), with fold change relative to normal tissue ranging from 12- to 67-fold in liver cancers; 2- to 75-fold in squamous cell lung cancers; and 1.5- to 5.5-fold in lung adenocarcinomas (**Table 1**). *AKR1B10* is also significantly over-expressed in leukemias (T-cell acute, B-cell acute, and chronic) and pancreatic cancers (**Table 1**; **Figure 1A**). *AKR1B10* over-expression thus appears to be less common than *AKR1B1* over-expression in cancer, and *AKR1B10* is under-expressed in colon, gastric, and head and neck cancers (**Table 1**). It should be noted that these associations are those that hold true across the studies contained within Oncomine, and multiple studies may have individually held a significant association of AKR expression with either the cancerous or normal state, but not in the broader comparison. Our methods also necessarily exclude studies not contained within the Oncomine database.

As shown in **Figure 1**, even for leukemia types in which AKRs are over-expressed compared to normal tissue at a high level of statistical significance, there is considerable heterogeneity amongst patients in terms of *AKR1B1* and *AKR1B10* expression (**Figure 1A**). This led us to ask whether AKR expression could identify certain types of patients within these leukemias, and we found that high levels of *AKR1B1* expression within B-cell leukemia patients was strongly associated with the presence of the TCF3-PBX1 gene fusion (**Figure 1B**), while under-expression of *AKR1B1* in chronic myelogenous leukemias was associated with the presence of the PML-RARA gene fusion (**Figure 1C**). Across all translocations and gene fusions in all leukemia types, *AKR1B1* over-expression is associated with the TCF3-PBX1 gene fusion and 11q23 MLL rearrangements, while under-expression is associated with the PML-RARA and ETV6-RUNX1 gene fusions (**Figure 2**). Other gene fusions, translocations, and point mutations examined in leukemias did not have a statistically significant, consistent pattern (**Figure 2** and data not shown).

We next asked whether expression of AKRs might be able to predict clinical outcome, specifically in terms of patient survival, disease recurrence, tumor grade, and metastasis. We found no significant associations with expression of *AKR1B1* and the presence of metastasis, tumor grade, or with disease recurrence in any cancer type, though some individual studies sometimes contained a significant relationship that did not hold up when all available data for that cancer type was considered (data not shown). *AKR1B1* over-expression was associated with decreased patient survival at 1 year post-prognosis in acute myeloid leukemias (**Figure 3A**), as well as decreased patient survival at 1 year post-prognosis in multiple myeloma (**Figure 3B**). *AKR1B1* over-expression was also associated with decreased survival in pancreatic cancer, however, only one small study (27 patients) within Oncomine contained patient survival data (data not shown). While no significant associations of patient survival with *AKR1B10* expression were observed, it is noteworthy that in the solid tumors where *AKR1B10* is most highly over-expressed, namely liver cancer and squamous cell lung carcinoma, there is a strong trend for *AKR1B10* over-expression predicting longer patient survival (**Figure 3C**).

Table 1 | AKR expression in human cancers.

Gene	Cancer type	Mean fold change(s) versus normal tissue, by study	Overall *p*-value	Median gene rank
AKR1B1	Bladder (infiltrating)	1.77, 1.26, 1.09	0.007	3659
AKR1B10	Bladder (infiltrating)	1.18, −1.80, −2.61, −3.72	0.107	2596
AKR1B1	Brain (astrocytomas)	2.31, 1.96, 1.96, 1.39, 1.27, 1.22	0.002	374.5
AKR1B10	Brain (astrocytomas)	1.12, −1.28, −1.27, −1.27, −1.09	0.074	5854
AKR1B1	Brain (glioblastomas)	2.15, 1.31, 1.23, 1.21, −1.64	0.002	5624
AKR1B10	Brain (glioblastomas)	1.46, 1.07, 1.02, −1.18, −1.00	0.421	7509
AKR1B1	Cervical	2.90, 2.12, 2.09, 1.14	1.32E-06	1152.5
AKR1B10	Cervical	1.09, −6.97, −5.30, −1.10	0.256	5532
AKR1B1	Colon	1.07, −1.50, −1.28, −1.12, −1.12, −1.06, −1.05, −1.04	0.118	4914
AKR1B10	Colon	−30.67, −15.31, −12.80, −10.60, −7.25, −1.47, −1.41	2.97E-09	252
AKR1B1	Esophageal	4.52, 2.99, 1.88, 1.54, 1.29	9.19E-04	3294
AKR1B10	Esophageal	1.68, 1.09, -3.17, −2.22, −2.02, −1.79	0.118	4784.5
AKR1B1	Gastric	1.18, 1.06, 1.04	0.116	8244
AKR1B10	Gastric	−8.15, −4.61	0.001	469
AKR1B1	Head and neck	2.61, 1.77, 1.76, 1.41	4.44E-04	619.5
AKR1B10	Head and neck	−5.01, −2.19, −2.07, −1.10	0.043	2276.5
AKR1B1	Kidney	3.11, 3.00, 2.85, 2.59, 2.42, 2.01, 1.90	3.61E-05	938.5
AKR1B10	Kidney	5.11, 1.73, 1.54, 1.01, −1.71, −1.35 −1.09	0.257	7125.5
AKR1B1	Leukemia (B-cell acute)	5.32, 2.39, 2.31, 1.92	6.95E-36	600
AKR1B10	Leukemia (B-cell acute)	3.38, 1.11, 1.08, 1.06	8.30E-06	5014.5
AKR1B1	Leukemia (T-cell acute)	4.52, 1.52, -1.02	1.91E-13	2762
AKR1B10	Leukemia (T-cell acute)	3.09, 1.05, −1.21	0.006	7632
AKR1B1	Leukemia (chronic)	1.27, 1.26, −1.48	1.47E-09	4993
AKR1B10	Leukemia (chronic)	1.07, −2.60, −1.23	6.02E-05	6924
AKR1B1	Liver	2.19, 1.28, 1.22, 1.09	0.066	5007.5
AKR1B10	Liver	66.99, 20.82, 14.49, 12.68	1.75E-11	366
AKR1B1	Lung (adenocarcinoma)	1.02, -2.43, −1.25, −1.19, −1.10, −1.08	0.374	4551
AKR1B10	Lung (adenocarcinoma)	5.62, 3.28, 2.58, 1.92, 1.57	4.90E-04	3068
AKR1B1	Lung (squamous)	1.42, -1.24, −1.11, −1.06	0.593	5655.5
AKR1B10	Lung (squamous)	74.71, 66.92, 34.11, 2.03	0.001	483
AKR1B1	Lymphoma	1.86, 1.33, 1.26	0.016	2006
AKR1B10	Lymphoma	1.08, −1.49, −1.22	0.116	5095
AKR1B1	Melanoma	2.43, 1.74, 1.03	0.006	1394
AKR1B10	Melanoma	1.01, 1.01, −1.48	0.266	8928
AKR1B1	Pancreatic	1.74, 1.74, 1.43, 1.41, 1.35, 1.33, 1.17, −2.47	0.069	2479.5
AKR1B10	Pancreatic	13.62, 5.32, 3.21, 2.91, 1.95, −2.56, −1.59	0.003	3600
AKR1B1	Prostate	−1.75, −1.71, −1.58, −1.53, −1.52, −1.48, −1.48, −1.45, −1.41, −1.37, −1.35, −1.31, −1.25, −1.17	0.01	667.5
AKR1B10	Prostate	1.61, 1.3, 1.16, 1.14, 1.05, 1.01, 1.00, -2.20, −1.55, −1.38, −1.03	0.878	5846

Expression of AKR1B1 and AKR1B10 mRNA was examined in all tumor types and hematological malignancies contained within the Oncomine database. Displayed in this table are the average fold changes for each study analyzed, overall p-value, and median gene rank for all cancer types where the overall p-value was significant for either under-expression (blue) or over-expression (red) of either AKR gene examined.

DISCUSSION

In this report we show that *AKR1B1* and *AKR1B10* are over-expressed, and less frequently under-expressed, in a cancer-type-specific manner. *AKR1B10* is most prominently up-regulated in cancers of the liver and lungs, consistent with previous reports (Fukumoto et al., 2005; Woenckhaus et al., 2006; Heringlake et al., 2010; Kang et al., 2011; Schmitz et al., 2011). *AKR1B1* over-expression is more common amongst different tumor types than *AKR1B10* over-expression, but at a generally lower magnitude (**Table 1**). Under-expression is less common for either AKR, with *AKR1B1* under-expressed in prostate tumors and *AKR1B10* under-expressed in colon and head and neck cancers (**Table 1**). Increased *AKR1B1* expression is also associated with the TCF3-PBX1 gene fusion and 11q23 MLL rearrangement in acute leukemias, while decreased expression is associated with the PML-RARA and ETV6-RUNX1 gene fusions (**Figure 2**). Only *AKR1B1* expression has a significant association with clinical outcome, being associated with reduced survival in acute myeloid leukemias and multiple myeloma (**Figure 3**). Recent reports have implicated AKRs in cellular responses to various stresses, including promotion of hypoxia-driven HIF1a signaling, inflammation, and resistance to chemotherapeutics (Dan et al., 2003; Plebuch et al.,

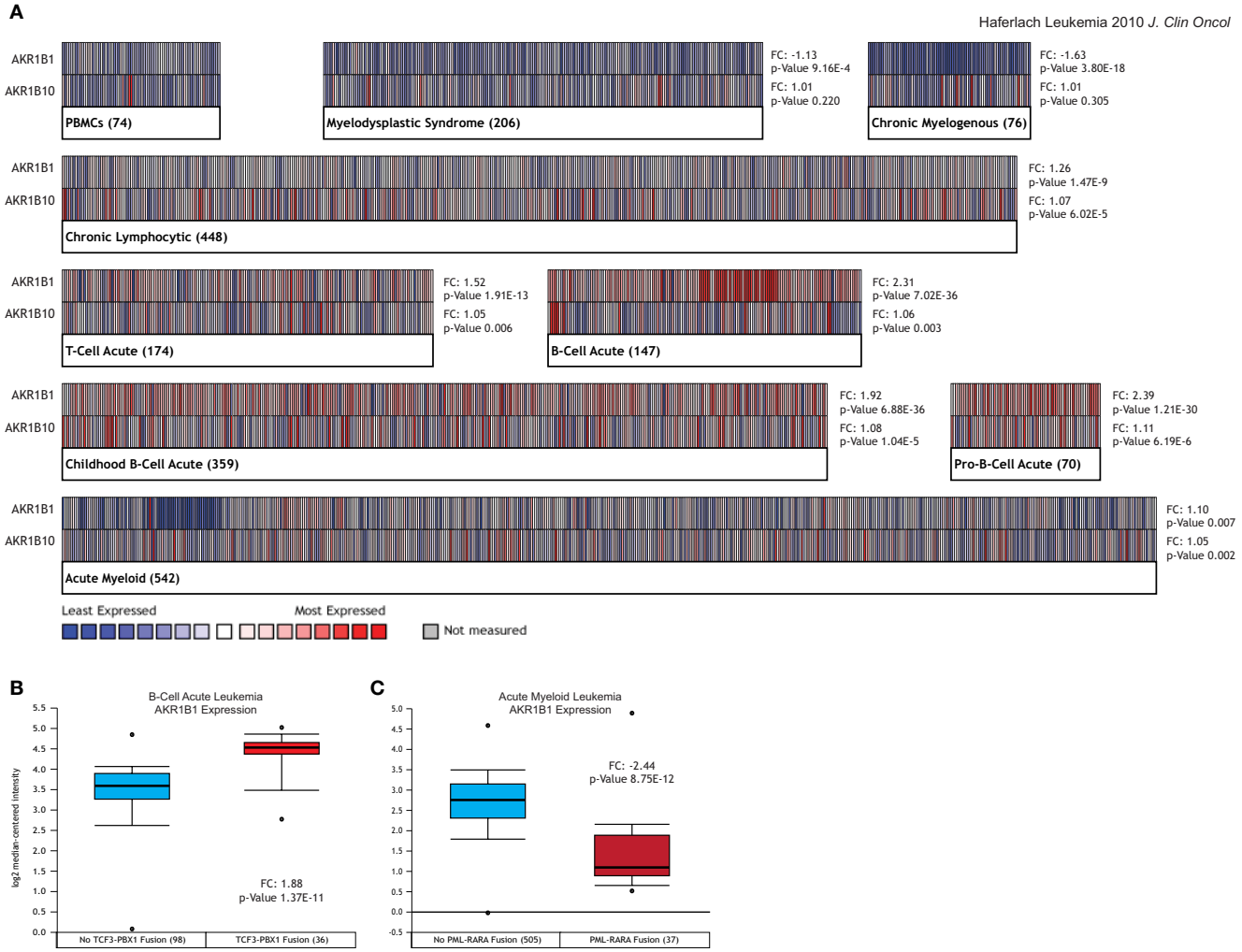

FIGURE 1 | AKR expression in leukemia patients. Expression of AKR1B1 and AKR1B10 mRNA was examined in 2093 human leukemia patients from the Haferlach et al. (2010) study in the Oncomine database. **(A)** Heatmap display of AKR1B1 (top rows) and AKR1B10 (bottom rows) expression within the indicated leukemia types. Fold changes relative to peripheral blood mononuclear cells (PBMCs) and *p*-value for that comparison within each leukemia type are listed next to their respective heatmaps. Numbers in parentheses next to the label of each heatmap represent the number of patients contained within that group in this study. **(B)** AKR1B1 mRNA expression in B-cell acute leukemia patients without (blue box) and with (red box) the presence of the TCF3-PBX1 fusion gene. **(C)** AKR1B1 mRNA expression in acute myeloid leukemia patients without (blue box) and with (red box) the presence of the PML-RARA fusion gene.

2007; Yadav et al., 2007, 2009, 2011; Matsunaga et al., 2011; Zhong et al., 2011). *AKR1B1* over-expression has also been associated with an EMT-like phenotype, is implicated in colon carcinogenesis, and notably, increased AKR1B1 protein expression and enzymatic activity has been reported in several cancer types (Saraswat et al., 2006; Tammali et al., 2009, 2011a,b; Ramana et al., 2010; Zablocki et al., 2011), further suggesting that AKRs play a functional role in tumor growth. Given the broad over-expression of AKRs, particularly *AKR1B1*, in human cancers and the critical processes that they appear to regulate, AKRs have potential to be useful therapeutic targets. AKR inhibitors have been in development for complications related to diabetes for many years, as AKR1B1 and the polyol pathway have been implicated in the pathogenesis of diabetic retinopathy, nephropathy, and cataract (Makiishi et al., 2003; Suryanarayana et al., 2004, 2007; Wolford et al., 2006; Reddy et al., 2008, 2011; Zablocki et al., 2011). While many of these AKR inhibitor drug development efforts have been halted due to toxicity, they exhibit much lower toxicity than many current cancer therapies.

AKR1B1 expression is increased by high blood glucose via NF-κB (Yang et al., 2008), providing a potential mechanism by which diabetes and elevated risk of developing certain cancers may be linked. AKR1B1 and the polyol pathway also contribute to hyperglycemic pseudohypoxia, which one could imagine linking the Warburg effect to tumor angiogenesis through HIF1a and perhaps bolstering neovascularization at oxygen tensions that would not normally promote it. Consistent with this, VEGF has been linked to diabetic retinopathy and nephropathy (Aiello et al.,

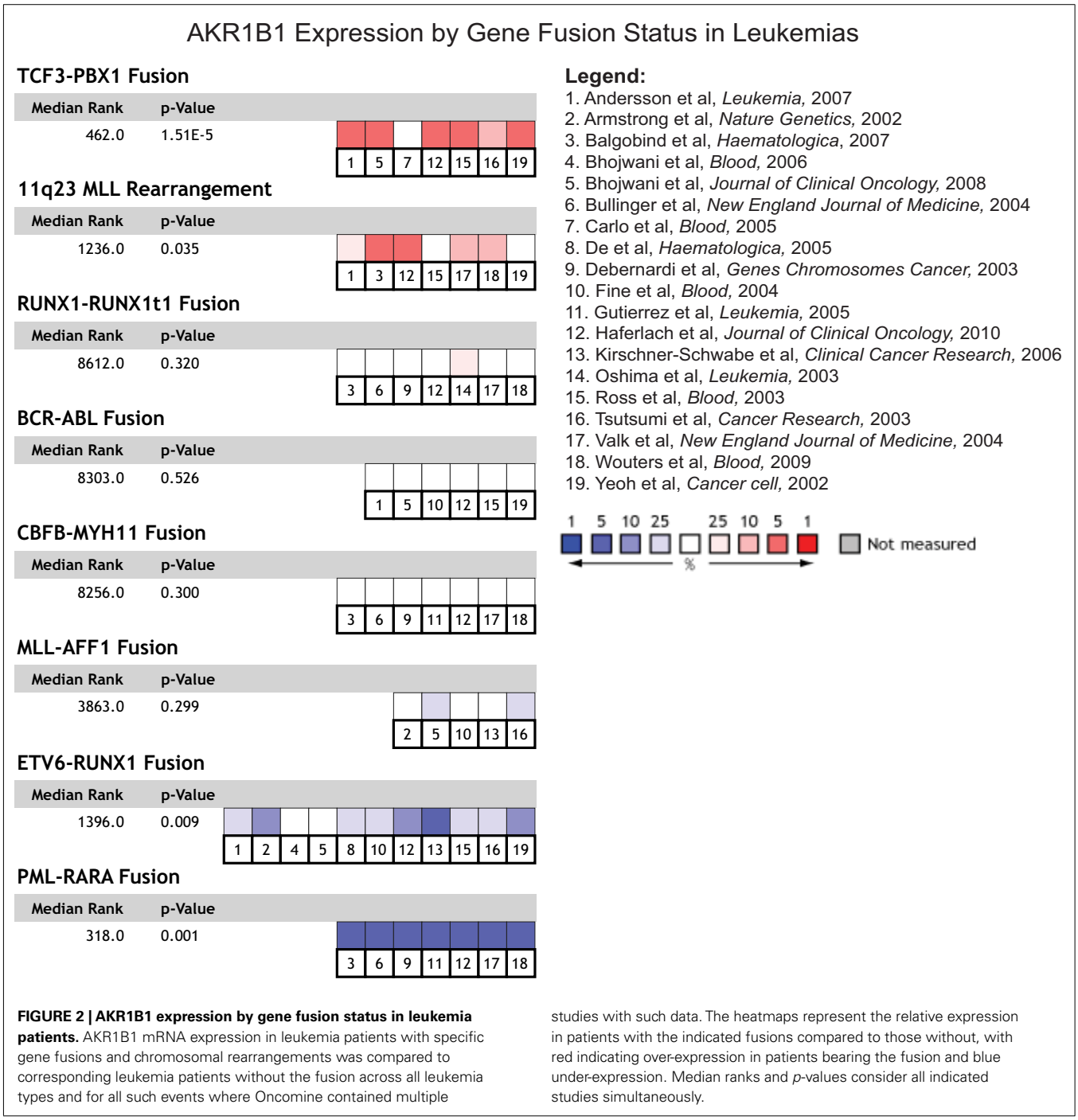

FIGURE 2 | AKR1B1 expression by gene fusion status in leukemia patients. AKR1B1 mRNA expression in leukemia patients with specific gene fusions and chromosomal rearrangements was compared to corresponding leukemia patients without the fusion across all leukemia types and for all such events where Oncomine contained multiple studies with such data. The heatmaps represent the relative expression in patients with the indicated fusions compared to those without, with red indicating over-expression in patients bearing the fusion and blue under-expression. Median ranks and *p*-values consider all indicated studies simultaneously.

1994; Cha et al., 2000; Ozaki et al., 2000), perhaps downstream of AKR1B1-driven pseudohypoxic effects. Intriguingly, patients with Von Hippel–Lindau disease often develop retinal angiomas and kidney tumors, suggesting that VHL-associated malignancies and diabetic complications may differ primarily by the degree of HIF1a and/or VEGF-dysregulation present. It is possible that diabetics are effectively primed to promote tumorigenesis by virtue of an already abnormally high level of hypoxia/HIF1a signaling. In light of all the signs pointing to the involvement of AKRs in human cancers, we hypothesize that AKRs are functionally linked to cancer progression, if not initiation as well. We also propose that AKR inhibitors would have value as cancer therapeutics in cancers that typically feature AKR over-expression, especially in the case of AKR1B1.

REFERENCES FOR STUDIES ANALYZED WITHIN THE ONCOMINE DATABASE

We apologize to our colleagues whose papers used in the meta-analyses are not cited here due the cumbersome nature of including these hundreds of references. For a list of studies used in the analyses for a given tumor type, please contact the authors.

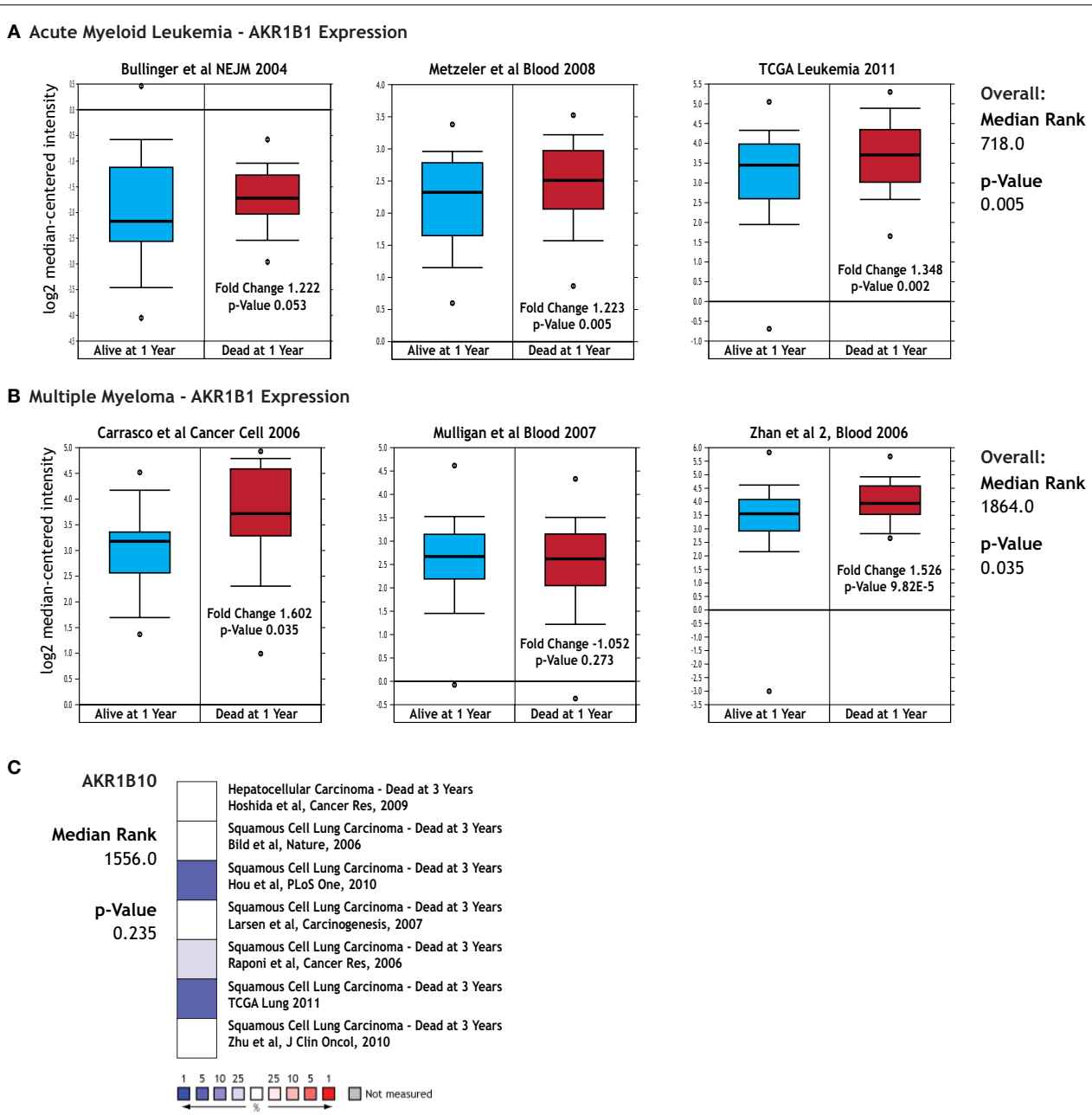

FIGURE 3 | AKR gene expression and clinical outcome. The relationship between AKR1B1 and AKR1B10 mRNA expression and clinical outcomes were examined using the Oncomine database. **(A)** Comparison of AKR1B1 expression in acute myeloid leukemia patients who were alive (blue boxes) and dead (red boxes) at 1 year post diagnosis. Individual *p*-values are indicated within each box plot and the *p*-value and median gene rank for all three studies is at the right of the panel. **(B)** Comparison of AKR1B1 expression in multiple myeloma patients who were alive (blue boxes) and dead (red boxes) at 1 year post diagnosis. Individual *p*-values are indicated within each box plot and the *p*-value and median gene rank for all three studies is at the right of the panel. **(C)** AKR1B10 expression relative to clinical outcome in liver cancer and squamous cell lung cancer. Colored boxes are a heatmap-style representation of AKR1B10 expression in patients dead relative to those alive at 3 years post diagnosis, with blue indicating under-expression and red over-expression. Median rank and *p*-value for this panel considers all indicated studies simultaneously.

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