Received: 4 June 2020 | Revised: 4 July 2020 | Accepted: 14 July 2020

DOI: 10.1111/cas.14579

REVIEW ARTICLE

Cancer Science WILEY

CCAR1 and *CCAR2* as gene chameleons with antagonistic duality: Preclinical, human translational, and mechanistic basis

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Funding information
Division of Cancer Prevention, National Cancer Institute, Grant/Award Number: CA090890 and CA122959

Abstract

Cell Cycle and Apoptosis Regulator 1 (CCAR1) and Cell Cycle and Apoptosis Regulator 2 (CCAR2) have emerged as key players in physiology and pathophysiology, with critical roles in the DNA damage response, nuclear receptor function, and Wnt signaling, among other activities. Contradictory reports exist on the functional duality of CCAR1 and CCAR2 as either tumor promoters or suppressors, suggesting that *CCAR1* and *CCAR2* have the hallmarks of gene chameleons. We review herein the mechanistic, preclinical, and human translational findings for CCAR1 and CCAR2, based on available RNA and protein expression data from human studies, The Cancer Genome Atlas (TCGA) data mining, gene knockout mouse models, and cell-based assays. Multiple factors contribute to the divergent activities of CCAR1 and CCAR2, including tissue type, mutation/genetic background, protein-protein interactions, dynamic regulation via posttranslational modifications, and alternative RNA splicing. An array of protein partners interact with CCAR1 and CCAR2 in the context of tumor promotion and suppression, including β-catenin, androgen receptor, $p21^{Cip1/Waf1}$, tumor protein p53 (p53), sirtuin 1, and histone deacetylase 3. Genetic changes frequently found in cancer, such as *TP53* mutation, also serve as critical determinants of survival outcomes in cancer patients. This review seeks to provide the impetus for further investigation into CCAR1 and CCAR2 as potential master regulators of metabolism, aging, and cancer.

KEYWORDS

apoptosis, CCAR1, CCAR2, cell cycle, DBC1

Abbreviations: APC-2, Anaphase Promoting Complex 2; AR, androgen receptor; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad 3-related; BET, bromodomain and extraterminal domain; BRD9, bromodomain-containing protein 9; CCAR1, Cell Cycle and Apoptosis Regulator 1; CCAR2, Cell Cycle and Apoptosis Regulator 2; *CCNB1*, *Cyclin B1*; CRC, colorectal cancer; DBC1, Deleted in Breast Cancer 1; DBC2, Deleted in Breast Cancer 2; DBIRD, DBC1- and ZIRD-containing; ERα, estrogen receptor α; FOXP3, Forkhead box P3; GATA2, GATA Binding Protein 2; HCC, hepatocellular carcinoma; hMOF, human MOF; hnRNP1A, heterogeneous nuclear ribonucleoprotein A1; IHC, immunohistochemistry; LST-3, Lateral Signaling Target-3; *MCC*, *Mutated in Colorectal Cancer*; *MYC*, *Myelocytomatosis*; Notch3, Neurogenic locus notch homolog protein 3; OS, overall patient survival; p21, $p21^{Cip1/Waf1}$; p53, tumor protein p53; Par-4, prostate apoptosis response-4; PTMs, posttranslational modifications; RFS, recurrence-free survival; SIRT1, Sirtuin 1; SWI/SNF, Switch/Sucrose Nonfermentable; TCGA, The Cancer Genome Atlas; THAP1, THAP-Domain-Containing Protein 1; ZIRD, ZNF-protein interacting with nuclear mRNPs and DBC1.

1 | INTRODUCTION

Cell Cycle and Apoptosis Regulator 1 (CCAR1) and Cell Cycle and Apoptosis Regulator 2 (CCAR2) evolved from the common ancestor Lateral Signaling Target-3 in *Caenorhabditis elegans*[1,2] (Figure 1). These paralog proteins have emerged as key players in physiology and pathophysiology, with roles in Wnt signaling, nuclear receptor function, adipogenesis, apoptosis, and the DNA damage response.[3-13] Such wide-ranging activities derive, in large part, from the diverse array of protein partners implicated in CCAR1 and CCAR2 function (Figure 2A,B).

Cell Cycle and Apoptosis Regulator 1 was first discovered as a regulator of apoptosis signaling in breast cancer cells and was named Cell Cycle and Apoptosis Regulator Protein-1.[10] Subsequently, CCAR2 gained attention as a modulator of tumor protein p53 (p53) activity in response to DNA damage signaling, inhibiting the activity of Sirtuin 1 (SIRT1) and histone deacetylase 3 (HDAC3) via protein-protein interactions.[1,6,14,15] The name originally ascribed to CCAR2, Deleted in Breast Cancer 1 (DBC1), is regarded as a misnomer because the protein can be overexpressed in mammary cancer and other malignancies.[16]

Conflicting reports exist on the roles of CCAR1 and CCAR2 in cancer etiology. For example, CCAR2 facilitates tumor suppressor functions of p53[6,14,17] or serves as an oncogenic driver of Wnt/β-catenin signaling,[4] thereby exhibiting "antagonistic duality".[18] So-called "gene chameleons" are becoming better understood in the context of their nuanced roles in the regulation of gene expression.[17-22] This review summarizes current clinical, preclinical, and molecular findings on CCAR family members in cancer etiology.

2 | CCAR1: TUMOR PROMOTION VS SUPPRESSION

Divergent actions of CCAR1 arise from changes in cell cycle, proliferation, growth, and survival, with phenotypic outcomes involving altered β-catenin/Wnt signaling,[3] nuclear receptor activity,[8,12] adipogenesis,[9] and apoptosis.[10-13] For example, in T-cell acute lymphoblastic leukemia cells, tumor promoter or suppressor outcomes depend on alternative splice variants of *CCAR1*,[13] giving rise to antagonistic duality (Figure 2A).

Immunohistochemistry (IHC) data for CCAR1 were reported in a handful of human translational studies. In hepatocellular carcinoma (HCC), CCAR1 levels were correlated with unfavorable overall survival (OS) and recurrence-free survival (RFS).[23] In colorectal cancer (CRC), CCAR1 interacted with and activated β-catenin.[3] Depletion of CCAR1 in colon cancer cells inhibited β-catenin-dependent target gene expression and suppressed anchorage-independent growth. Furthermore, CCAR1 regulated nuclear receptor signaling by recruiting the Mediator complex to affect key proliferation genes[12] and stabilized androgen receptor (AR) and GATA Binding Protein 2 (GATA2).[8] In accordance with the reported IHC findings for HCC,[23] *CCAR1* mRNA levels were associated with significantly reduced OS (Figure 3A), as was the case for renal cancer (Figure 3B), whereas the reverse scenario was detected for ovarian cancer (Figure 3C), with CCAR1 protein immunolocalized to the nuclear compartment in tissue microarrays (Figure 3D,E).

In breast cancer cells, CCAR1 was reported to induce apoptosis.[10] Overexpression of CCAR1 caused elevated levels of cyclin-dependent kinase inhibitor $p21^{Cip1/Waf1}$ (p21) and reduced the transcriptional

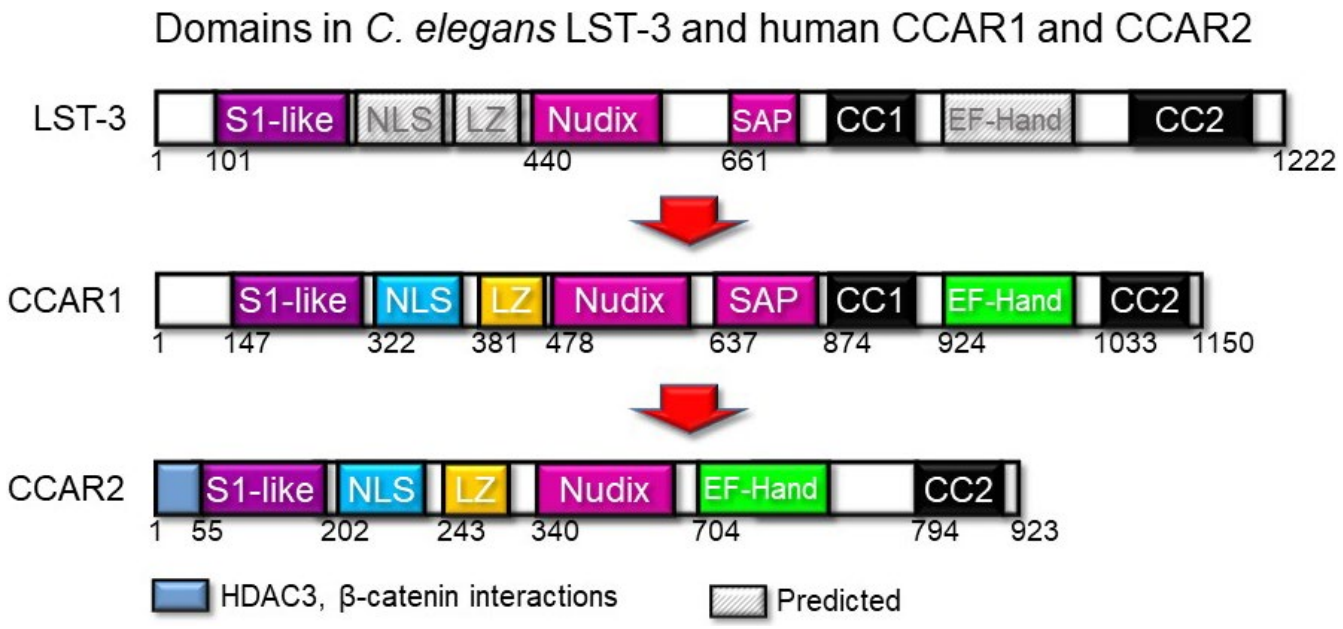

FIGURE 1 Comparison of protein domains in Cell Cycle and Apoptosis Regulator 1 (CCAR1) and Cell Cycle and Apoptosis Regulator 2 (CCAR2) with the common ancestor Lateral Signaling Target-3 (LST-3) in *Caenorhabditis elegans*. CC, protein-protein interaction domain; LZ, leucine zipper; NLS, nuclear localization signal; S1-like, homology to an RNA interaction domain; SAP, homology to DNA-binding motif for chromosomal organization

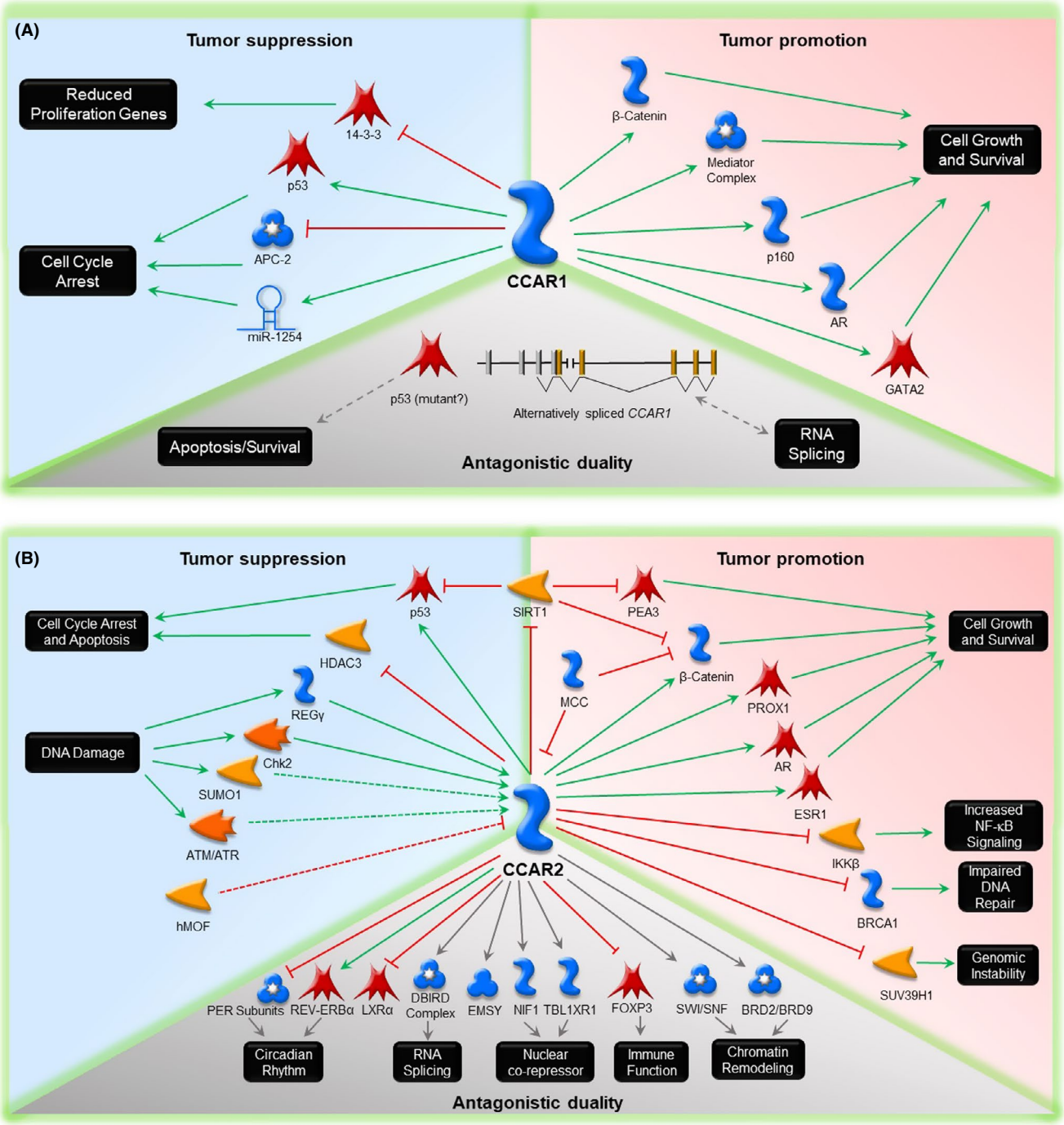

FIGURE 2 A, Cell Cycle and Apoptosis Regulator 1 (CCAR1) and B, Cell Cycle and Apoptosis Regulator 2 (CCAR2) protein partners leading to tumor suppression (cyan), promotion (pink), or potential antagonistic duality (grey). Green arrows = activation; red lines = inhibition; grey lines = not fully elucidated; dashed lines = predicted interactions. For all other abbreviations, refer to the Abbreviations section

activity of proliferative genes, such as *Myelocytomatosis* (*MYC*) and *Cyclin B1* (*CCNB1*).[10] CCAR1 was also shown to activate p53, but the mechanisms were not elucidated,[12] especially in the context of p53 mutation status (see below).

Because of the low *CCAR1* expression in some breast cancer patients, attempts were made to induce CCAR1 levels and/or alter its function.[24-26] CCAR1 "functional mimics" duplicated CCAR1 binding to Anaphase Promoting Complex 2 (APC-2) and halted the cell cycle to enhance apoptosis.[24] Recently, the 5′ UTR sequence of *CCAR1* was shown to stabilize and increase the activity of microRNA miR-1254 that is highly downregulated in breast cancer.[25] Withaferin A, a bioactive compound from the medicinal plant *Withania somnifera*, upregulated CCAR1 in mesothelioma, resulting in the inhibition of proteasome activity and the induction of apoptosis.[26]

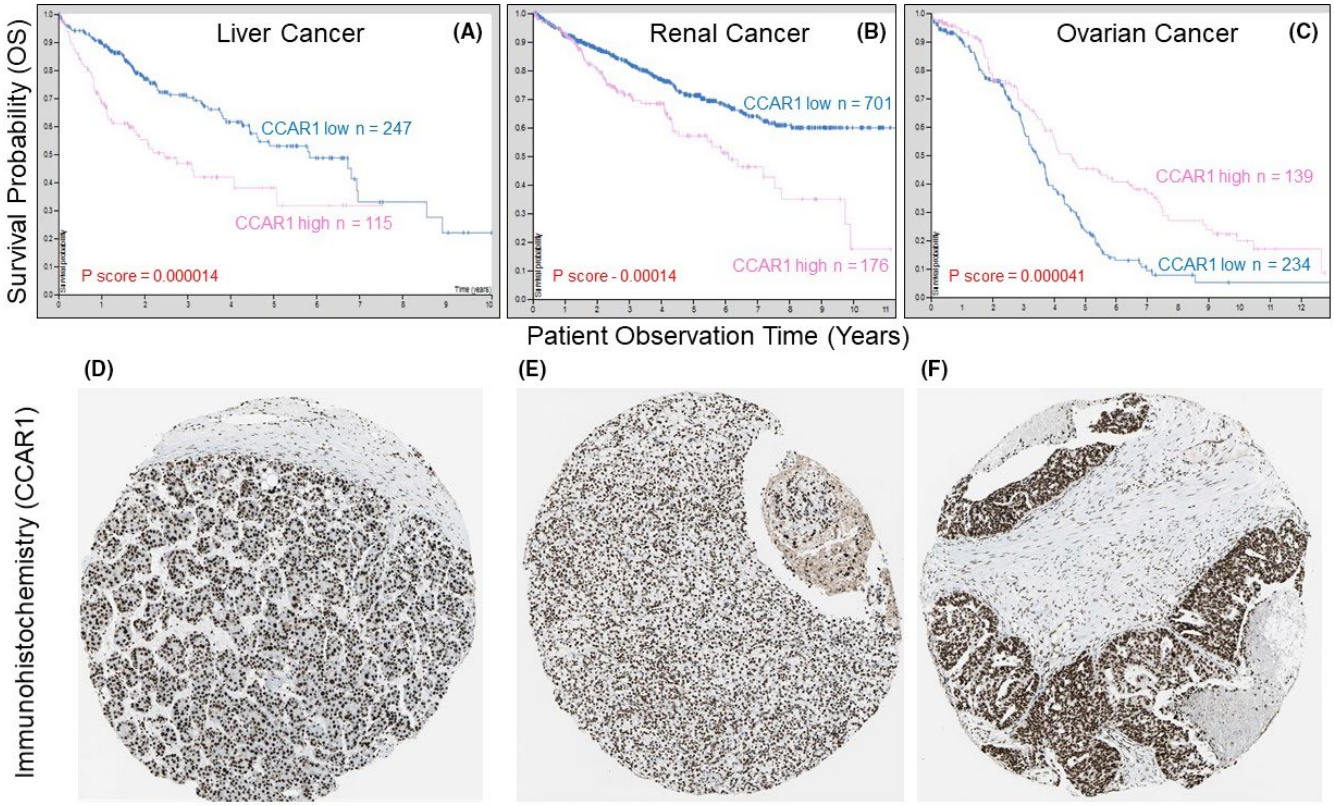

FIGURE 3 A-C, Overall survival (OS) in liver, renal, and ovarian cancer patients with high vs low *CCAR1* mRNA expression in tumors. D-F, immunodetection of nuclear Cell Cycle and Apoptosis Regulator 1 (CCAR1) for the corresponding tumor types shown in A-C; immunohistochemistry (IHC) images were obtained from the Human Protein Atlas (https://www.proteinatlas.org/)

3 | CCAR2: TUMOR PROMOTION VS SUPPRESSION

A genetic screen was undertaken for potential tumor suppressor genes located in a region of human chromosome 8 that was deleted in breast cancer.[16] Candidate genes included *DBC1* and *Deleted in Breast Cancer 2* (*DBC2*). The former gene designation proved to be a case of erroneous "guilt by association," given the typical expression patterns in mammary cancer; hence the preferred naming as CCAR2. This contrasts to *DBC2* in the same genetic locus, which is as a bona fide tumor suppressor gene.[16]

Subsequently, multiple studies examined CCAR2 expression in various human cancers and the associated clinical outcomes,[27-31] which supported an oncogenic role in certain instances and a tumor suppressor role in others (Table 1). Molecular analyses implicated a diverse array of protein partners (Figure 2B), as discussed below.

Based on loss of heterozygosity, a tumor suppressor role for CCAR2 was proposed in CRC and in head and neck malignancies.[32,33] In gastric cancer, however, high CCAR2 expression was associated with lower disease stage, attenuated lymph node invasion/metastasis, and better overall prognosis and survival.[30,31] Elevated CCAR2 also predicted better clinicopathological variables and OS in gall bladder carcinoma patients.[34] Likewise, CCAR2 was associated with favorable clinical outcomes, such as reduced lymph node metastasis and tumor differentiation, in laryngeal and hypopharyngeal carcinoma.[35] In pancreatic ductal adenocarcinoma, the majority of tumors showed high CCAR2 expression; however, this was associated with better OS, and the tumors expressing less CCAR2 tended to be poorly differentiated.[36]

As noted for CCAR1 (Figure 3), CCAR2 can be a "friend or foe" depending on the cancer type (Figure 4). For example, CCAR2 predicted poor OS in liver cancer, but improved prognosis in ovarian and renal cancer (Figure 4A-C), with the protein immunolocalized to the nuclear compartment in tissue microarrays (Figure 4D-F).

Data from The Cancer Genome Atlas (TCGA) indicated that *CCAR2* "high" expression was associated with improved OS for cancers of the breast ($P = .008$) and colon ($P = .037$), and with higher RFS in prostate cancer ($P = .04$) (Figure 5A-C). Opposite trends for CCAR2 (Figure 5D-F) are discussed below.

Genetic knockout of *Ccar2* led to spontaneous lymphomas, liver tumors, lung tumors, and teratomas as well as poor OS compared with C57BL/6 wild-type mice.[17] A tumor suppressor role of *Ccar2* was attributed to Ccar2-mediated regulation of p53 stability. However, *Ccar2* null status in the 129/JxC57BL/6J background did not enhance tumorigenesis,[37] indicating discordant outcomes according to mouse strain/genetics.[38]

In cell-based assays, depletion of CCAR2 decreased apoptosis in response to DNA-damaging agents, such as etoposide or radiation.[6,14,39,40] Overexpression of CCAR2 led to increased sensitivity upon exposure to DNA-damaging agents,[40-42] via a direct role of

TABLE 1 Tumor suppressor vs promoter roles for CCAR2 in various cancer types

Cancer type	Sample type	Method	Outcome	Reference
Tumor suppressor role				
Colorectal cancer	51 sporadic CRCs	SNP Array	LOH on 8p (containing CCAR2) in 40 microsatellite stable sporadic colon cancer patients	[32]
Gall bladder carcinoma	104 gallbladder carcinomas	IHC	CCAR2 is associated with better OS and clinicopathologic variables	[34]
Gastric cancer	452 gastric cancers	IHC	CCAR2 is associated with lower stage, lesser lymphatic invasion, and better OS	[30]
	557 cohort gastric cancers	IHC	CCAR2 is related to lower stage, lymph node metastasis, and better prognosis	[31]
Laryngeal and hypopharyngeal carcinoma	120 LSCC or HSCC	IHC	CCAR2 is correlated to lower lymph node metastasis and tumor differentiation	[35]
	41 HNSCC Cell Lines	SNP Array	LOH on 8p22-p21.3 (containing CCAR) (88.7%)	[33]
Pancreatic ductal adenocarcinoma	104 stage I and II PDAC	IHC	CCAR2 is associated with better survival and differentiated tumors	[36]
Tumor promoter role				
Breast cancer	48 breast core-needle biopsies	IHC	CCAR2 is associated with tumor nuclear grade	[72]
	122 breast core-needle biopsies	IHC	CCAR2 is associated with distant metastatic relapse, increased tumor stage, poor OS & RFS	[54]
	202 ER-negative breast cancers 128 ER-negative/HER2-positive	IHC	CCAR2 is related to lower RFS in ER(−) and ER(−)/HER2(+) cancers	[51]
Clear cell renal carcinoma	200 CRCC	IHC	CCAR2 expression correlates with shorter OS, RFS, and CSS	[36]
Colorectal cancer	186 CRC	IHC	CCAR2 is overexpressed in tumor compared with adjacent normal, and is associated with tumor grade, TNM stage, metastatic status, and poor OS	[59]
	200 CRC	IHC	CCAR2 expression correlates with lower RFS	[4]
Diffuse large B-cell lymphoma	101 DLBCL	IHC	CCAR2 is associated with high clinical stage, elevated serum lactate dehydrogenase levels, prognostic index score, shorter OS & RFS	[57]
Esophageal squamous cell carcinoma	165 ESCC & 34 normal	IHC	CCAR2 is overexpressed in ESCC and associated with poor prognosis	[53]
Gastric cancer	142 gastric adenocarcinomas	IHC	CCAR2 is overexpressed in tumors, associated with stage, lymph node metastasis, and lower OS	[29]
	187 gastric carcinomas	IHC	Phosphorylated CCAR2 is associated with higher tumor grade, poor OS & RFS	[27]
	177 gastric cancers	IHC	CCAR2 is associated with stage, lymph node metastasis, tumor invasion, shorter OS & RFS	[28]
Hepatocellular carcinoma	158 HCC	IHC	CCAR2 is associated with poor OS & RFS	[55]
	55 matched HCC and normal	IHC	CCAR2 is overexpressed in HCC and is associated with tumor size, stage, and differentiation	
Osteosarcoma	35 Osteosarcoma	IHC	CCAR2 is associated with shorter OS, RFS, and higher clinical stage	[58]
Ovarian carcinoma	104 Ovarian carcinomas	IHC	CCAR2 is overexpressed in tumors and associated with stage, metastasis, platinum resistance, histological grade, poor OS & RFS	[60]
Soft tissue sarcoma	104 Soft tissue sarcomas	IHC	CCAR2 is associated with stage, grade, mitotic counts, distant metastasis, lower OS & RFS	[52]

Abbreviations: CCAR2, Cell Cycle and Apoptosis Regulator 2; CRC, colorectal cancer; CRCC, clear cell renal carcinoma; DLBCL, diffue large B-cell lymphoma; ER, estrogen receptor; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; HSCC, hypopharyngeal squamous cell carcinoma; IHC, immunohistochemistry; LOH, loss of heterozygosity; LSCC, laryngeal squamous cell carcinoma; OS, overall patient survival; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival; SNP, single nucleotide polymorphism.

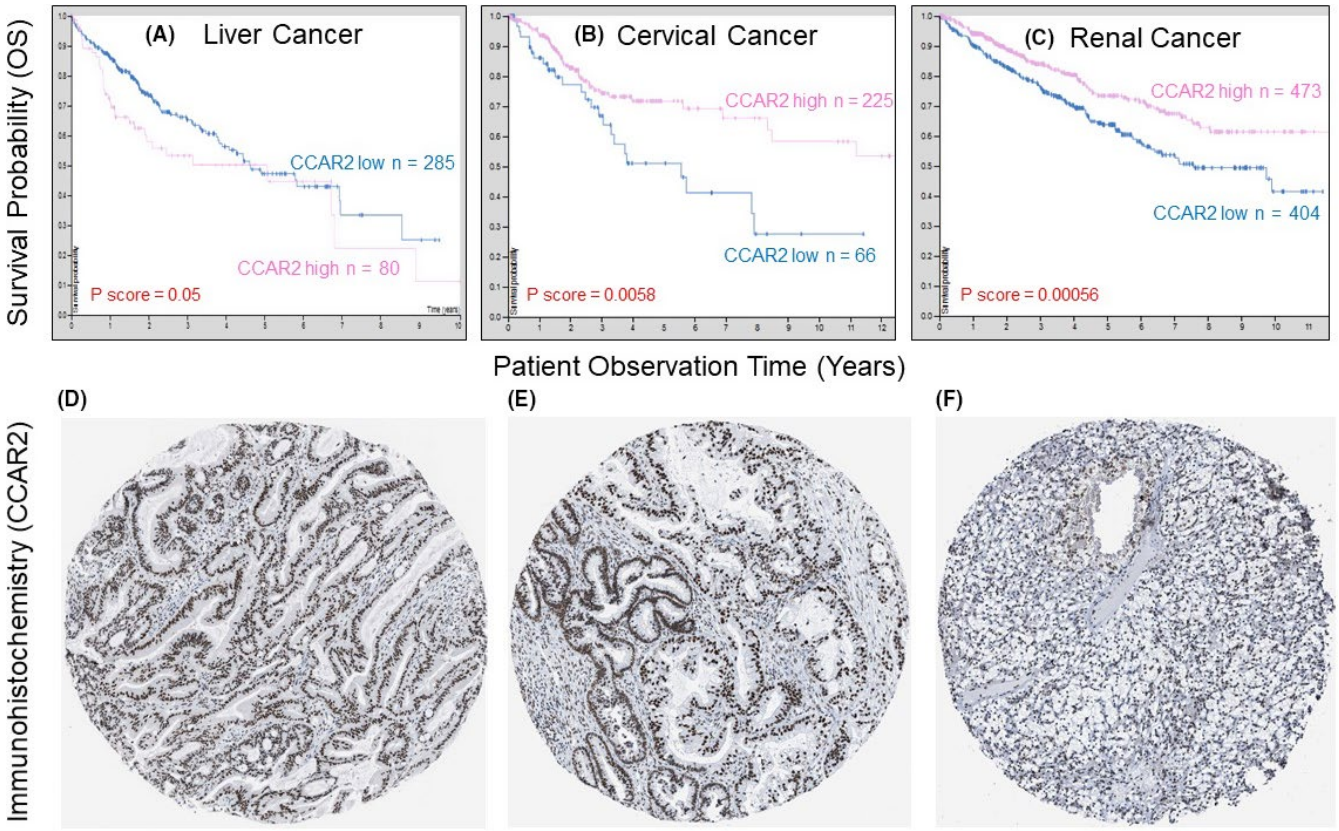

FIGURE 4 A-C, OS in liver, cervical, and renal cancer patients with high vs low *CCAR2* mRNA expression. D-F, immunodetection of nuclear Cell Cycle and Apoptosis Regulator 2 (CCAR2) for the tumor types shown in A-C; IHC images were obtained from the Human Protein Atlas, see Figure 3 legend

CCAR2 in DNA damage signaling[43,44] or indirectly through its ability to activate p53.[6,14,17] Tumor suppressor functions of CCAR2 highlighted a key role for CCAR2/SIRT1 protein-protein interactions.[6] Inhibition of SIRT1 by CCAR2 allowed p53 to be acetylated and activated, triggering apoptosis,[6,14] whereas in cells that lacked endogenous SIRT1/CCAR2 interactions, no apoptosis occurred.[45] Similarly, ataxia telangiectasia mutated (ATM)/ataxia telangiectasia and Rad 3-related (ATR) proteins phosphorylated CCAR2 at Thr454 following DNA damage, which increased SIRT1 binding.[39,42] Recent studies implicated other protein partners, posttranslational modifications (PTMs), and long noncoding RNAs.[41,44,46-48] For example, CCAR2 was acetylated by human MOF (hMOF), also known as Lysine Acetyltransferase 8, and these acetylation sites disrupted CCAR2/SIRT1 binding and increased SIRT1 activity.[40,49] Interestingly, the N-terminus of CCAR2 binds to HDAC3 (Figure 1), inhibiting deacetylase activity and altering the subcellular distribution.[50] Thus, CCAR2 serves as a potential regulator of class I and class III deacetylases associated with oncogenesis.

Although high *CCAR2* expression in TCGA data predicted improved survival in breast, colon, and prostate cancer patients (Figure 5A-C), the reverse scenario was observed for large B-cell lymphoma, kidney clear cell carcinoma, and renal chromophobe carcinoma (Figure 5D-F). Reports also have noted that high CCAR2 expression was associated with reduced OS and RFS in osteosarcoma, soft tissue sarcoma, clear cell renal carcinoma, diffuse large B-cell lymphoma, breast cancer, esophageal squamous cell carcinoma, CRC, and HCC.[4,51-59] Tumor stage/grade, lymph node metastasis, and distant metastasis were associated with high CCAR2 expression in many cancer types.[28,55,57-60]

Interestingly, duality for CCAR2 has been noted in CRC and gastric cancer according to p53 mutation status. Wild-type and mutant forms of p53 typically exert opposing effects during tumorigenesis, and both forms can be stabilized by CCAR2 through SIRT1 inhibition and p53 acetylation.[17] Because CCAR2 can interact with both wild-type and mutant p53, these protein-protein interactions can dictate whether CCAR2 functions as a tumor suppressor or promoter. For instance, in low-grade glioma, TCGA data indicated RFS was independent of CCAR2 expression (Figure 6A) and p53 mutation status (Figure 6B). However, taking the *TP53* WT (green line) and *TP53* mutant status (black line) into Figure 6C,D, respectively, highly significant differences in RFS were observed with CCAR2 as a covariate. Specifically, with *TP53* WT, low CCAR2 expression was associated with poor prognosis (Figure 6C, blue vs red lines, $P < .002$), whereas in the *TP53* mutant background, the reverse was true, with low CCAR2 predicting better survival (Figure 6D, blue vs red lines, $P < .005$).

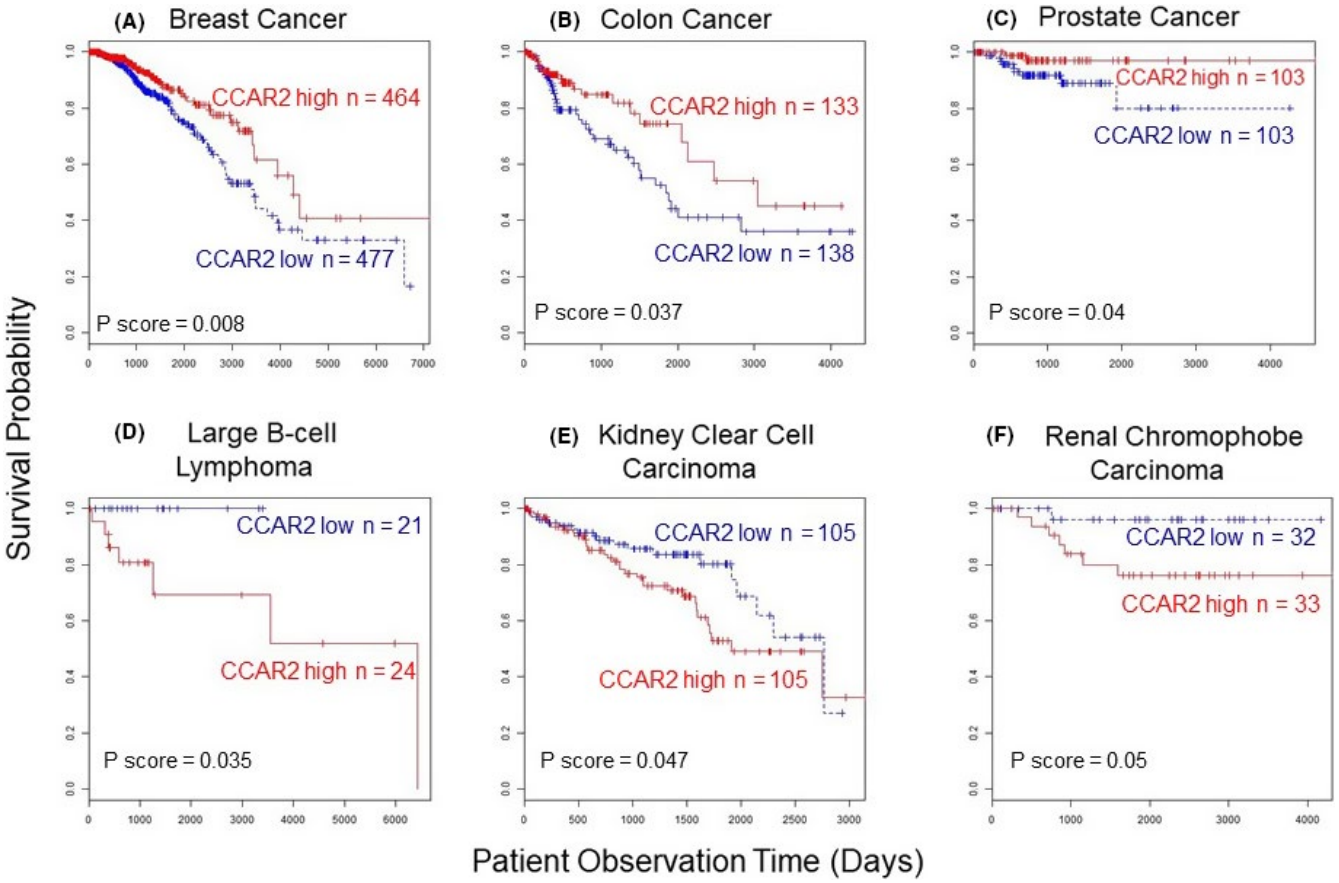

FIGURE 5 High *CCAR2* expression (red lines) predicted favorable survival outcomes in A, breast, B, colon, and C, prostate cancer, but poor survival in D, large B-cell lymphoma, E, kidney clear cell carcinoma, and F, renal chromophobe carcinoma. Results from The Cancer Genome Atlas (TCGA) database indicating overall patient survival (OS), except for recurrence-free survival (RFS) in panel C

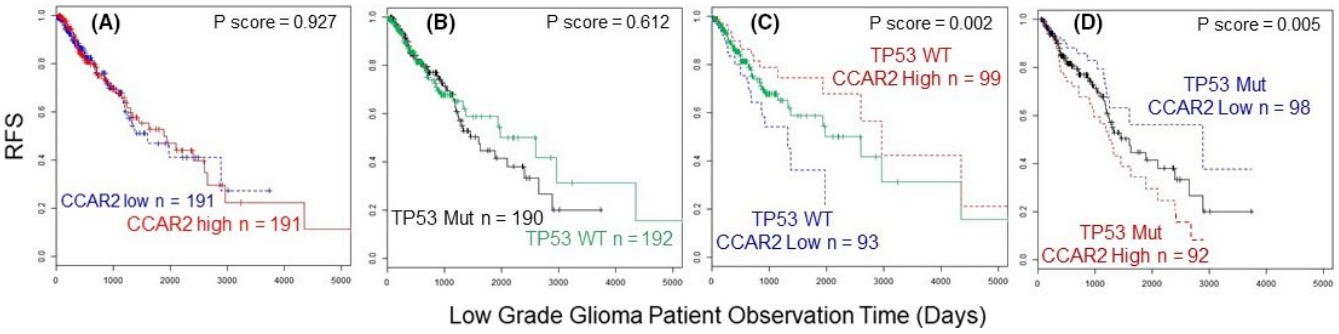

FIGURE 6 Kaplan-Meier curves for *CCAR2* and *TP53* mutation status in glioma. Results from The Cancer Genome Atlas (TCGA) database indicating recurrence-free survival (RFS), all panels. A, Comparison of *CCAR2* high vs *CCAR2* low expression; B, comparison of *TP53* wild type vs *TP53* mutant status; C, wild type *TP53* with *CCAR2* high vs *CCAR2* low expression as a covariate; D, mutant *TP53* with *CCAR2* high vs *CCAR2* low as a covariate. Mut, mutant *TP53;* WT, wild-type *TP53*

4 | POSTTRANSCRIPTIONAL MODIFICATIONS AFFECTING CCAR1 AND CCAR2 DUALITY

The functional duality of CCAR2 also is influenced by PTMs, including phosphorylation and acetylation.[61-67] For example, in gastric cancer, phosphorylated CCAR2 but not unphosphorylated protein was associated with poor OS, RFS, and higher tumor grade.[27] Phosphorylation of CCAR2 by casein kinase-2α upregulated epithelial-mesenchymal transition-related genes, such as *matrix metalloproteinases* and *N-cadherin 2*.[27]

As noted above, CCAR2 serves as a regulator of class I and class III deacetylases and is subject to reversible acetylation. CCAR2 acetylation by hMOF at lysines K112 and K215 disrupted CCAR2/SIRT1 binding, leading to increased SIRT1 activity.[40,49] Recently,[68] CCAR2 was identified as an early target for acetylation

by sulforaphane, a dietary preventive agent that caused inhibition and turnover of HDAC3 in colon cancer cells.[69] N-terminal acetylation of CCAR2 at K54 and K96 sites diminished its interactions with β-catenin, interfering with Wnt coactivator functions of CCAR2, whereas a C-terminal K916 acetylation site provided a bromodomain and extraterminal domain (BET)/bromodomain-containing protein 9 (BRD9) "acetyl switch" that was linked mechanistically to the suppression of adenomatous colon polyps in a preclinical model of colorectal cancer.[68] Under the same conditions, acetylation of CCAR1 was not observed,[68] indicating that CCAR1 and CCAR2 can undergo differential regulation via PTMs, depending on the circumstances involved.

CCAR2 also influences PTMs on other key cellular proteins. For example, CCAR2 activated β-catenin in the colon by binding to and promoting Lys49 acetylation of β-catenin *via* SIRT1 inhibition.[4,67] *Mutated in Colorectal Cancer (MCC)*, a gene that is commonly mutated and inactivated in CRC, keeps β-catenin under check by sequestering the CCAR2/β-catenin complex in the cytosol and maintaining β-catenin in the deacetylated form. However, when *MCC* is mutated, the protein product (R506Q) is unable to relocate CCAR2 to the cytosol, and the brake on β-catenin is released, thereby promoting oncogenesis.[67]

5 | CONCLUSIONS

Although CCAR2 associations have been corroborated experimentally for relatively few proteins, recent proteomic analyses[15] identified hundreds of candidates in the CCAR2 interactome, some of which are illustrated in Figure 2B. However, mechanistic leads have yet to be pursued in many cases. For example, CCAR2 interactions are noteworthy in the case of Switch/Sucrose Nonfermentable (SWI/SNF) chromatin remodeling factors that are commonly mutated in cancer. Mutation status was highlighted for p53, with divergent survival outcomes for low-grade glioma patients at high vs low CCAR2 expression levels (Figure 5C,D). Antagonistic duality due to p53 mutation also likely affects CCAR1 (Figure 2A), for which even less is known in terms of the interacting partners.

Another noteworthy example is provided by Forkhead box P3 (FOXP3) (Figure 2B). Interaction with CCAR2 destabilizes FOXP3, a master regulator of regulatory T cells, diminishing immunosuppressive functions,[70] with implications for cancer immune surveillance and autoimmune diseases. In the case of BRD2/BRD9 interactions with CCAR2 (Figure 2B), competition among the "readers" of acetylated histone and nonhistone proteins provided a mechanistic explanation for the synergy observed due to combined deacetylase and bromodomain inhibition in CRC prevention.[68]

Alternative splicing mechanisms also warrant further investigation. For example, CCAR2 regulates alternative splicing mechanisms via associations with ZNF-protein interacting with nuclear mRNPs and DBC1 (ZIRD) and heterogeneous nuclear ribonucleoprotein A1 (hnRNP1A) in the DBC1- and ZIRD-containing (DBIRD) complex.[71] Competitive interactions of Prostate apoptosis response-4 (Par-4)/THAP-Domain-Containing Protein 1 (THAP1) and Neurogenic locus notch homolog protein 3 (Notch3) on the *CCAR1* promoter resulted in alternative *CCAR1* pre-mRNA splicing (Figure 2A), and transcripts with opposing activities on cell survival in leukemia.[13]

A fundamentally important question concerns the extent to which new therapeutic avenues might be realized in the clinical setting, given that *CCAR1* and *CCAR2* have the hallmarks of gene chameleons.[18] Based on recent findings,[68] CRC patients might be stratified according to high vs low CCAR2/β-catenin expression before using combined deacetylase plus bromodomain inhibition for precision medicine. A similar approach might be considered in the context of p53 mutation and high CCAR2 expression for glioma patients (Figure 6D).

In summary, this review provided a direct comparison of CCAR1 and CCAR2 as dynamically regulated proteins with diverse roles in tumor promotion and suppression (Table 1). Elucidating the functions of CCAR1 and CCAR2 during cancer development will require a better understanding of the diverse array of interacting partners (Figure 2A,B), many of which have established roles in malignancy, such as p21, p53, β-catenin, SIRT1, and HDAC3. Despite the available preclinical, human translational, and mechanistic information, large gaps exist in the scientific literature. This review seeks to provide the impetus for further investigation into CCAR1 and CCAR2 as potential master regulators of metabolism, aging, and cancer.[1]

ACKNOWLEDGEMENTS

Authors' original research was supported in part by grants CA090890 and CA122959 from the US National Cancer Institute (NCI), NCI PREVENT contract No. HHSN261201500018I (Task Orders HHSN26100004, 75N91019D00021), the John S. Dunn Foundation, and a Texas A&M Chancellor's Research Initiative. Laboratory members who contributed to the original work on CCAR2, β-catenin, and HDAC inhibition[68,69] are gratefully acknowledged.

DISCLOSURE

Authors declare no competing interests.

AVAILABILITY OF SUPPORTING DATA

All information is available in the public domain, including PubMed, TCGA, and the Human Protein Atlas (https://pubmed.ncbi.nlm.nih.gov/tcga; https://portal.gdc.cancer.gov/repository; https://www.proteinatlas.org/).

AUTHORS' INFORMATION

Each author approved of the submitted version and agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy and integrity of the work are appropriately investigated, resolved, and documented. Author affiliations are provided on page 1.

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How to cite this article: Johnson GS, Rajendran P, Dashwood RH. *CCAR1* and *CCAR2* as gene chameleons with antagonistic duality: Preclinical, human translational, and mechanistic basis. *Cancer Sci*. 2020;111:3416–3425. https://doi.org/10.1111/cas.14579