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Cancer: Phosphodiesterase type 4C (PDE4C), the forgotten subfamily as a therapeutic target

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ABSTRACT

Phosphodiesterase type 4 (PDE4) enzymes specifically hydrolyse cAMP in many cell signalling systems that are transduced by hormones and other primary messengers. The physiological function of the four PDE4 subfamilies (A, B, C and D) are numerous and varied due to the differentially localised plethora of isoforms that can be detected in cardiovascular, CNS and immune systems. Of the four subfamilies, least is known about PDE4C probably due to its restricted distribution pattern, scarcity of selective inhibitors and the lack of developed research tools. Here, for the first time, we chart the discovery of PDE4C, describe its regulation and highlight cancers where future development of PDE4C selective small molecules may have potential.

1. Introduction

Phosphodiesterases (PDEs) are the only family of enzymes that can rapidly terminate cyclic nucleotide signals by hydrolysing them into their inactive forms (Baillie et al., 2019). Dysregulation of cyclic nucleotide signalling is a major hallmark of disease, associated with cardiovascular disease (CVD), central nervous system (CNS) disease, inflammatory disease, autoimmune disease, metabolic disease, infertility, and cancer. Resultingly, PDEs continue to represent attractive therapeutic targets, offering a targeted approach to treating a broad-spectrum of disease pathologies through dynamically reshaping cyclic nucleotide nanodomains. Forming a superfamily of eleven PDE isoforms (PDE1–11), PDE4, 7 and 8 are the only isoforms capable of specifically catalysing the hydrolysis of cAMP (Lugnier, 2022). PDE4 is by far the most studied cAMP degrading PDE family, encoded by four genes (PDE4A-D) and giving rise to over 20 unique isozymes via alternative mRNA splicing (Lugnier, 2022). PDE4B and PDE4D are both highly characterised, with sub-family selective inhibitors making significant impact within the clinical setting (Richeldi et al., 2022; Berry-Kravis et al., 2021). PDE4A is less characterised, exhibiting a more restricted expression pattern in the brain (McPhee et al., 2001). Subsequently, PDE4A has been studied primarily in the context of the CNS (Havekes et al., 2016), with PDE4A selective inhibitor development remaining within its infancy (Recht et al., 2012). Contrastingly, PDE4C research has been slower to progress, with key information regarding its expression, localisation and function significantly lacking. Given the clear importance of PDE4A, B and D in (i) tightly regulating cAMP homoeostasis and (ii) driving disease pathogenesis, and the high sequence homology of all PDE4 isoforms (differentiated primarily by their N-termini), it is highly likely that PDE4C is also of major significance. Thus, this review will discuss the existing findings characterising PDE4C's role in regulating cAMP homeostasis and in cancer.

2. Discovery and characterisation of PDE4C

Cloning of PDE4C was first achieved in 1989 by the Conti group following screening of cDNA libraries generated from rat testis and Sertoli cells (Swinnen et al., 1989). A partial clone was isolated and named 'ratPDE1′ (now known as PDE4C1). The deduced amino acid sequence showed homology to other already cloned PDEs, with tissue distribution predominantly being identified within the kidney and testis. Cloning of human PDE4C1 was first reported in 1993 by Bolger and colleagues (called "DPDE1″ or "PDE21″) who isolated a 5′ segment of the catalytic region (Bolger et al., 1993). Following this, an almost complete sequence of Rat PDE4C1 ("RPDE36″) was cloned in 1994, highlighting the presence of its catalytic domain, UCR1 and UCR2 regions (Bolger et al., 1994). Chromosomal localisation mapped the PDE4C gene to human chromosome 19 (Milatovich et al., 1994). Full length human PDE4C was later cloned from a substantia nigra cDNA library, exhibiting a high level of nucleotide sequence conservation to other human PDE4 genes (A,B and D), and to rat PDE4C (Engels et al., 1995). As was the case with PDEA, B and D, additional PDE4C isozymes were discovered,

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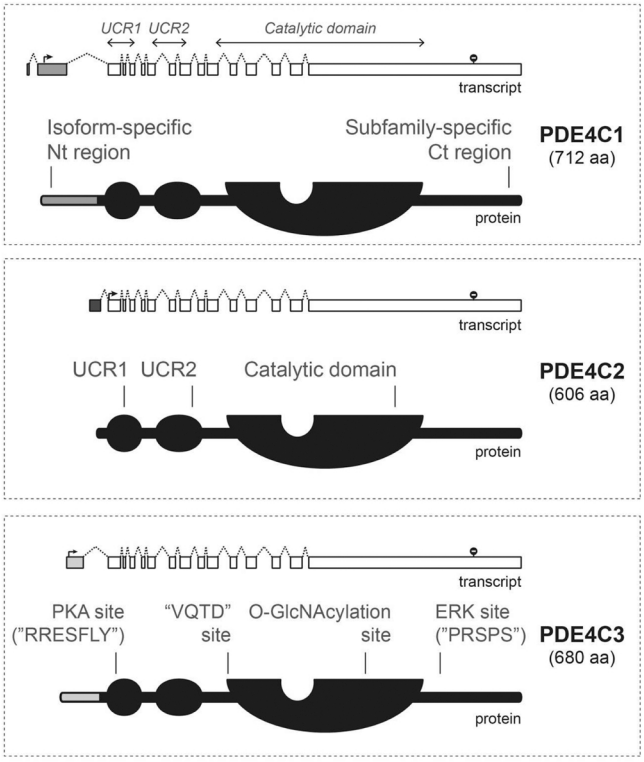

Fig. 1. Modular structure of PDE4C. The diagram depicts the three isoforms of PDE4C, each with a unique N-terminal region. The UCR regions, catalytic unit and C-terminal parts are highly conserved between isoforms. The exons on mRNA and post-translational modification sites on proteins are also indicated. Note that the post-translational modification sites are conserved in all 3 isoforms but only shown on PDE4C3 for clarity.

with human PDE4C2 being isolated from a glioblastoma (U87) cell line (Owens et al., 1997). Not only did this study suggest the existence of a third PDE4C splice variant, it characterised PDE4C2′s molecular weight (~80 kDa), affinity for cAMP (K_m 0.6 μM), Rolipram IC50 (0.023 μM) and reaffirmed restricted tissue distribution (primarily within neuronal cells). Evidence of other distinct PDE4C isoforms was also presented in 1997, where putative new splice variants from human lung and testis were isolated, some with in-frame stop codons and deletions that produced shorter but still active enzymes, apart from one termed "PDE4C-delta54″ which had no activity (Obernolte et al., 1997). It remains unclear whether some of these forms encode physiologically relevant proteins as other evidence of them has not been forthcoming. However, full evaluation of the genomic organisation and localisation of the human PDE4C gene concluded that some of the previously reported PDE4C sequences were in fact the same and that the PDE4C gene gives rise to only 3 products – i.e., PDE4C1–3 (Sullivan et al., 1999).

3. PDE4C structure and post-translational modifications

Unlike the other PDE4 subfamilies, available evidence suggests that the protein products of the PDE4C gene are expressed solely as longform enzymes. Resultingly, each PDE4C enzyme consists of a unique N-terminal region, two conserved regulatory regions (UCR1 and UCR2) a conserved catalytic domain and a sub-family specific C-terminal sequence (general PDE4 modular structure reviewed in (Tibbo and Baillie, 2020) (Fig. 1). As longforms, PDE4C enzymes are predicted to form dimers (Richter and Conti, 2002) mediated in part by an electrostatic association between UCR1 and UCR2 regions (Beard et al., 2000). Although experimental evidence has not been produced to show that PDE4C isoforms form homo- and hetero-oligomers, the fact that the sequences of the oligomerisation domains in UCR1/UCR2 are highly similar to those of the other sub-families suggests that this is likely (Xie et al., 2014). This notion was further bolstered by a study probing residues that underpin PDE4D5 dimerisation, which identified highly conserved regions in the catalytic core region that were also required for oligomerisation (Bolger et al., 2015). Co-crystal structures of PDE4 longforms (Burgin et al., 2010; Cedervall et al., 2015) confirmed that interactions form between the (i) UCR1/UCR2 cassettes of each monomer (ii) UCR2 region and the catalytic domain, and (iii) the catalytic domain of each monomer (Burgin et al., 2010; Cedervall et al., 2015). Although none of the PDE4s used in these structural studies were PDE4C specific, the highly conserved nature of the regions involved suggest that these principles also hold true for this subfamily.

As PDE4s are involved in shaping cAMP gradients following activation of Gs-coupled receptors (Fertig and Baillie, 2018), the cell has developed mechanisms to boost or diminish PDE4 activity to exert fine control over this function. Most of these mechanisms involve transient post-translational modifications of PDE4 including phosphorylation, SUMOylation and ubiquitination (reviewed in (Baillie et al., 2019)). A feedback control mechanism involving the kinase activated by cAMP (protein kinase A, PKA) is driven by PKA phosphorylation within the UCR1 region that transiently activates longform PDE4s (Lim et al., 1999) (Fig. 1). This mechanism is germane to the PDE4C family as the PDE4C UCR1 houses the PKA consensus motif (RRESFLY) that is common to all longforms. Indeed, when PDE4C2 UCR1 is phosphorylated by PKA there is a consequential release of auto-inhibition which causes a 50% increase in activity (MacKenzie et al., 2002). The activation of the enzyme is nullified if the phospho-accepting serine in PDE4C is mutated or a PKA inhibitor is used and can conversely be mimicked by substitution of the phospho-accepting serine with a negatively charged amino acid (MacKenzie et al., 2002). Another important phosphorylation event for PDE4s is the modification by ERK MAP kinases (Hoffmann et al., 1999). A consensus ERK phosphorylation site (PRSPS) (Fig. 1) exists in the C-terminal region of the catalytic unit of PDE4B/C/D subfamilies. Phosphorylation favours the auto-inhibitory state of PDE4B/C/D longforms (Baillie et al., 2000). A 40% inhibition of PDE4C2 was recorded following cell stimulation with EGF, a robust activator of ERK MAP kinases and this was negated following mutation of the phospho-accepting serine residue (Baillie et al., 2000).

Another modification that cross-talks with the PKA and ERK phosphorylation of PDE4 longforms is the covalent addition of the small protein SUMO, where the SUMO E2 ligase, UBC9, is known to SUMOylate PDE4 at the N-terminal region of its catalytic domain (Li et al., 2010).

As SUMO is covalently attached only to surface associated lysine residues, usually within the motif *h*K*x*E/D (where *h* is a hydrophobic residue, and *x* can be any amino acid), sites of SUMOylation can be predicted (Hay, 2013). The SUMOylation of PDE4 longforms alters the conformation of the proteins so that it augments the activity associated with (i) increased activity recorded following PKA phosphorylation and (ii) negates enforced auto-inhibition following ERK phosphorylation. In effect, SUMOylation induces a super-activated enzyme. However, this only happens in PDE4A and PDE4D longforms as the SUMO consensus "VKTD" is replaced with "VQTD" in PDE4C enzymes (Fig. 1), barring SUMOylation via the paucity of the acceptor lysine (Li et al., 2010).

Finally, a recent paper has indicated that the PDE4C subfamily can be differentiated from the others by way of an O-GlcNAcylation site in the catalytic domain (Fig. 1) over a region where there is slight divergence between PDE4C and PDE4A/B/D (Shen et al., 2017). The physiological function of this differentiating post translational modification is unknown but highlights the likelihood that PDE4C is uniquely regulated and warrants investigation.

4. PDE4C in cancer

The function of individual PDE4 subfamilies and isoforms is largely influenced by their differential expression and localisation in cells/

Table 1
Overall Survival Analysis of PDE4C in the Twenty Cancer Datasets Available on THPA. Data compiled from The Human Protein Atlas (Uhlen et al., 2017), www.proteinatlas.org).

Cancer	P Value by Log Rank Test	Association with Survival	5 Year Probability of Survival (%)	
			High PDE4C Expression	Low PDE4C Expression
Renal Cancer	7.30E-10	Deleterious	55	78
Glioma*	8.10E-04	Deleterious	3*	16*
Pancreatic Cancer	0.0025	Deleterious	14	35
Head & Neck Cancer	0.014	Protective	48	39
Urothelial Cancer	0.024	Protective	53	38
Stomach Cancer	0.027	Protective	38	34
Cervical Cancer	0.040	Protective	72	59
Melanoma*	0.040	Deleterious	0*	52*
Breast Cancer	0.042	Deleterious	75	84
Ovarian Cancer	0.057	N/A	26	38
Liver Cancer	0.077	N/A	42	55
Thyroid Cancer	0.092	N/A	93	90
Lung Cancer	0.11	N/A	38	49
Colorectal Cancer	0.12	N/A	61	62
Endometrial Cancer	0.13	N/A	70	79
Prostate Cancer	0.22	N/A	96	99
Testicular Cancer	0.26	N/A	97	98
Carcinoid Cancer	N/A	N/A	N/A	N/A
Skin Cancer	N/A	N/A	N/A	N/A
Lymphoma	N/A	N/A	N/A	N/A

* 3-year survival probability shown.

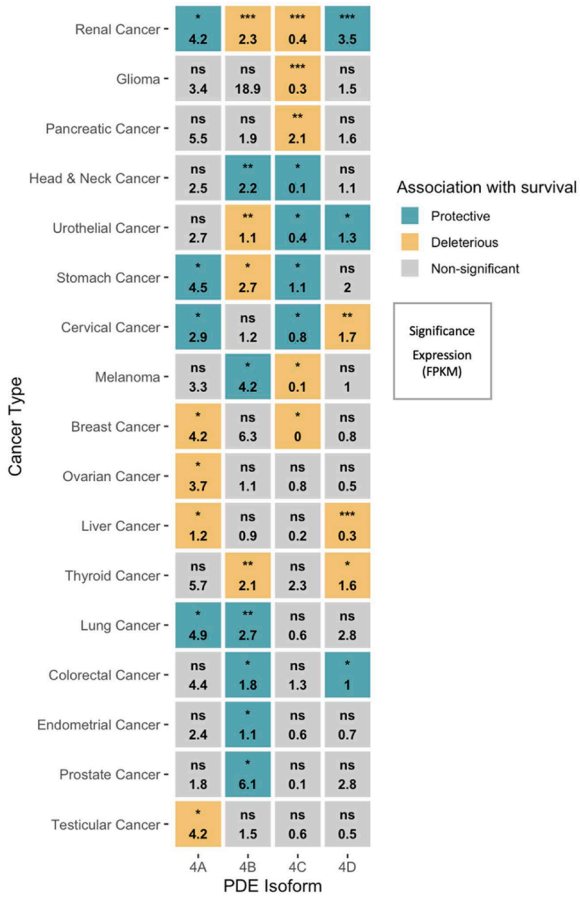

Fig. 2. Association between PDE4 isoform mRNA expression and cancer survival. Associations were determined by Kaplan-Meier survival analysis and log rank tests (***p < 0.001, **p < 0.01, *p < 0.05, ns = not significant). Normalised mean expression across samples is also indicted (FPKM). Data compiled from The Human Protein Atlas (Uhlen et al., 2017), www.proteinatlas.org).

tissue, dynamically shaping compartmentalised cAMP nanodomains (Fertig and Baillie, 2018). As is the case with PDE4A/B/D, it is becoming clear that aberrant expression of PDE4C subfamily is also linked with several different disease states. Here we discuss the literature on PDE4C, specifically focusing on cancer.

The Human Protein Atlas (THPA) has provided broad and valuable data about PDE4C in a variety of cancers (Uhlen et al., 2017), www.proteinatlas.org). THPA is an open-source platform which compiles a wide range of data, including omics, immunohistochemistry, and systems biology to map the human proteome. One feature provided by THPA that is of particular value to cancer research is the overall survival analysis of gene expression using datasets from the omics database The Cancer Genome Atlas (TCGA, www.cancer.gov/ccg/research/genome-sequencing/tcga). For each cancer investigated, samples are allocated by high or low PDE4C expression, and the impact on overall survival is estimated. Expression thresholds are determined automatically to yield the biggest difference in survival between the two groups, and significance is calculated by a log rank test of survival probabilities.

Of the twenty cancers described in THPA, nine of them indicated a significant association between PDE4C and overall survival (Table 1). PDE4C was found to be deleterious in five cancers: renal cancer, glioma, pancreatic cancer, melanoma, and breast cancer. Conversely, PDE4C was found to be protective in four cancers: head and neck cancer, urothelial cancer, stomach cancer, and cervical cancer.

To differentiate the influence on these cancers of PDE4C from other isoforms, THPA survival data was also collected for PDE4A, PDE4B and PDE4D (Fig. 2). Further, the mean mRNA expression of each isoform across all the samples was found. Mean expression below FPKM 1 was considered low expression. Firstly, PDE4C was lowly expressed in most cancers relative to the other isoforms. Of the nine cancers where PDE4C had a significant association with survival, PDE4C was the sole significant PDE4 family in glioma and pancreatic cancer. However, PDE4C exhibited low mean expression in glioma, especially relative to PDE4B. In the other seven cancers, PDE4C was significant alongside at least one other isoform. In cancers where PDE4C had a low mean expression relative to other isoforms, the impact of PDE4C signalling may be obscured by the higher expressed PDE4s. Despite this, compartmentalisation may enable these low levels of PDE4C to exert a distinct functional effect regardless of the abundance of other isoforms. These data provide an important starting point and a resource for validation in research directed towards PDE4C in specific cancers.

Increased gene and protein expression of PDE4C is associated with worse survival outcomes and decreased therapeutic response in several cancers including myelodysplastic syndromes (MDS, rare blood cancers), pancreatic cancer, and lung cancer (Chamseddine et al., 2016; Chen et al., 2022; He et al., 2017). In MDS, higher PDE4C expression was also suggestive of a worse response to hypermethylation therapeutics (Chamseddine et al., 2016). Of note however, expression of PDE4C was much lower relative to other PDE4 enzymes. The impact of PDE4C on cAMP signalling may be obscured by other isoforms unless the enzymes are highly compartmentalised in this cancer type. In pancreatic cancer, PDE4C was identified as part of a prognostic signature for worse overall survival, which is consistent with THPA survival data (Table 1) (Chamseddine et al., 2016). In lung cancer, PDE4C was implicated as a

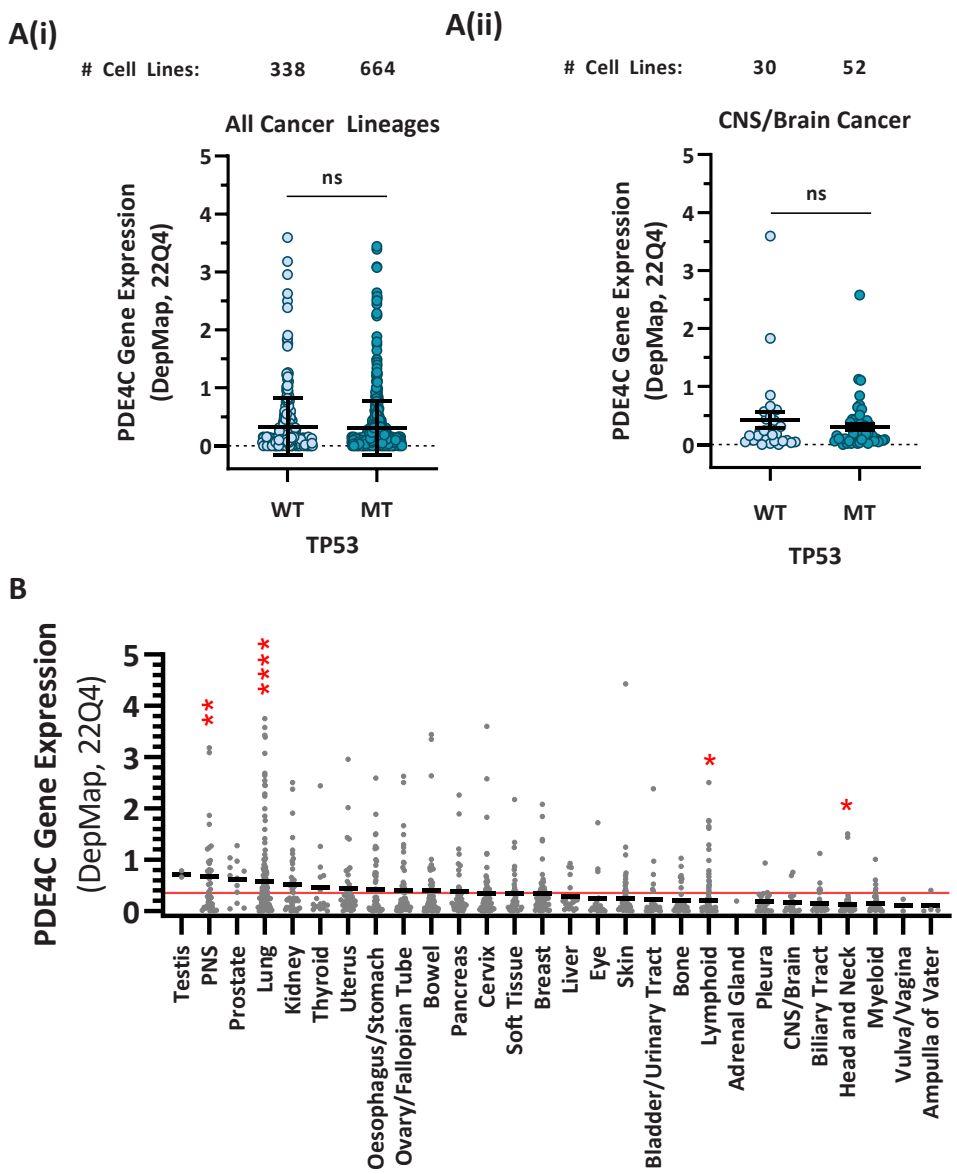

Fig. 3. PDE4C Gene Expression – DepMap 22Q4. A(i) PDE4C gene expression (MEAN ± STDEV) in human cancer cell lines (from >25 lineages) that are TP53 wild type (WT, n = 338) vs. TP53 mutant (MT, n = 664). A(ii) PDE4C gene expression (MEAN ± STDEV) in human CNS/brain cancer cell lines that are TP53 WT (n = 30) vs. MT (n = 52). Ns, not significant; unpaired t-test. (B) PDE4C gene expression (MEAN) in specific cancer lineages. Red horizontal line represents MEAN PDE4C gene expression of all cancer lineages combined. Red asterisk(s) highlight lineages whose PDE4C gene expression levels are significantly different vs. MEAN of all lineages (n = 1370). * , $P < 0.05$; * *, $P < 0.01$; * ** *, $P < 0.0001$; one-way ANOVA with Tukey's multiple comparison analysis.

target by the tumour suppressor microRNA (miRNA) miR-542–50 (including, non-small cell lung cancer (NSCLC), adenocarcinomas and squamous cell carcinoma) (He et al., 2017). miRNA-542–5p expression strongly links to better survival outcomes in patients, and silencing of PDE4C by miRNA-542–5p may contribute to this effect (He et al., 2017). Additionally, a novel transcript of PDE4C was found only in foetal lung and melanoma cells, which may also be linked to this (and/or a similar) process (Obernolte et al., 1997).

Restriction of cAMP signaling by PDE4s has been implicated in inflammatory diseases and may exert an oncogenic effect (Chamseddine et al., 2016). This may be especially prominent in MDS, which are driven by pro-inflammatory signalling (Chamseddine et al., 2016). Since one of the key actions of PDE4 inhibitors is their anti-inflammatory effect, this highlights their potential therapeutic value for the treatment of cancers with a high pro-inflammatory profile (such as MDS). However, further elucidation of the underlying mechanisms of these conditions is required before the potential benefit of PDE4 inhibitors can be evaluated. In thyroid cancers, where both PDE4C and PDE4D expression are upregulated, the prognostic influence is less clear (Persani et al., 2000). Tissue from thyroid adenomas with oncogenic mutations that lead to constitutive adenylate cyclase (AC) activation and increased cAMP generation were studied. Intriguingly, an endogenous compensatory ten-fold higher activity of PDE4C and PDE4D was discovered, which restrained cAMP levels equivalent to healthy tissue, despite the increased cAMP production (Persani et al., 2000). This observation was suggested as either protective, where cAMP regulation may prevent cancer initiation, or as deleterious, where PDE activity may promote cancer by avoiding cAMP-triggered cell cycle arrest. Akin to this, PDE4C expression appears protective in other cancer types. In stomach adenocarcinoma, transcriptome analysis of primary tissue from TCGA cohort revealed PDE4C mRNA to be consistently downregulated and to have a strong positive association with overall survival (Zhang et al., 2020). This trend was validated by THPA overall survival data (Table 1).

In brain cancer, PDE4C promoter hypermethylation and decreased PDE4C protein expression were found to be negatively associated with overall survival (Bao et al., 2014). Furthermore, PDE4C promoter hypermethylation, and downregulation of PDE4C mRNA and protein were identified prognostic factors in high grade gliomas (Bao et al., 2014). Surprisingly, this disagrees with THPA overall survival data (Table 1). Possible reasons for this discrepancy could be that THPA data did not account for glioma grade, and that the two studies may be using a different cut-off for high and low PDE4C expression. Nevertheless,

similar findings would be expected, and further investigation into the link between PDE4C and overall survival is clearly required. Mechanistic insight into the functional role of PDE4C in glioma was provided by the same promoter methylation study (Bao et al., 2014). By carrying out gene set variation analysis on transcriptomic data, a link was found between decreased PDE4C expression and downregulated apoptosis pathways / upregulated cell migration pathways in glioma patients. Following this, the relationship between PDE4C and apoptosis was explored by investigating PDE4C and p53 at the protein level. In the glioma cell line U87, PDE4C protein expression was found to increase by use of a methylation inhibitor, then knocked down using siRNA, and finally, PDE4C was overexpressed by transfection. In each of these cases, p53 protein expression tracked the changes in PDE4C expression, suggesting a directional relationship. Additionally, as shown by flow cytometry and a migration assay, overexpression of PDE4C in these cancer cell lines increased apoptosis and decreased mobility and invasion (Bao et al., 2014).

Other studies have identified a protective relationship between PDE4C and p53 (Garritano et al., 2013). Transcriptomic analysis of cancer cell lines harbouring loss of function p53 mutations that prevent its action of regulating transcription of target genes highlighted that PDE4C was consistently downregulated. Furthermore, a p53 regulatory element was identified within the promoter region of the PDE4C gene, which suggests that wild type p53 upregulates PDE4C gene expression (Garritano et al., 2013). Taken together, these observations suggest that PDE4C regulates, and is regulated by p53, and that any perturbation of this protective relationship may promote tumourigenesis and tumour maintenance.

Finally, utilising publicly available PDE4C gene expression data within the DepMap Portal (Gene Expression, 22Q4: https://depmap.org/portal/), generated from > 1350 human cancer cell lines, we sought to test the above hypothesise. No correlation between PDE4C gene expression in TP53 wild type vs. TP53 mutant cancer cell lines was observed (Fig. 3A(i)). This was also true when specifically comparing PDE4C gene expression in TP53 wild type vs. TP53 mutant CNS/Brain Cancer specific cell lines (Fig. 3A(ii)). Admittedly, these data do not take in to account specific PDE4C isoforms, nor does gene expression always correlate with protein expression and/or activity. Moreover, in contrast to the aforementioned findings, no significant difference in PDE4C gene expression was observed in CNS, stomach, thyroid, or pancreatic cancer (Fig. 3B). However, PDE4C gene expression was found to be significantly (i) lower in Lymphoid and Head & Neck cancer cell lines, and (ii) higher in lung and peripheral nervous system cancer cell lines (as found previously (He et al., 2017)(Fig. 3B). Whether up/down-regulation in these cancer-specific contexts correlates with PDE4 inhibitor/activator sensitivity warrants investigation.

PDE4C's role in cancer progression therefore appears to be highly heterogenous and future research will benefit from characterising PDE4C via a multi-omics approach when assessing its potential as a tractable biomarker/therapeutic target in human cancer.

Declaration of Competing Interest

George. S. Baillie and Connor M. Blair are founders of Disruptyx Therapeutics Ltd. George S. Baillie is Editor in Chief of Cellular Signalling Journal.

Data availability

Data will be made available on request.

Acknowledgements

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