Gene 577 (2016) 101–108

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Gene Wiki Review

Protein kinase A catalytic subunit isoform *PRKACA*; History, function and physiology

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ARTICLE INFO

Article history:
Received 1 October 2015
Received in revised form 17 November 2015
Accepted 23 November 2015
Available online 12 December 2015

Keywords:
Protein kinase A signaling
Phosphorylation
Regulatory subunits
Catalytic subunits
A-kinase anchoring proteins
Pathological cAMP signaling

ABSTRACT

Our appreciation of the scope and influence of second messenger signaling has its origins in pioneering work on the cAMP-dependent protein kinase. Also called protein kinase A (PKA), this holoenzyme exists as a tetramer comprised of a regulatory (R) subunit dimer and two catalytic (C) subunits. Upon binding of two molecules of the second messenger cAMP to each R subunit, a conformational change in the PKA holoenzyme occurs to release the C subunits. These active kinases phosphorylate downstream targets to propagate cAMP responsive cell signaling events. This article focuses on the discovery, structure, cellular location and physiological effects of the catalytic subunit alpha of protein kinase A (encoded by the gene *PRKACA*). We also explore the potential role of this essential gene as a molecular mediator of certain disease states.

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1. Introduction

Since the discovery of protein phosphorylation as a universal means for cell communication, it has become apparent that protein kinases play crucial roles in all aspects of cellular life (Scott and Pawson, 2009). These enzymes are responsible for the transfer of the γ-phosphate group of adenosine 5′-triphosphate (ATP) to a protein substrate, usually a serine, threonine or tyrosine but can also transfer to a histidine or lysine (Hunter, 1995, 2000). Bioinformatic analyses have identified on the order of 540 different protein kinase genes that

Abbreviations: PKA, cyclic-AMP dependent protein kinase/protein kinase A; cAMP, 3′,5′-cyclic adenosine monophosphate; ATP, adenosine 5-triphosphate; C subunits, catalytic subunits; R subunits, regulatory subunits; AKAP, A-kinase anchoring protein; AGC group of kinases, protein A, protein G and protein C group of kinases; PKI, protein kinase inhibitor.

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http://dx.doi.org/10.1016/j.gene.2015.11.052
0378-1119/

comprise the human kinome (Manning et al., 2002a). This represents about 2% of the genome (Manning et al., 2002a). Although the number of kinases varies across species, it is worthy to note that gene duplication events have enlarged several plant, Dinoflagellata and *Arabidopsis* kinomes (Manning et al., 2002b). Irrespective of their size, kinomes can be divided into 9 sub-families, one of which is called the AGC group. This subgroup of the kinome includes the protein kinase A, G and C families of serine/threonine kinases. The common feature of these enzymes is that they are responsive to changes in local concentrations of cytoplasmic second messengers such as cyclic AMP or lipids. In humans, this group consists of 63 protein kinases corresponding to the protein kinase G and protein kinase C family of kinases, Akt/protein kinase B, Aurora kinases, ribosomal protein S6 kinases, as well as the phosphoinositide-dependent kinases (Manning et al., 2002a). AGC kinases regulate a multitude of cellular processes including glucose metabolism, cell division and development, the stress responses and molecular aspects of synaptic transmission and contextual memory (Yeaman et al., 1977; Maller and Krebs, 1977; Lester et al., 2001; Smith et al., 2010; Snyder et al., 2005). A prominent member of the AGC kinases is the cAMP-dependent protein kinase, also called protein kinase A (PKA) (Taylor et al., 2012). This review article focuses exclusively on the structure, function, cellular location and pathophysiological effects of this key enzyme.

2. History

Our appreciation of mammalian PKA signaling has its origins in the pioneering work of biochemists Edmond H. Fischer and Edwin G. Krebs on the role of protein phosphorylation and the control of glycogen metabolism. Fischer and Krebs were working together on glycogen phosphorylase, an enzyme that is activated by a protein kinase called phosphorylase kinase (Fischer and Krebs, 1955). One of their key breakthroughs was realizing that activation of phosphorylase kinase was catalyzed by another enzyme that was dependent on the recently discovered second messenger, cAMP, reported by Earl Sutherland a few years earlier (Rall et al., 1957; Sutherland and Rall, 1958; Krebs et al., 1959). Accordingly Fischer and Krebs named their new enzyme cAMP-dependent protein kinase and purified the kinase in 1968 (Walsh et al., 1968). Fischer and Krebs won the Nobel Prize in Physiology or Medicine in 1992 for this discovery and subsequent work on phosphorylation and dephosphorylation, particularly how it relates to cAMP dependent protein kinase activity (Fischer and Krebs, 1955). Today, the cAMP-dependent protein kinase is more frequently denoted as protein kinase A, or simply PKA. PKA is a serine/threonine kinase that is responsible for phosphorylating a broad array of downstream substrates, the extent of which depends on cellular localization (Sim and Scott, 1999; Tasken and Aandahl, 2004). Not surprisingly PKA is considered as an essential regulator of many cell signaling events (Dessauer and Tasken, 2013; Carnegie et al., 2009).

Shortly after the discovery of PKA, there was a concerted effort by several investigators including Edwin Krebs, Jackie Corbin, and Susan Taylor, to discern the molecular components and stoichiometry of the bovine and rabbit enzyme complexes. In retrospect perhaps the most surprising finding was that the catalytic activity of PKA resided in a dedicated catalytic (C) subunit that was constrained in an inactive state by a range of regulatory (R) subunits (Corbin et al., 1977, 1978; Zoller et al., 1979; Bechtel et al., 1977; Ringheim and Taylor, 1990). Elegant biochemical studies demonstrated the R subunits of PKA exist in two forms, designated as RI and RII on the basis of their elution from ion exchange columns (Corbin et al., 1977, 1978; Zoller et al., 1979; Bechtel et al., 1977; Ringheim and Taylor, 1990). Subsequently, it was discovered that there are two RI subunits (termed RIα and RIβ) and two RII subunits (termed RIIα and RIIβ). The intact PKA holoenzyme exists as a tetramer of two regulatory subunits in contact with two catalytic subunits (Rannels and Corbin, 1980). This tetrameric protein complex constitutes the type I and type II PKA holoenzymes (Taylor et al., 2012). The uniqueness of this holoenzyme configuration was not fully appreciated until the beginning of kinome analyses when it was realized that of the over 540 human protein kinases, only one other AGC kinase, called CK2, exists in a tetramer complex. In contrast, the vast majority of protein kinases contain intramolecular regulatory sequences that reside within the same polypeptide chain as the catalytic core of the enzyme (Manning et al., 2002a).

During the characterization of the PKA holoenzymes, the Krebs lab discovered an endogenous protein inhibitor of the enzyme that acted independent of cAMP (Walsh et al., 1971). This 75 amino acid heat stable protein kinase inhibitor termed PKI was proposed to modulate the free catalytic subunit, but only after cAMP-dependent dissociation from the regulatory subunit (Scott et al., 1985a, 1985b). The mechanistic core of PKI resides in a pseudosubstrate sequence, RRNAI, that binds with high affinity to the active site of the C subunit (Scott et al., 1986). In fact, a peptide that encompasses residues 5 to 24 of PKI potently inhibits the C subunit with an inhibition constant of 2–4 nM (Scott et al., 1986).

With the advent of recombinant DNA technology, the extent and diversity of the mammalian PKA subunits was soon realized. Cloning studies by Stan McKnight and others identified four possible C subunit genes (Cα, Cβ, Cγ and the related gene Cχ) and confirmed the presence of the four R subunit genes (Lee et al., 1983; Uhler et al., 1986a, 1986b; Scott et al., 1987; Jahnsen et al., 1988, 1986; Eide et al., 2003). Moreover, the overexpression and purification of these recombinant proteins from bacteria made them ideal targets for structural analysis. A major milestone was the crystallization of the PKA Cα subunit by Susan Taylor and colleagues in 1991 (Knighton et al., 1991, 1992). This revealed for the first time the bi-lobed structure of the kinase core, a protein fold that has now been observed in well over 100 kinase structures (Taylor et al., 2012).

3. *PRKACA*

The human *PRKACA* gene is located on chromosome 19 at p13.1 on the reverse strand (Tasken et al., 1996). This gene, which is approximately 26,000 nucleotides long, encodes the PKA catalytic subunit alpha (Cα) isoform. *PRKACA* has 10 exons which transcribe into a 351 amino acid protein (40 kDa) (Shoji et al., 1981; Soberg et al., 2013).

Three alternately spliced transcripts of human *PRKACA* have been identified, denoted Cα1, Cα2 (also known as Cαs) and Cα3. The canonical Cα1 form that is ubiquitously expressed throughout human tissue encodes the 351 amino acid protein, while Cα2 is primarily expressed in sperm cells and contains a different 5′ exon that initiates transcription at an alternate start codon (Fig. 1A) (Uhler and McKnight, 1987; Showers and Maurer, 1986, 1988; San Agustin et al., 1998; Reinton et al., 2000). This results in Cα2 differing in the first 15 amino acids as compared to Cα1 (Fig. 1B). A third variant of Cα called isoform 3 has also been reported, but has yet to be characterized (Strausberg et al., 2002).

As previously mentioned there are three isoforms of the catalytic subunit of PKA; Cα, which is thought to be the predominant isoform and expressed in most tissues; Cβ, which is also expressed in various tissues, coded by the gene *PRKACB* (Uhler et al., 1986b). In contrast Cγ, encoded by *PRKACG* gene is most likely expressed only in the testis (Beebe et al., 1990). Yet there is little if any evidence that the Cγ protein is transcribed or has any functional significance in testis physiology. It is also worth noting that a fourth C subunit related gene *PRKX* has also been identified. Although the physiological significance of this putative C subunit isozyme is unclear, a number of decisive biochemical studies have conclusively demonstrated that Cχ can interact with the R subunits to form a modified PKA holoenzyme (Zimmermann et al., 1999).

Over 90 organisms are known to have *PRKACA* orthologs (Soberg et al., 2013). The primary structure of the protein is conserved from humans to mice, zebrafish, and yeast. In mice, targeted deletion of this gene results in growth retardation in the small number of animals that survive (Skalhegg et al., 2002), while a Cα deficiency has also

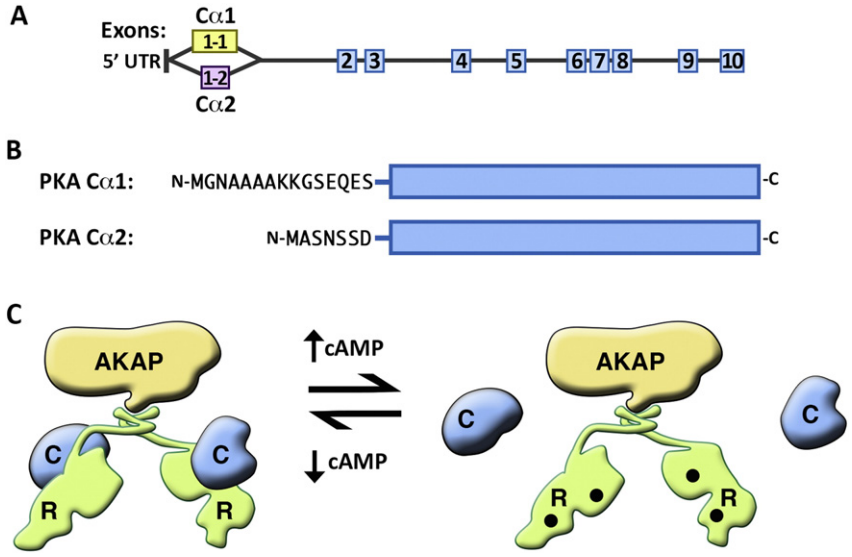

Fig. 1. A) Alternate splicing of *PRKACA* exon 1: PKA Cα1 and PKA Cα2. This schematic depicts alternate splicing in exon 1 of *PRKACA* that gives rise to two distinct transcripts. B) Alternate forms of PKA Cα. This schematic shows the differences in the amino terminal amino acid sequence of Cα1 and Cα2. The remainder of the sequence is identical. C) The anchored PKA holoenzyme. This schematic representation of the protein components of an anchored PKA holoenzyme shows the C subunits (blue) and the R subunit dimer (green) in complex with an AKAP (yellow). Following stimulation of cAMP synthesis, the second messenger (black) binds to the regulatory subunits in a manner that releases the catalytic subunits to phosphorylate target substrates.

been linked to spinal neural tube defects (Huang et al., 2002). On the other hand, a double knockout of Cα and Cβ or haploinsufficiency of Cβ in the context of a Cα total knockout is embryonic lethal. In contrast, deletion of Cβ results in phenotypically normal mice (Skalhegg et al., 2002; Qi et al., 1996). These seemingly contradictory results argue for a high degree of redundancy in the C subunit genes and a complex utilization of C subunit isozymes in different tissues (Brandon et al., 1995).

4. PKA signaling

4.1. Tetrameric holoenzymes

Inactive PKA exists as a holoenzyme, comprised of two regulatory (R) subunits and two catalytic subunits (Krebs and Beavo, 1979). In the presence of cAMP, the holoenzyme becomes active by binding two cAMP molecules cooperatively to each R subunit, resulting in a conformational change in the R subunits, thus releasing the two C subunits to phosphorylate downstream targets (Fig. 1C) (Welch et al., 2010). There are two distinct types of R subunits, RI and RII, of which there are two isoforms of each type, RIα, RIβ, RIIα, and RIIβ. PKA holoenzymes that contain either RI or RII are termed PKA type I or type II, respectively. The RI and RII isoforms differ in their localization, expression level and are believed by some to have differential sensitivities for cAMP (Corbin et al., 1977, 1978; Cadd and McKnight, 1989). More recently it has been realized that the differential localization of the type I and type II PKA holoenzymes is an important determining factor that dictates their physiological roles (Sim and Scott, 1999; Tasken and Aandahl, 2004; Langeberg and Scott, 2015).

Structural elucidation of the R subunits has always lagged behind our understanding of the catalytic subunits, in no small part because these modular proteins are flexible in nature (Weber et al., 1987; Su et al., 1995; Zawadzki and Taylor, 2004; Zhang et al., 2012; Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 1999). Nonetheless, a concerted effort over the past 20 years has resulted in high-resolution X ray structures for the cAMP binding sites and fragments of the RI and RII subunits in complex with Cα. Although an X ray structure of an intact PKA holoenzyme has eluded investigators, the amino-terminal docking and dimerization domains have been resolved to reveal a four helix bundle that not only forms the interface for R subunit dimerization but also created a pocket for the association of mammalian RI or RII with a family of A-kinase anchoring proteins (AKAPs) (Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 2001; Perino et al., 2011). As will be discussed later, this latter group of proteins is critical for the subcellular tethering of PKA in proximity to preferred substrates. More recently, negative stain single particle electron microscopy has been used to resolve the structure of an intact PKA holoenzyme in complex with an AKAP. This structure revealed that there are regions of intrinsic disorder within the R subunits of PKA that impart a high degree of flexibility and rotation to the C subunit when it is part of the holoenzyme complex (Smith et al., 2013). In fact, the anchored C subunit of PKA can move with relative freedom within a zone of 160 Å when bound to the R subunit dimer (Langeberg and Scott, 2015). Ongoing studies are trying to establish the functional significance of this new model for anchored PKA in a cellular context.

4.2. AKAPs

Specificity of PKA signaling is attained through the binding of the R subunits to scaffolding proteins called A-kinase anchoring proteins, or AKAPs (Scott et al., 1990). AKAPs are a diverse family of about 50 proteins that vary in localization and structure that all share the ability to bind the R subunits of PKA (Dessauer and Tasken, 2013; Dessauer, 2009). The trademark feature in all AKAPs is the amphipathic helix that binds with high affinity to the R subunits (Carr et al., 1991). AKAPs target the PKA holoenzyme to different subcellular locations in proximity to other proteins to optimize signal transduction. This process allows for local cAMP-responsive events to occur within specific compartments of the cell (Bauman et al., 2006). Recently, AKAP–PKA complexes were evaluated with electron microscopy and a three-dimensional reconstruction of the holoenzyme revealed that the AKAP–PKA complex has some flexibility, which might further allow PKA to adopt the optimal conformation for substrate phosphorylation (Smith et al., 2013). Although the majority of AKAPs preferentially associate with the RII subunit, there is reason to believe that RI subunits can also be compartmentalized though interaction with anchoring proteins (Huang et al., 1997a, 1997b). In addition there are a few RI selective anchoring proteins that only compartmentalize the type I PKA (Kovanich et al., 2010; Means et al., 2011).

Perhaps the most biologically relevant feature of AKAPs is their ability to cluster PKA with other classes of signaling enzymes (Tasken and

Aandahl, 2004; Klauck et al., 1996; Dodge et al., 2001; Carlisle Michel et al., 2004; Bauman et al., 2007). By constraining broad specificity enzymes such as PKA, PKC, and the protein phosphatases PP1 and PP2B in customized macromolecular units, AKAP complexes allow cells to efficiently and accurately respond to the transient production of diffusible second messenger signals. This concept was first proposed in 1995 when it was shown that the anchoring protein AKAP79/150 not only compartmentalized PKA, but also sequestered the protein phosphatase PP2B (Coghlan et al., 1995). As a result, the opposing actions of a protein kinase and a protein phosphatase were constrained within the confines of the same macromolecular complex (Coghlan et al., 1995). It was subsequently shown that the proximity of both enzymes to phosphoprotein substrates such as ion channels and cytoskeletal components enhanced the bi-directional control of neuronal events that underlie synaptic transmission, glucose homeostasis, cardiac transcriptional regulation and higher-order cognitive function in genetically modified mice (Carnegie et al., 2008; Gold et al., 2012; Hinke et al., 2012; Nystoriak et al., 2014; Wong et al., 2008; McCartney et al., 1995; Kritzer et al., 2014).

5. *PRKACA* and disease

5.1. Cardiovascular diseases

Given its prominent role in normal physiology it is not surprising that there has been much interest in how PKA phosphorylation goes wrong in disease (Esseltine and Scott, 2013). Probably the most common pathological effects of defective cAMP signaling underlie the onset of coronary heart disease and cardiomyopathies (Bristow et al., 1982, 1984; Bristow, 1984; Diviani et al., 2011). It has been known since the early 1960's that blocking β adrenergic stimulation of cAMP synthesis is protective against heart disease (Black and Stephenson, 1962). Moreover, prolonged elevation of cAMP is observed in heart failure and the onset of several cardiomyopathies (Bers, 2008; Lefkowitz, 2004). Yet despite the prominence of heart disease as a global health problem in the first world, less is known about the specific role of PKA in this process. That being said there are two aspects of cardiac pathophysiology where PKA phosphorylation events are known to be mis-regulated. First, excitation–contraction coupling of cardiomyocytes requires the rhythmic and coordinated action of the calcium and cAMP signaling pathways (Bers, 2008; Dodge-Kafka et al., 2006). Although some consider it controversial, it has been postulated that changes in the phosphorylation status of the L-type calcium channel ($Ca_V1.x$), the ryanodine receptor, and the SERCA modulating protein phospholamban underlie the onset of various heart ailments including dilated cardiomyopathies (Marx et al., 2000, 2001; Lehnart et al., 2005). Whether these defects occur at the level of the channels, cAMP metabolism, or mis-localization of anchored PKA remains a matter of contentious debate. Nonetheless, it is evident that modulation of PKA activation is a therapeutic strategy that manages some stages of progressive and congestive heart failure (Olson, 2004; McKinsey and Olson, 2005; Lygren et al., 2007; Lygren and Tasken, 2008). Second, membrane depolarization by cardiac potassium channels is key to the transduction of electrical impulses from the sino atrial node of the heart. An elegant series of studies suggest that mutations in a gene encoding the A-kinase anchoring protein Yotiao/AKAP6 underlie the onset of arrhythmias (Marx et al., 2002; Kurokawa et al., 2004). Interestingly, this anchoring protein associates with the KCNQ1 subunit of potassium channel (Kass and Moss, 2003). Further study is necessary to more precisely pinpoint the functional consequences of the genetic lesion and whether or not anchored PKA is a driver or a passive player in this process. Nonetheless, it is possible that the mis-localization or mis-regulation of PKA in the sinoatrial node may be a contributing factor to the onset of certain arrhythmias (Chen et al., 2007).

5.2. Tumors of the adrenal cortex

Somatic mutations have been found in *PRKACA* that result in Cushing's syndrome. Cushing's syndrome is a disease caused by excess glucocorticoid production that can be a result of adrenocortical (ACT) and ACTH-producing pituitary tumors (Lacroix et al., 2015). These tumors include adrenocortical adenomas (ACA), adrenocortical carcinomas (ACC) and bilateral adrenal hyperplasia (BAH). Overproduction of glucocorticoids caused by Cushing's syndrome can result in other disorders, like hypertension, osteoporosis, diabetes as well as interfering with hormone production from the pituitary. Recently several groups have independently reported that whole-exome sequencing of cortisol-producing ACTs resulted in the identification of c.T617G heterozygous mutation that results in an amino acid substitution, Leu206Arg (Beuschlein et al., 2014; Goh et al., 2014; Sato et al., 2014; Cao et al., 2014). This mutation was only found in ACAs, with a varying frequency of approximately 20% to 70% depending on the study. This mutation L206R is found in the p + 1 loop of PKA, and interferes with binding between the catalytic subunit and the R subunits of PKA in the presence of cAMP. Further studies have confirmed this mutation in *PRKACA*, and concluded that the Leu206Arg mutation of PKA results in higher basal PKA activity (Cao et al., 2014; Di Dalmazi et al., 2014).

Three insertions have been found in patients with adrenocortical adenomas; c.595_596insCAC that results in an insertion of a tryptophan (Leu199_Cys200insTrp), c.600_601insGTG that results in a insertion of valine (p.Cys200_Gly201insVal), and a missense mutation, c.639C > G that changes Ser213 to Arg while inserting four amino acids (Di Dalmazi et al., 2014; Espiard and Bertherat, 2015). This mutation is found in a highly conserved region of the catalytic subunit of PKA, and is thought to elevate basal activity of PKA. In contrast, the Leu206Arg, Leu199_Cys200insTrp, and the Cys200_Gly201insVal mutations are all found near the autoinhibitory sequence of the regulatory subunit (Di Dalmazi et al., 2014). This region is involved in keeping the catalytic subunit inactive by blocking the active site in the absence of cAMP (Di Dalmazi et al., 2014). Collectively these findings provide further evidence that disruption of this conserved structure of the catalytic subunit of PKA can lead to aberrant and unregulated kinase activity (Stratakis, 2014). Germline gene amplification of *PRKACA* has also been recently reported in Cushing's syndrome patients that resulted in bilateral adrenal hyperplasia. Interestingly, exome sequencing revealed that none of these harbored mutations in the *PRKACA* gene, but rather exhibited increased copy numbers of *PRKACA* transcript (Lodish et al., 2015; Carney et al., 2015).

Carney complex (CNC) is another disease of the adrenal gland, which presents as somatotroph–pituitary adenomas, testicular Sertoli cell calcified tumors, benign thyroid nodules, differentiated thyroid cancer, and most commonly, primary pigmented nodular adrenocortical disease (Berthon et al., 2015). Inactivating mutations in the gene that encodes RIα (*PRKAR1A*) have been identified in over 60% of patients with CNC (Espiard and Bertherat, 2015; Kirschner et al., 2000; Horvath et al., 2010). While the exact mutations differ from family to family, these mutations usually lead to a premature stop codon and the RNA gets promptly degraded. One molecular explanation is that a decrease in the cellular RIα pool allows the catalytic subunit to roam unregulated and increases the kinase activity in tissues.

When taken together all of these above findings infer that increased transcripts of PKA, disruption of the C subunit binding to the R subunits or pathological changes in the cellular stoichiometry of PKA subunits can underlie a variety of diseases. Thus it would appear that each of these endocrine disorders are perpetuated by defective cAMP signaling and misregulated PKA activity.

5.3. PRKACA and cancer

Although PKA is not traditionally considered to be an oncogene, there is a growing body of literature that suggests this kinase may

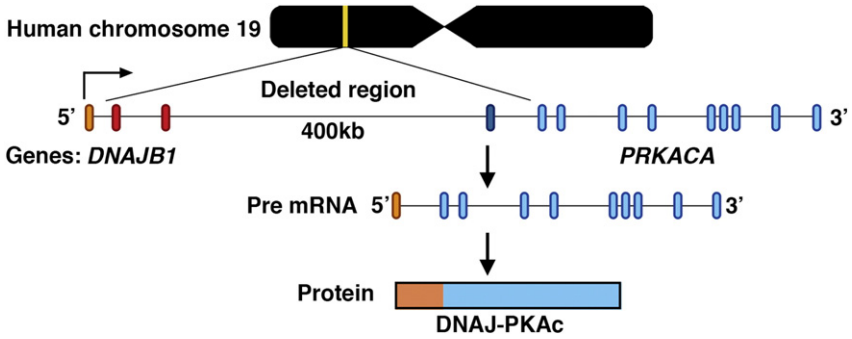

Fig. 2. A lesion in chromosome 19 underlies the formation of a chimeric DNAJ-PKAc protein in patients with fibrolamellar hepatocellular carcinoma (FL-HCC). A 400-kilobase pair deletion in chromosome 19 is found in almost all FL-HCC tumors sequenced. This deletion event results in the in-frame fusion of the first exon of *DNAJB1* (orange) with exons two through ten of *PRKACA* (blue). This deletion event results in the production of a fusion pre-mRNA, and is eventually translated into a functional protein (DNAJ-PKAc).

contribute in some ways to the progression of cancer. For example, extracellular PKA catalytic subunit has been detected in the serum of a variety of cancer patients, including colon, renal, rectal, prostate, lung, adrenal carcinomas and lymphomas (Cho et al., 2000; Cvijic et al., 2000; Porter et al., 2001). Increased *PRKACA* transcripts have also been observed in breast cancer, specifically in patients that are resistant to trastuzumab, which is a common treatment for HER2 positive breast cancer (Moody et al., 2015). In these instances, *PRKACA* can be used as a biomarker for cancer as well as a prognostic tool (Moody et al., 2015).

More recently, there has been a lot of interest in fibrolamellar hepatocellular carcinoma (FL-HCC) and *PRKACA*. This began when Honeyman et al. described a 400 kb deletion on chromosome 19 in 100% of FL-HCC patients (Honeyman et al., 2014). This genetic lesion resulted in an in-frame fusion of two genes — *DNAJB1*, which is the gene that codes for the heat shock protein 40, and *PRKACA*. Other groups have also validated this deletion, and confirmed the fusion of the first exon of *DNAJB1* to exons two through ten of *PRKACA*, shown in Fig. 2 (Cornella et al., 2015; Xu et al., 2014; Cheung et al., 2015). Further analyses of FL-HCC tissues show an increase in protein levels in tumor tissues. This increase in transcript is believed due to the fusion protein being under the control of the *DNAJB1* promoter (Honeyman et al., 2014). Again, this is consistent with the above hypothesis that increased PKA levels in tissues can lead to disease.

6. Conclusion

As should be evident from this synopsis of published reports and personal perspectives, the field of PKA signaling has grown from a purely biochemical curiosity into a multifaceted discipline with clear implications for disease. In the next few years it will be imperative that we make an effort to translate the biochemical breakthroughs in our understanding of the structure and function of this ubiquitous enzyme into a more detailed appreciation of how PKA signaling falls apart in disease states.

Although there are many promising leads to follow up, conceivably the most intriguing challenge comes in the development of therapeutics to combat fibrolamellar hepatocellular carcinoma (FL-HCC). The recent discovery of the DNAJ–PKAc fusion as an oncogenic element beautifully underscores the advantages of combining state of the art genomics with detailed structural information (Honeyman et al., 2014; Cheung et al., 2015). Yet, it remains to be seen if DNAJ–PKAc is the genetic driver in the etiology of FL-HCC. It will be interesting to see if the detailed structural information on the DNAJ–PKAc reveals a mechanism that impacts the substrate specificity or how subcellular location of this pathological form of the enzyme is controlled.

It is worthy to note that FL-HCC is not the sole target for PKA directed therapies. For example, developing strategies that target some of the PKA C subunit mutant forms that underlie Cushing's syndrome may hold some therapeutic promise, as will small molecules to help reform the type I PKA holoenzymes in patients with Carney complex (Cao et al., 2014; Espiard and Bertherat, 2015). That being said, only time will tell if PKA represents a disease locus or a viable target for drug discovery.

Acknowledgments

This review and the corresponding Gene Wiki article are written as part of the Cardiac Gene Wiki Review series—a series resulting from a collaboration between the journal GENE, the Gene Wiki Initiative, and the BD2K initiative. The Cardiac Gene Wiki Initiative is supported by National Institutes of Health (GM089820 and GM114833). Additional support for Gene Wiki Reviews is provided by Elsevier, the publisher of GENE. The authors would like to thank Lorene K. Langeberg and members of the Scott lab for their assistance and critical evaluation of the manuscript. JDS and RET are supported by The Howard Hughes Medical Institute and National Institutes of Health grants DK54441 and DK105542 (JDS). RET is supported by Interdisciplinary Training Grant in Cancer, T32 CA080416. The corresponding Gene Wiki entry for this review can be found here: https://en.wikipedia.org/wiki/PRKACA.

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