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MEN1, MEN4, and Carney Complex: Pathology and Molecular Genetics

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Abstract

Pituitary adenomas are a common feature of a subset of endocrine neoplasia syndromes, which have otherwise highly variable disease manifestations. We provide here a review of the clinical features and human molecular genetics of multiple endocrine neoplasia (MEN) type 1 (MEN1) and Carney complex (CNC). Both diseases are hereditary autosomal dominant syndromes that can present with pituitary adenomas. MEN1 is caused by inactivating mutations in the *MEN1* gene, whose product menin is involved in multiple intracellular pathways contributing to

transcriptional control and cell proliferation. MEN1 clinical features include primary hyperparathyroidism, pancreatic neuroendocrine tumours and prolactinomas and other pituitary adenomas. A subset of patients with pituitary adenomas and other MEN1 features have mutations in the *CDKN1B* gene; their disease has been called MEN type 4 (MEN4). Inactivating mutations in the type 1α regulatory subunit of protein kinase A (PKA) (the *PRKAR1A* gene), that lead to dysregulation and activation of the PKA pathway, are the main genetic cause of CNC, which is clinically characterised by primary pigmented adrenocortical disease (PPNAD), spotty skin pigmentation (lentigines), cardiac and other myxomas and acromegaly due to somatotropinomas or somatotrope hyperplasia.

Introduction

About 5 % of pituitary adenomas occur in a familial setting [1]. The majority of these familial pituitary tumours are due to multiple endocrine neoplasia (MEN) type 1 (MEN1) [2]. Other genetic causes include Carney complex (CNC), MEN type 4 (MEN4), mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene leading to familial isolated pituitary adenomas (FIPAs) and McCune-Albright syndrome (MAS). Recently mutations in succinate dehydrogenase subunits (*SDHx*) and *DICER1* as well as Xq26.3 microduplication have also been associated with pituitary tumours. Genetic conditions (germline or somatic) leading to pituitary tumours are summarised in table 1.

Despite the relative rarity of syndromic pituitary adenomas, the study of their genetic causes has contributed significantly to the understanding of pituitary tumourigenesis in general. MAS and CNC are caused by mutations in members of the cAMP-dependent protein kinase (protein kinase A or PKA) pathway [3, 4]; similarly, the PKA pathway, which contributes to pituitary proliferation and hormone secretion, is also altered in approximately 40% of sporadic somatotropinomas [5-10].

On the other hand, no single consistent genetic mechanism for pituitary tumourigenesis has emerged yet. Classic tumour suppressor genes, such as *TP53* or *RB1*, or oncogenes, including *Ras*, are all involved but not thought to be major contributors to germline predisposition to pituitary tumourigenesis [11-14]. *MEN1* and *CDKN1B*, whose mutations can cause pituitary tumour formation in the context of multiple endocrine neoplasia syndromes, were shown to be mutated or down-regulated only in few sporadic tumours [15-19]. Similarly, mutations in *AIP* and *PRKAR1A*, which lead to familial pituitary tumours in the context of FIPA and CNC, respectively, do not seem to contribute significantly to sporadic pituitary tumours [10, 20-24], although AIP expression is reduced in some sporadic somatotropinomas in the absence of *AIP* mutations [25], probably due to the actions of different microRNAs [26, 27]. The variable and incomplete penetrance of these hereditary pituitary tumour syndromes suggests that additional circumstances are required for pituitary tumourigenesis. These have not been clearly defined yet, even though some candidate loci have been reported for *AIP*-associated tumours [28, 29], and a possible association was suggested between a *CDKN1B* variant and tumour multiplicity in MEN1 [30]. However these additional circumstances required for pituitary tumourigenesis in the context of genetic syndromes may well involve the same pathways controlling cell proliferation and hormone secretion that are also dysfunctional in sporadic pituitary adenomas.

MAS is a genetic but not hereditary condition caused by somatic, postzygotic mutations in the α-subunit of the G_s protein (GNAS), leading to somatotrope or somatolactotrope hyperplasia and growth hormone (GH) hypersecretion in approximately 20% of patients [3, 31, 32]. Inactivating germline mutations in *AIP* were recently discovered to be the genetic cause in about 20% of FIPA patients [33]. These patients have mostly somatotropinomas or prolactinomas (and sometimes non-functioning pituitary adenomas and rarely corticotropinomas), and no other recurrent clinical manifestations [33, 34]. MAS, FIPA due to *AIP* mutations and their contribution to pituitary pathology are described in detail elsewhere [3, 31-34].

Mutations in different subunits of *SDH* can lead to hereditary pheochromocytoma and paraganglioma syndromes [35] and recently *SDHx* mutations were also reported to be associated with pituitary adenomas [36-39]. Pituitary blastoma, manifesting mostly in early childhood and leading to Cushing's syndrome, was recently described [40, 41]. Germline mutations in *DICER1* were reported in almost all cases of pituitary blastoma [40-42]; interestingly, germline *DICER1* mutations also cause other early childhood tumours summarised as pleuropulmonary blastoma-familial tumour and dysplasia syndrome (see table 1). However, in the few cases that have been reported the manifestation of another *DICER1*-related tumour in association with pituitary blastoma is rare [42]. We have recently reported Xq26.3 microduplication in association with early childhood-onset gigantism, termed X-linked acrogigantism [43]. This is probably due to overexpression of GPR101, a G-protein coupled orphan receptor that is located in this region, and downstream PKA pathway activation; interestingly a GPR101 mutation is found in some cases of sporadic acromegaly [43]. A possible association was suggested between neurofibromatosis type 1 and acromegaly or gigantism in a few case reports [44]; this growth hormone excess is due to optic pathway tumours that are hypothesised to suppress hypothalamic somatostatin secretion, and hence will not be discussed in detail here.

In this review, we present an update on the clinical manifestations and human molecular genetics of three of the above referenced diseases, all caused by genetic defects in the germline, MEN1, MEN4 and CNC.

Multiple endocrine neoplasia type 1

Multiple endocrine neoplasia type 1 (MEN1, MIM*131100) is an autosomal dominant disorder, leading to parathyroid neoplasms, pancreatic neuroendocrine tumours and pituitary adenomas [45]. Other MEN1-associated endocrine and non-endocrine neoplasms, including adrenocortical tumours, carcinoids and facial

angiofibromas, may also occur [45, 46]. The prevalence of MEN1 is about 1:30,000 [45], but geographical clustering due to a founder effect can be observed [47, 48]. There is considerable phenotypic variability of tumour type manifestations even within the same family [49].

The penetrance of MEN1 is generally high, with biochemical signs present in >95% and clinical signs in 80% of patients by the fifth decade of life [49-51]; for instance, the age-related penetrance at 50 years is 73-75 % for primary hyperparathyroidism, 31-48 % for pituitary adenomas and for 45-49 % islet cell tumours [51, 52]. However the age of presentation of specific tumour types is highly variable, and may range from 9-25 for the earliest to 68-77 years for the latest tumour manifestation [51]. MEN1 patients have a decreased life expectancy and MEN1-associated mortality is mostly due to enteropancreatic malignancy [51-55]. MEN1-associated mortality has improved since the 1980s due to more intense screening programs, better perioperative survival and, since protein pump inhibitors became available, reduced mortality due to gastrinoma-associated gastric ulcer perforation and haemorrhage [54].

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is frequently the presenting feature of MEN1 [49] and also the most common MEN1-associated clinical manifestation that occurs in more than 90 % of mutation carriers [46, 49, 51]. MEN1-associated PHPT develops approximately 30 years earlier than sporadic PHPT, and has an almost even gender ratio whereas sporadic PHPT has a 75% female preponderance [56]. PHPT in the context of MEN1 is associated with higher severity of bone involvement with borderline rather than elevated parathyroid hormone levels and only mildly elevated serum calcium [57]. Usually MEN1-associated PHPT is due to multiglandular hyperplasia whilst there is more often one evident adenoma in sporadic PHPT [58-61]. Consequently surgery is often more challenging, involving intraoperative identification and removal of all four glands, and recurrence rates are

high [62, 63]. In addition, supernumerary or ectopic parathyroid glands occur in up to 20 % of patients [59] and their identification is crucial to prevent recurrence. In conjunction with open bilateral neck exploration, total thymectomy is also often performed since this is the most common location for ectopic parathyroid glands; intraoperative parathyroid hormone measurement can aid to determine successful removal of all overactive glands [64].

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNET) are also a frequent feature of MEN1 in up to 75 % of patients [46, 49, 51], but patients are often asymptomatic and the real prevalence may be higher [46, 65]. These tumours are most often gastrinomas, insulinomas or nonfunctioning PNETs, occasionally glucagonomas, VIPomas or somatostatinomas [46, 51, 54]. Most MEN1 patients have multiple microadenomas in pancreas and duodenum, only few of which become clinically relevant [66, 67], consequently metastases are frequently present (30-50 %) at the time of appearance of symptoms [67, 68]. Gastrinomas associated with excessive gastric acid production and gastric ulceration, referred to as Zollinger-Ellison syndrome, are a major contributor to MEN1-associated mortality [48, 69]. MEN1-associated gastrinomas are usually located in the duodenum, and are small and multicentric compared to the larger and mostly singular sporadic gastrinomas [70-72]; consequently the surgical resection of a single tumour is not likely to be curative and therapy of small non-metastatic tumours is primarily symptomatic [46]. Importantly, gastrinomas are relatively rare in the general population, and 20 % of patients with gastrinomas have MEN1 [72]. Non-functioning PNETs have recently attracted attention due to the finding that their prevalence and associated mortality are higher than previously thought [54, 73]. Their prognosis is worse than that of functioning PNETs and clinical assessment is difficult due to the absence of specific symptoms or biochemical markers [54, 73]. Insulinomas are the first manifestation of MEN1 in 10 % of patients, and even though there is often more than one tumour,

surgery is recommended [64]. VIPomas, glucagonomas and somatostatinomas are rare, however if present they have a high risk of malignancy [67, 74], and surgery should be performed in the absence of distant metastases [74].

Pituitary adenomas

The frequency of pituitary adenomas (PAs) in MEN1 is around 40% depending on the patient population [46, 49, 51, 75]; conversely, only 3% of patients with PA have MEN1 [2]. Mean age of presentation is around 38 years, but can vary between 5 years and the ninth decade of life [75, 76]. PAs are the first MEN1 manifestation in about 20 % of patients [52, 75]. PAs are most commonly prolactinomas, followed by non-functioning PAs, somatotropinomas and corticotropinomas; this distribution is approximately the same as that seen in sporadic PAs. However in MEN1 PAs there is a higher incidence of multiple hormone expression and multiple adenomas [75, 77]. MEN1-associated PAs are more aggressive than sporadic PAs, are macroadenomas in 85 % of cases compared to 40 % in sporadic PAs, and they may infiltrate surrounding tissues more frequently [75, 77]. This is accompanied by a worse rate of hormonal control in MEN1 PAs [75]: 44 % of MEN1-associated prolactinomas are resistant to dopamine agonist therapy [75, 78]. The presence of pituitary enlargement in imaging studies does not preclude elevated hormone production elsewhere, and in rare cases, PNETs that secrete hypothalamic hormones and lead to excessive secretion of pituitary hormones have been encountered [77, 79, 80]. Sporadic PAs and MEN1 PAs are similarly more common in females than in males (approximately 70 % female in MEN1 patients); there is currently no explanation for this although oestrogen was hypothesised to stimulate the proliferation of pituitary cells, as seen experimentally [75, 81].

Other MEN1-associated features

Approximately 40% of MEN1 patients develop additional functioning or non-functioning endocrine tumours [51]. Most commonly these are benign non-

functioning adrenocortical lesions, but primary aldosteronism, adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome or (more rarely) adrenal hyperandrogenism due to adrenal adenomas are found in about 15 % [82]. This is significantly higher than the rate of endocrine activity among sporadic adrenal incidentalomas, indicating that adrenocortical tumours or bilateral hyperplasia in MEN1 are frequently functional [82]. Facial angiofibromas occur in up to 88% of patients and collagenomas in up to 72 % [83, 84], and their presence may aid diagnosis (the presence of three facial angiofibromas and one collagenoma is 75 % sensitive and 95 % specific for MEN1) [84]. Pheochromocytoma is rarely observed (<1 %) [82]. Interestingly, MEN1 patients have impaired fasting glucose (17 % vs. 6 % in controls) that cannot be adequately explained by the presence of hormone secreting tumours or previous pancreatic surgery, and may contribute to cardiovascular mortality [85, 86].

Molecular genetics

The genetic cause of MEN1 was initially localized to 11q13 and later identified as the tumour suppressor gene *MEN1*, which consists of 10 exons and codes for the protein menin [87-89]. Loss of heterozygosity (LOH) of the *MEN1* locus is frequently found in MEN1 tumours [87, 90, 91].

Menin is a 610 amino acid protein with no homology to other known proteins; its expression is ubiquitous and the mechanism of how loss of function of menin leads to MEN1 is still unclear [88, 89, 92]. Menin predominantly localises to the nucleus, containing two classical nuclear localisation signals (NLSs) and at least one further non-classical NLS in its C-terminus [93, 94]. In the nucleus it can associate with chromatin [95], dsDNA [96], the lysine-specific histone methyltransferases KMT2A and KMT2B [97, 98] and components of a transcriptional repressor complex also including histone deacetylases (HDACs) [99]. Menin interacts with transcription factors including activating protein-1 (AP-1), JunD, nuclear factor-κB (NF-κB), β-

catenin, mothers against decapentaplegic (SMAD) family members and oestrogen receptor α (ERα) [97, 100-106]. Menin binds to cytoskeletal proteins, e.g. vimentin [107], and cytoplasmic cell signalling mediators including Akt1/protein kinase B (PKB) and forkhead box protein O1 (FoxO1) [108, 109]. Some of the known menin interaction partners are depicted in Fig. 1. Menin was shown to play a role in cell proliferation [110-112], apoptosis [113, 114] and genome integrity [115]. Menin and KMT2A in complex regulate expression of several Hox genes as well as *CDKN1B*, and they interact with ERα to coactivate ERα-mediated transcription [97, 106, 116, 117]. Interestingly, chromosomal rearrangements involving KMT2A lead to mixed-lineage leukaemia, and in this context menin was shown to be required for KMT2A-dependent oncogenic transformation [118]. This illustrates the functional versatility of menin in different tissues that may also help to understand the yet unexplained tissue selectivity of MEN1-associated tumours even in the presence of the same mutation.

Hundreds of *MEN1* mutations have been described, which are located along the whole coding region and splice sites of the gene [119]. While most MEN1 cases are familial, 10 % of cases occur in a non-familial context and are due to *de novo MEN1* mutations [119]. The majority of mutations leading to MEN1 are frameshift deletions or insertions and nonsense mutations leading to truncation or absence of the protein [51, 119]. Missense mutations leading to single amino acid substitutions were assumed to cause less severely impaired protein function, but no notable difference was observed in clinical manifestation of those patients [51]. Some mutations leading to single amino acid substitutions were demonstrated to lead to proteasomal degradation and hence markedly reduced protein levels [120], while other mutations lead to nonsense-mediated mRNA decay [121]. A reduction of interaction capacity of menin with its binding partners was also shown for some mutations leading to single amino acid substitutions [97, 100]. Some intronic mutations were demonstrated to lead to alternative splicing, suggesting that they are causative for MEN1 [122-124]. Interestingly, in approximately 10 % of patients with clinical MEN1, no *MEN1* gene mutations could be identified [119, 125-127]. In a

small number (1 %) of these cases, large deletions of one exon or more could be detected using multiple ligation-dependent probe amplification (MLPA) or long-range PCR amplification [128, 129]. In the remaining cases, the phenotype may be due to intronic mutations that are not detected by routine sequencing, however the involvement of mutations in other genes cannot be excluded.

Genotype-phenotype correlation

Due to the large number of different mutations in combination with the heterogeneity of disease manifestations it has proved difficult to establish subtle genotype-phenotype correlations in MEN1. One study found that all patients with frameshift mutations have PNETs [130], while another study showed a higher rate of malignant tumours for mutations in MEN1 exons 2, 9 and 10 [131]. However, no genotype-phenotype correlation could be consistently confirmed in different patient populations [51, 119]. In addition, studies of unrelated kindreds with the same mutation showed large variability of different MEN1 associated tumours [50, 132], and there are reports of identical twins with different MEN1 manifestations [133-135]. Remarkably, some families with particular *MEN1* mutations develop only isolated hyperparathyroidism, while the same mutations in other families lead to full MEN1 [119]. Epigenetic mechanisms caused by environmental factors may influence disease phenotype in patients carrying the same *MEN1* mutation [136]. Recently, a specific variant of the *CDKN1B* gene was demonstrated to be disease modifying in MEN1 patients with truncating *MEN1* mutations, causing a higher number of MEN1 related tumours [30].

MEN4

In the approximately 10 % of patients with a MEN1-like phenotype where no *MEN1* mutations could be detected, other genes were suspected to be responsible for the clinical manifestation [119, 125-127]. A rat model displaying a MEN1-like phenotype was discovered to harbour a mutation in the *CDKN1B* gene, leading to

premature termination [137]. *CDKN1B* transcription is regulated by menin [116, 138]. *CDKN1B* encodes for the cyclin-dependent kinase inhibitor $p27^{Kip1}$, which participates in cell cycle regulation by interaction with cyclin-dependent kinases [139], and in turn, $p27^{Kip1}$ levels are regulated *via* the mitogen-activated protein kinase (MAPK) and the phosphatidyl inositol-3 kinase (PI3K) pathways [140, 141]. In a small number (up to 3 %) of *MEN1* mutation-negative patients fulfilling the diagnostic criteria for MEN1, mutations in *CDKN1B* have been detected and the corresponding clinical syndrome has been termed MEN4 (MIM#610755) [137]. Mutations in some of those patients were shown to either lead to decreased cellular levels of $p27^{Kip1}$ by reduced translation or proteasomal degradation, or to functional defects causing reduced binding to interacting partners or decreased nuclear localisation [137, 142-144]. Interestingly, a novel mechanism of *CDKN1B* loss of function leading to MEN4 was recently discovered: a 4 bp deletion in an upstream ORF within the *CDKN1B* 5'UTR led to decreased translation reinitiation and decreased $p27^{Kip1}$ levels [145].

Primary hyperparathyroidism is present in all the MEN4 patients reported so far, but tumour manifestations seem to be more variable than in MEN1 and due to the small number of patients so far reported a comprehensive phenotype has not been established [146]. PAs (corticotropinomas, somatotropinomas and non-functioning), as well as neuroendocrine tumours, uterine neoplasms, adrenocortical masses and thyroid tumours have been described in the MEN4 context [137, 142-144, 147].

Carney complex

Carney complex (CNC, MIM#160980) is a rare endocrine tumour syndrome with currently about 750 documented cases worldwide [148, 149]. Initially described as the complex of myxomas, spotty skin pigmentation (lentigines), and endocrine overactivity, the familial syndrome is inherited in an autosomal dominant fashion [150, 151]. Further manifestations include primary pigmented nodular adrenocortical disease (PPNAD) leading to Cushing's syndrome, PAs, thyroid nodules, testicular neoplasms, ovarian cysts, psammomatous melanotic schwannomas, ductal breast adenomas and osteochondromyxomas [152]. Most CNC patients initially present with ACTH-independent Cushing's syndrome due to PPNAD or heart myxomas, although abnormal skin pigmentation may be present at birth and is most often the first manifestation [152-154]. The majority of CNC cases are caused by inactivating germline mutations in the type 1α regulatory subunit of protein kinase A (*PRKAR1A*) gene [155], and those mutations lead to CNC with a penetrance close to 100 % [148, 149]. About 70 % of CNC cases occur in a familial context [148].

Cushing's syndrome due to PPNAD

PPNAD is most frequently seen in the context of CNC, and 60 % of CNC patients have PPNAD [148, 156]. Conversely, of all patients with PPNAD, about 80 % have CNC while 20 % have isolated PPNAD, where no other CNC-associated lesions could be detected [148]. PPNAD typically manifests at a young age (median age 34 years) and leads to ACTH-independent adrenocortical Cushing's syndrome [148]. Diagnosis can be challenging in cases of cyclical (14 %) or subclinical Cushing's syndrome (19 %) [156]. Interestingly, most CNC patients with PPNAD have a paradoxical increase of cortisol secretion after dexamethasone administration, which is diagnostically particularly useful in patients with normal baseline cortisol levels [156].

Pituitary adenomas

While 75 % of CNC patients have abnormal GH, IGF-1 or prolactin levels basally or during dynamic testing, PAs can only be detected in about 10 % [148, 152, 157, 158]. This may be due to prolonged periods of somatolactotrope hyperplasia preceding adenoma formation [152, 158-160]. CNC-associated PAs are mostly positive for GH or GH and prolactin, and can lead to acromegaly or gigantism, and rarely to clinically significant hyperprolactinaemia [151, 157-161]. A minority of adenomas also stained positive for thyroid-stimulating hormone (TSH), luteinising hormone (LH) or α-subunit [159, 161] but these do not cause a clinical phenotype. CNC-related adenomas are often multiple, surrounded by hyperplasia, and mostly microadenomas, but there are also cases of very aggressive and invasive macroadenomas [159].

Cardiac myxomas

CNC-associated cardiac myxomas can be found in 30 % of CNC patients [148]. They have an even age and gender distribution and occur anywhere in the heart as opposed to sporadic cardiac myxomas more frequently occurring in the left atrium and in older females [152]. Tumours can be multiple and can recur after removal [148]. The age of manifestation varies between 3-67 years [148]. Although these are benign neoplasms, they can lead to serious complications including cardiac insufficiency, stroke or pulmonary embolism [152].

Skin manifestations

Lentiginosis (present in 70 % of the patients) and other pigmented cutaneous lesions (blue, Spitz and compound naevi and café-au-lait spots, 50 %) are frequently observed and may be present at birth or appear in early childhood [148, 152].

Cutaneous myxomas are found in 20 % of CNC patients [148]. Twenty percent of affected women have mammary myxomas [148]. Other skin tumours include lipomas, collagenomas and ear canal trichofolliculoepitheliomas.

Other CNC-associated tumours

Psammomatous melanotic schwannomas are a relatively rare manifestation of CNC; however, they cause significant morbidity and can even be the cause of death of CNC patients, because they can (depending on their location) cause significant neurologic deficits, obstructive pulmonary disease, or increased intracranial pressure. Finally, they can become malignant and when they do they are aggressive tumours with frequent lung or cerebral metastases [152].

Testicular neoplasms occur in more than two thirds of male patients (by ultrasonography) and are mostly large cell calcifying Sertoli cell tumours [148]. Thyroid nodules can also be observed frequently, but thyroid cancer is rare [148].

Molecular genetics

The most frequent genetic cause (in about 73% of the patients) of CNC is a *PRKAR1A* defect [4, 148, 162]. *PRKAR1A* acts as a tumour suppressor by haploinsufficiency, although loss of the wild-type allele is also found in most CNC-associated tumours [4, 152, 162].

PRKAR1A encodes for the type 1α regulatory subunit (R1α) of PKA. PKA is a heterotetramer composed of two catalytic subunits (Cα, Cβ, Cγ or Cx) and two regulatory subunits (R1α, R1β, R2α or R2β). Stimulation of the G_s protein leads to activation of adenylyl cyclase that produces cAMP. cAMP is then bound by PKA regulatory subunits, which leads to activation of PKA by dissociation of the regulatory subunits from the active sites of the catalytic subunits. The active catalytic subunits are then free to act as a serine/threonine kinases phosphorylating

downstream targets both in the cytoplasm and in the nucleus. These downstream targets include CREB (cAMP responsive element binding protein), which in turn mediates CRE (cAMP responsive element)-dependent transcription [163, 164] (Figure 2A).

A reduction of R1α levels therefore causes disinhibition of PKA, leading to an increase of cAMP-stimulated PKA activity [4, 165-167] (Figure 2B). R1α deficiency leads to decreased SMAD3 expression, thereby reducing transforming growth factor β (TGFβ)-mediated apoptosis in adrenocortical cells [168]. In addition, MAPK pathway activity was shown to increase in response to inactivating *PRKAR1A* mutations, causing increased cell proliferation [165, 169, 170]. R1α deficiency also leads to an up-regulation of different components of the Wnt signalling pathway [171, 172]. Interestingly, some CNC patients with PPNAD have somatic mutations in the β-catenin gene (*CTNNB1*) within the adrenal nodules, which is also part of the Wnt signalling pathway [173, 174].

More than 120 different *PRKAR1A* mutations have been identified to date in CNC patients [148, 155, 162, 167]. Sanger sequencing is used for the large majority of routine clinical sequence analysis and recently, large deletions have been identified in about 20 % of those patients previously thought to be *PRKAR1A* mutation-negative by array-based comparative genomic hybridisation [175]. Almost all mutations generate a premature stop codon, either directly or by frameshift, leading to nonsense-mediated mRNA decay and absence of the R1α protein [4, 155], although some *PRKAR1A* mutations in CNC were demonstrated to lead to expressed R1α that had lost its inhibitory effect on PKA signalling [166, 167].

Genotype-phenotype correlation

No obvious genotype-phenotype correlation could initially be detected in CNC patients with different *PRKAR1A* mutations; most different mutations invariably lead to the absence of the R1α protein [155]. However, a small intronic deletion in

PRKAR1A which has been identified in CNC patients can also be found in some cases of isolated PPNAD; this mutation also leads to nonsense-mediated decay but is associated with lower penetrance than CNC [176]. In addition, *PRKAR1A* mutation carriers manifest with myxomas, thyroid tumours, schwannomas and Sertoli cell tumours more frequently and generally present earlier than CNC patients where no *PRKAR1A* mutations were found [148]. Patients with large deletions of *PRKAR1A* were suggested to present with CNC at an earlier age (14 years vs. 20 years) [149, 175].

Conclusions

The multifactorial and heterogeneous pathogenesis of pituitary tumours is reflected by the multitude of different tumour manifestations in genetic syndromes that also cause pituitary adenomas, such as MEN1 and CNC. The study of such rare diseases can contribute immensely to the faster diagnosis and better monitoring of affected patients, as reflected by the improvement of MEN1-associated mortality over the last decades. Moreover, the study of multiple endocrine neoplasia syndromes will also aid our understanding of endocrine physiology and tumourigenesis.

Interestingly, pituitary adenomas are mostly benign and only very rarely acquire malignant properties. MEN1-associated pituitary adenomas and FIPAs due to *AIP* mutations are more aggressive than sporadic PAs, with more frequent macroadenomas and a younger age at manifestation in *AIP*-associated FIPAs [75, 177, 178]. Conversely, pituitary hyperplasia is presumed to precede adenoma formation; in MAS and CNC, a pituitary adenoma is rarely observed, however there are prolonged periods of pituitary hyperplasia in conjunction with abnormal GH, IGF-1 or prolactin levels [159]. Each of these diseases can therefore serve as a model for the understanding of the steps leading to pituitary tumourigenesis.

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The authors have nothing to disclose

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Figure legends

Figure 1. Interacting partners of menin. Menin interacts with transcription factors including nuclear factor-κB (NF-κB), JunD, β-catenin, activator protein-1 (AP-1), mothers against decapentaplegic (SMAD) family members and oestrogen receptor α (Erα); with proteins regulating chromatin structure including histone deacetylases (HDACs) and the histone methyltransferases KMT2A and KMT2B; with cytoskeletal proteins such as vimentin, with cytoplasmic cell signalling mediators including forkhead box protein O1 (FoxO1) and Akt1/protein kinase B (PKB); and with DNA repair proteins including Fanconi anaemia group D2 protein (FANCD2).

Figure 2. The PKA pathway. A. Ligand activation of the G-protein coupled receptor (GPCR) leads to activation of the stimulatory G-protein (G_s) and its α-subunit in turn activates adenylyl cyclase (AC). AC converts ATP into cAMP. In the basal state, PKA consists of two regulatory subunits (R) bound to two catalytic subunits (C). cAMP-binding to R causes dissociation from C, which is now free to act as a serine/threonine kinase. It can activate cAMP-responsive element binding protein (CREB) by phosphorylation, which mediates transcription of genes with cAMP-responsive element (CRE)-containing promoters. The PKA pathway contributes to the control of cell proliferation and differentiation, metabolism and hormone secretion. The phosphodiesterases (PDEs) hydrolyse cAMP, thereby reducing PKA pathway activity. B. In Carney complex, R1α levels are reduced, leading to increased PKA activation, reduced transforming growth factor β (TGFβ)-mediated apoptosis, increased mitogen activated protein kinase (MAPK)-dependent proliferation and a stimulated Wnt signalling pathway.

Table 1. Genetic conditions that lead to pituitary adenomas.

	Genetic cause	General pathology	Endocrine pathology
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1* (90 %)	• Facial angiofibromas • Collagenomas • Lipomas	• Primary hyperparathyroidism • Pancreatic neuroendocrine tumours • Pituitary adenomas (mostly prolactinomas)
Carney complex (CNC)	*PRKAR1A* (73 %)	• Myxomas (cardiac, cutaneous, mammary) • Lentigines	• Primary pigmented nodular adrenocortical disease • Gonadal tumours • Thyroid tumours • Acromegaly (somatolactotrope hyperplasia)
MEN4	*CDKN1B* (100 %)	• Uterine tumours	• Primary hyperparathyroidism • Pituitary adenomas (corticotropinomas, somatotropinomas, non-functioning pituitary adenomas) • Adrenocortical tumours • Thyroid tumours • Gastrointestinal neuroendocrine tumours
McCune-Albright syndrome (MAS)	*GNAS* (90 %)	• Polyostotic fibrous dysplasia • Café-au-lait spots	• Acromegaly/gigantism (somatolactotrope hyperplasia) • Precocious puberty • Adrenal Cushing's syndrome • Thyrotoxicosis
Familial isolated pituitary adenoma (FIPA)	*AIP* (20 %)	None	• Pituitary adenoma (mostly somatotropinomas)
Familial pheochromocytoma/ paraganglioma syndromes	*SDHx (40 %)*		• Paraganglioma • Pheochromocytoma • Pituitary adenoma
DICER1 syndrome (pleuropulmonary blastoma-familial tumour and dysplasia syndrome)	*DICER1 (90 %)*	• Pleuropulmonary blastoma • Cystic nephroma • Embryonal rhabdomyosarcoma	• Pituitary blastoma (Cushing's syndrome) • Sertoli-Leydig cell tumour • Multinodular goiter
X-linked acrogigantism (X-LAG)	Xq26.3 microduplication		• Gigantism (early childhood onset somatotropinoma or somatotrope hyperplasia)

Figure 1

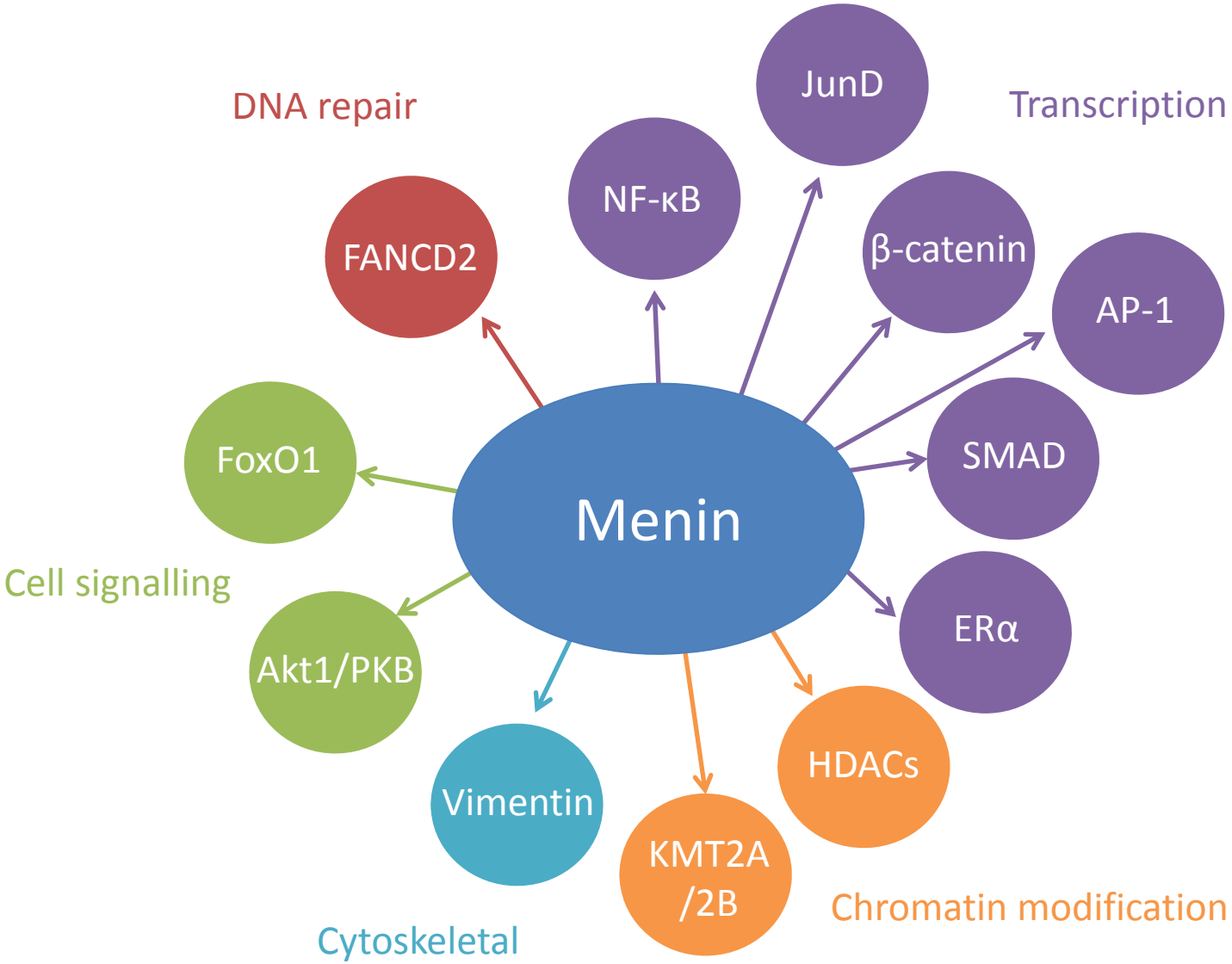

DNA repair
JunD
Transcription factors
NF-κB
FANCD2
β-catenin
AP-1
FoxO1
Menin
SMAD
Cell signalling
ERα
Akt1/PKB
HDACs
Vimentin
KMT2A
/2B
Chromatin modification
Cytoskeletal

Figure 2A

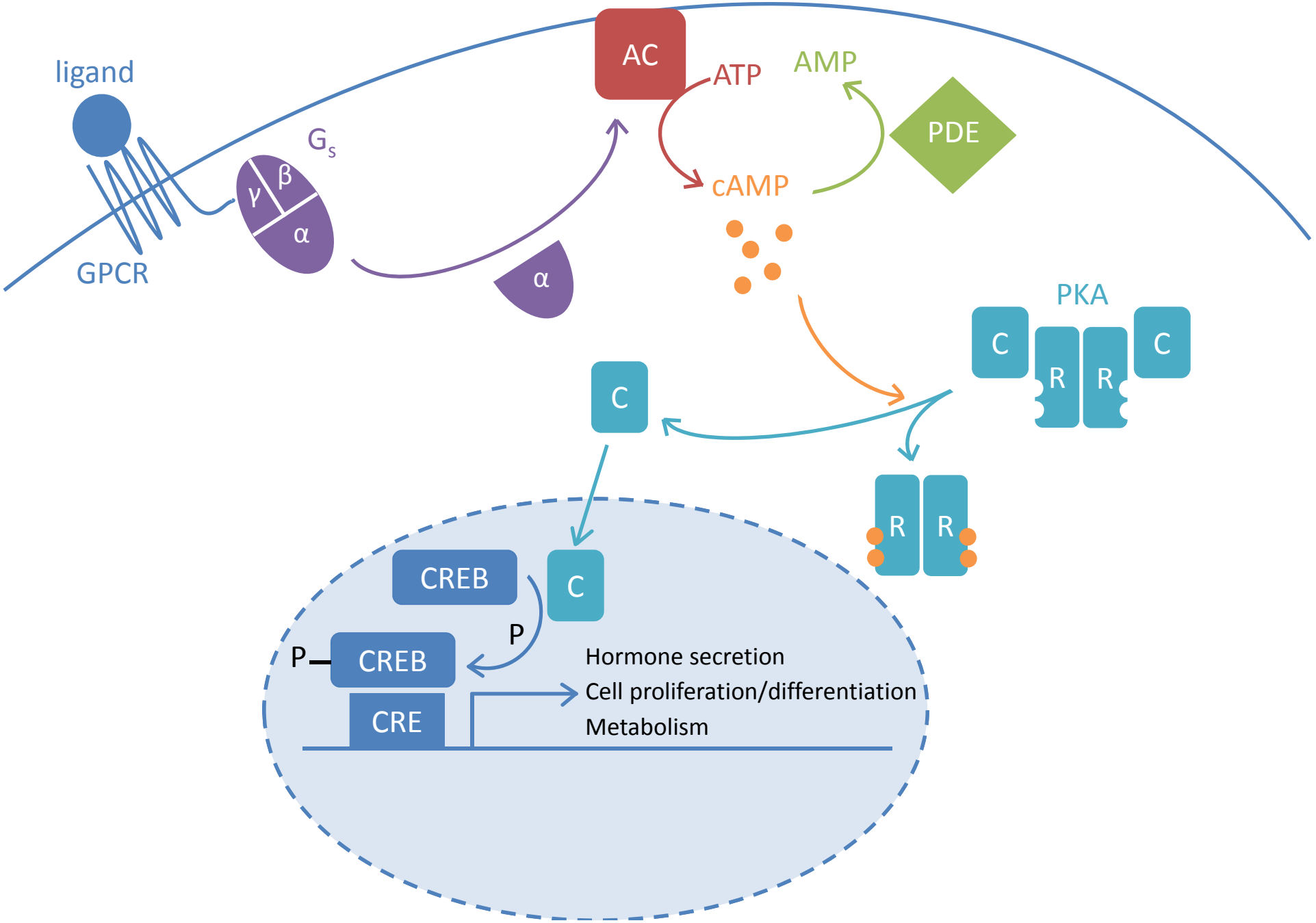
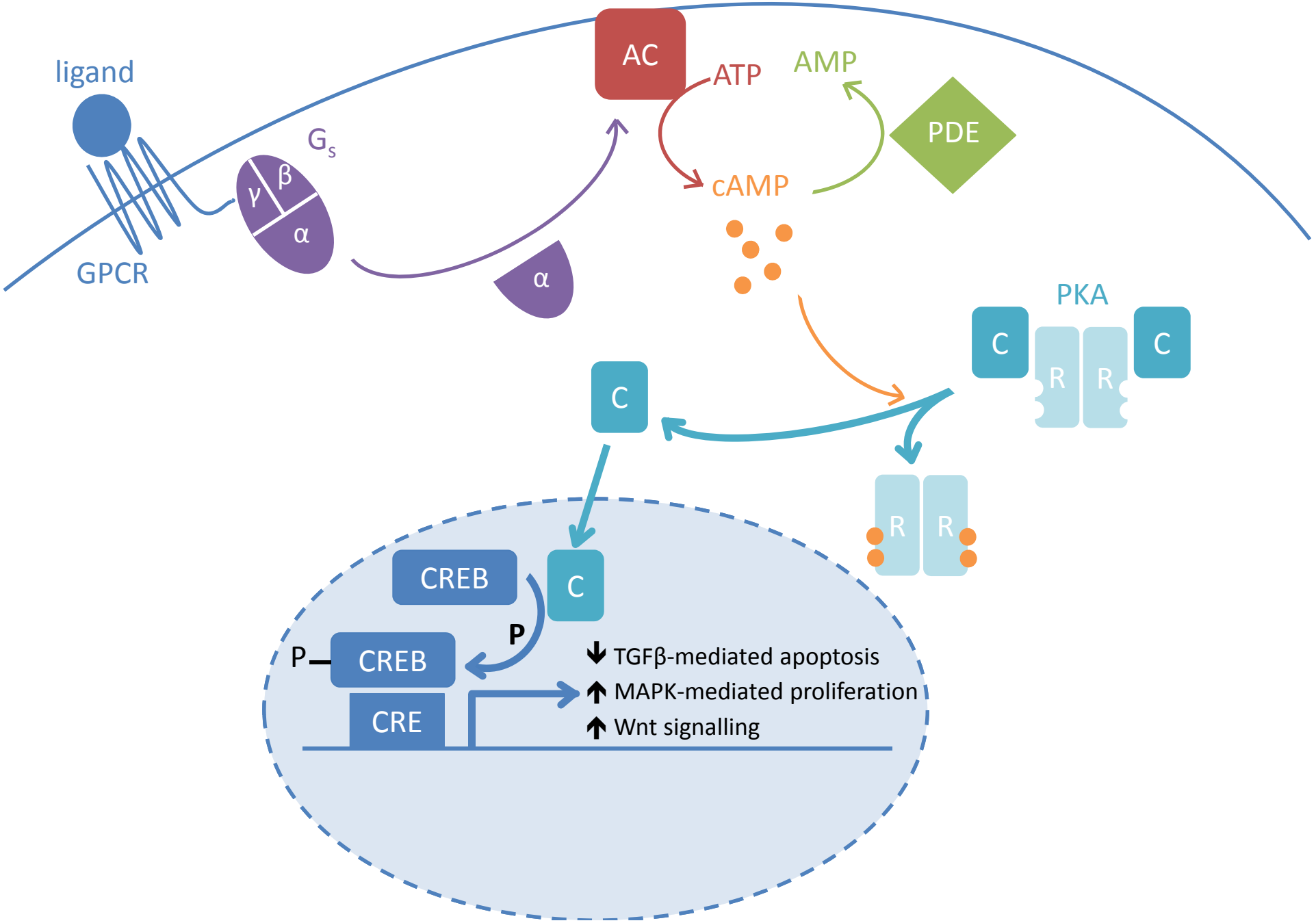

ligand
GPCR
G_s
γ
β
α
α
AC
ATP
AMP
PDE
cAMP
PKA
C
R
R
C
C
R
R
CREB
C
P
P
CREB
CRE
Hormone secretion
Cell proliferation/differentiation
Metabolism

Figure 2B


ligand
GPCR
G_s
γ
β
α
α
AC
ATP
AMP
PDE
cAMP
PKA
C
R
R
C
C
R
R
CREB
C
P
P
CREB
CRE
↓ TGFβ-mediated apoptosis
↑ MAPK-mediated proliferation
↑ Wnt signalling