The authors' reply

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We thank Ben-Shlomo and Melmed for their comments concerning the role of adrenocorticotropin hormone (ACTH) and thyrotropin secreting hormone (TSH) receptors in pituitary cancer. We may owe some clarification, as we did not intend to implicate the ACTH and TSH receptors as causing pituitary cancer through a mechanism that acts on endogenous pituitary gland receptors. Indeed, we have not stated this in the text of the review, nor does table 1 specify this. Pituitary tumours are characterized by the hyper-secretion of TSH and ACTH, resulting in systemic complications in the target organs of these hormones, the thyroid and adrenal glands. Given this information, we included these receptors in the pituitary section of table 1 on the basis that a characteristic of this cancer is the over-production of ACTH and TSH, which bind to their cognate G-protein-coupled receptors (GPCRs) in their target organs. This is well reviewed in the provided reference[1] (reference 147 in the article). Our earlier version(s) of the text were more descriptive of this topic, but space limitations did not permit an in-depth treatment of this particular subject in the final version. Thus, table 1 was left with the receptors listed, and a reference to a review on the topic.

On the other hand, we agree on the role of TSH receptors and their mutations in thyroid tumours, which we believe was well described in the text (Page 87, first column, second paragraph) and in table 1, in agreement with Ben-Shlomo's and Melmed's comments. We did not describe these mutations in the context of pituitary tumours. Neither we nor the text of the review is at odds with the statements of Ben-Shlomo and Melmed, and we feel that a clarification is most practical.

Table 1 has been modified to reflect this point and is shown below.

We would like to thank Ben-Shlomo and Melmed for bringing this to our attention.

1. Kaltsas, G. A. & Grossman, A. B. Malignant pituitary tumours. *Pituitary* **1**, 69–81 (1998).

Table 1 | **GPCRs in cancer**

Cancer	Receptor	Ligand	Process	Selected references
Breast cancer	PAR1	Thrombin	Growth; metastasis; angiogenesis	12,132,133
	EP2; EP4	PGE2	Growth; metastasis; angiogenesis	42,44,134
	CXCR4	SDF1	Metastasis; angiogenesis	70
	GPR30	Oestrogen	Growth? Hormone-therapy resistance?	23–26
Colon cancer	EP2, EP4	PGE2	Growth; metastasis; angiogenesis	30–34
	LPA_1	LPA	Growth	126
	ET receptors	Endothelin-1	Survival	41
	PAR1	Thrombin	Growth; migration	135
	Frizzleds	Wnts	Growth	62
Head and neck cancer	CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	136
	CXCR4	SDF1	Metastasis	137
	EP receptors	PGE2	Growth; angiogenesis; metastasis	46
	GRPR	GRP	Growth; survival	138
	PAR1	Thrombin	Metastasis; angiogenesis	13
Small-cell lung cancer	GRPR	GRP	Growth	3,16,17,139
	NMB-R	Neuromedin B	Growth	3,16,17
	CCK_1; CCK_2	CCK	Growth; survival	3
	CXCR4	SDF1	Growth; metastasis	140
Non-small-cell lung cancer	EP receptors	PGE2	Growth; metastasis; angiogenesis	45,141
	CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	142
	CXCR4	SDF1	Migration; metastasis	143
	β1AR; β2AR	NNK	Growth?	144
Ovarian cancer	LPA_1–LPA_3	LPA	Growth; metastasis; angiogenesis	4,15
	CXCR2	GROα	Growth; angiogenesis	15
Pancreatic cancer	GRPR	GRP	Growth	145
	CCK_1; CCK_2	CCK	Growth	3
Parathyroid gland cancer	CASR	Calcium	Growth	146
Pituitary cancer	TSH receptor*	TSH‡	Growth; survival	51,147
	ACTHR†	ACTH‡	Growth	147
Prostate cancer	PAR1	Thrombin	Growth; invasion	14,89
	ET_A	Endothelin 1	Growth; survival; metastasis	14,18
	AT1	Angiotensin II	Growth	148
	EP2, EP4	PGE2	Growth; metastasis; angiogenesis	27
	LPA_1	LPA	Growth; invasion	14
	B1, B2	Bradykinin	Growth; survival; invasion	14,19
	GRPR	GRP	Growth; migration	14
Melanoma	MC1R	MSH	Sensitivity to UV-induced DNA damage	50,149
	CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	150
	ET_B	Endothelin-1/3	Growth	151
Basal-cell carcinoma	Smoothened	Sonic hedgehog	Growth	57,58,152
Testicular cancer	LH receptor	LH	Growth	153
Thyroid cancer	TSH receptor	TSH	Growth	51,56

Many G-protein-coupled receptors (GPCRs) contribute to the aberrant growth and survival of cancer cells, as well as to tumour-induced angiogenesis and metastasis. Examples of some of the GPCRs most frequently implicated in human cancer are listed. ACTHR, adrenocorticotropic hormone receptor; β1AR and β2AR, β1- and β2-adrenergic receptors; CASR, calcium sensing receptor; CCK, cholecystokinin; ETRA, endothelin receptor type A; ETRB, endothelin receptor type B; GPR30, G-protein-coupled receptor 30; GRPR, gastrin-releasing peptide receptor; IL8, interleukin 8; LH, luteinizing hormone; LPA, lysophosphatidic acid; MC1R, melanocortin 1 receptor; MSH, melanocortin 1; NMBR, neuromedin B receptor; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PGE2, prostaglandin E2; SDF1, stromal cell-derived factor 1; TSH, thyroid stimulating hormone. *TSH acts on TSH receptor in the thyroid. †ACTH acts on ACTHR in the adrenal glands. ‡Overproduced by pituitary tumours.