Medullary Thyroid Carcinoma – Distinction towards Neuroectodermal Tumours: Reply to the Letter by Paschou and Vryonidou

Mikael Nilsson^a E. Dillwyn Williams^b

^aUniversity of Gothenburg, Göteborg, Sweden; ^bUniversity of Cambridge, Cambridge, UK

Dear Editor

We thank Drs. Paschou and Vryonidou for their kind remarks about our paper [1]. The main discussion point they raise is about the similarities between the features of medullary thyroid carcinoma (MTC) and intestinal neuroendocrine tumours, and their differences from the cancers of the same organs showing epithelial differentiation. We believe it is important to distinguish neuroendocrine tumours not only from adenocarcinomas, but also from neuroectodermal tumours, and would like to clarify the reasons. Neuroendocrine cells share some morphological and functional features with neural cells (e.g. granule structure and secretion of signalling peptides), but they are clearly not of neural crest origin, they derive from the same stem cells as the proper epithelium [2]. This is true for neuroendocrine cells in gut and in other endodermal organs such as the lungs, pancreas and prostate and for their neuroendocrine tumours. In contrast, neuroectodermal tumours are a separate group that can be found in a variety of peripheral organs, and although tumour cell features may vary considerably between subgroups depending on the ancestral differentiated cell type, they are all of neural crest origin [3]. Until recently MTC has been considered a crest-derived neuroendocrine tumour, and as such it differed from both classical neuroectodermal and classical neuroendocrine tumours [4]. The demonstration that thyroid C cells, like neuroen-

docrine cells of the intestines, are of endodermal origin [5] thus makes sense, rationalizing the former difficulties in understanding the pathogenesis of medullary carcinoma and mixed MTC tumours.

The derivation of C cells from the endoderm rather than the neural crest may at first seem to make it more difficult to understand the association between MTC and pheochromocytoma. However, the types of tumours found in inherited syndromes primarily depend on the mutated genes involved in growth control rather than on the embryological origins of the organs involved. Good examples include Lynch syndrome where a mutated DNA repair gene is associated with an increased incidence of colon, endometrial, ovarian and other cancers, and Li Fraumeni syndrome where germline mutations in p53 are associated with sarcomas and cancers of the breast, brain and adrenal glands, and with leukaemias. Similarly, the *RET* gene is associated with lesions of both neural crest origin (neuroma and pheochromocytoma) and of endodermal origin (medullary carcinoma and parathyroid adenoma).

We fully agree with Drs. Paschou and Vryonidou that understanding the genes and their mutations involved in carcinogenesis, such as *RET* for MTC, will play a major role in improving treatment. Nonetheless, it is also important to consider embryonic cell and tissue origin as this may determine organ-specific traits of tumour

growth and other contextual features that will impact on the tumour microenvironment, which we now know may significantly influence targeted therapy and the development of drug resistance. For example, in neuroendocrine tumours accumulating evidence indicates that a pair of forkhead box transcription factors, *Foxa1* and *Foxa2*, that play crucial roles in endoderm development and organogenesis from the same germ layer also participate in both neuroendocrine differentiation and tumorigenesis [6–8]. There is also considerable evidence that *Foxa1/2* can be involved in tumour progression, invasion and metastasis and that their effects may in part be mediated through interaction with *Nkx2-1* [9], a thyroid transcription factor. This group of genes merits further study in both C and follicular cell-derived thyroid cancers.

We conclude by hoping that our paper may stimulate further discussion on the need to correlate embryology, genetics and pathology in understanding the origins, associations, behaviour and treatment of tumours.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Nilsson M, Williams ED: On the origin of cells and derivation of thyroid cancer: C cell story revisited. *Eur Thyroid J* 2016;5:79–93.
- 2 May CL, Kaestner KH: Gut endocrine cell development. *Mol Cell Endocrinol* 2010;323:70–75.
- 3 Maguire LH, Thomas AR, Goldstein AM: Tumors of the neural crest: common themes in development and cancer. *Dev Dyn* 2015;244:311–322.
- 4 Adams MS, Bronner-Fraser M: Review: the role of neural crest cells in the endocrine system. *Endocr Pathol* 2009;20:92–100.
- 5 Johansson E, Andersson L, Ornros J, Carlsson T, Ingesson-Carlsson C, Liang S, et al: Revising the embryonic origin of thyroid C cells in mice and humans. *Development* 2015;142:3519–3528.
- 6 Qi J, Nakayama K, Cardiff RD, Borowsky AD, Kaul K, Williams R, et al: Siah2-dependent concerted activity of HIF and FoxA2 regulates formation of neuroendocrine phenotype and neuroendocrine prostate tumors. *Cancer Cell* 2010;18:23–38.
- 7 Chiaverotti T, Couto SS, Donjacour A, Mao JH, Nagase H, Cardiff RD, et al: Dissociation of epithelial and neuroendocrine carcinoma lineages in the transgenic adenocarcinoma of mouse prostate model of prostate cancer. *Am J Pathol* 2008;172:236–246.
- 8 Khor A, Stahlman MT, Johnson JM, Olosn SJ, Whitsett JA: Forkhead box A2 transcription factor is expressed in all types of neuroendocrine lung tumors. *Hum Pathol* 2004;35:560–564.
- 9 Li CM, Gocheva V, Oudin MJ, Bhutkar A, Wang SY, Date SR, et al: Foxa2 and Cdx2 cooperate with Nkx2-1 to inhibit lung adenocarcinoma metastasis. *Genes Dev* 2015;29:1850–1862.