Expression and regulation of the early embryonic stem cell genes in parathyroid tumours

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Introduction
Evidence suggested an embryonic epigenetic signature in parathyroid tumours, with deregulated microRNAs and gene methylation. In embryonic stem cells, the Wnt/β-catenin signalling regulates the expression of the core stemness genes, namely NANOG, OCT4 and SOX2. Though constitutive nuclear accumulation of β-catenin has not been detected, the Wnt/β-catenin pathway might be deregulated in parathyroid tumours, as Wnt signalling inhibitors have been found reduced.

Aim of the study
To investigate the expression of early embryonic stem cell (ESC) genes in adult human parathyroid tumours.

Results
Core stem genes analysis in parathyroid tumours: POUSF1/OCT4, SOX2 and NANOG transcripts were detected in almost all parathyroid adenomas (PDAs; n=22), and atypical PDAs (n=3), besides the variable expression of ESC genes KLF4, EGR1, and REX1/ZFP42 [A]. OCT4, SOX2 and NANOG proteins expression were analysed by immunohistochemistry in archival series of tumours and normal parathyroid glands [B]. Parathyroid carcinomas (n=8) had more NANOG-expressing cells (mean positive cells 40%) compared to PDAs (n=11; mean positive cells 10%), while PDAs (n=22) showed a higher proportion of SOX2-expressing cells, though SOX2-expressing cells occurred in half of tumours [C]. NANOG and SOX2 mRNA levels showed a positive correlation [D].

Some PDAs-derived cells expressing SOX2 were positive for PTH immunostaining:

Staining of contiguous sections showed that clustered SOX2 expressing cells also coexpressed PTH.

Expression of β-catenin in parathyroid tissues: β-catenin highly accumulated at membrane and cytoplasm levels in normal glands (n=4) and in PDAs (n=16), though PDAs were heterogeneous showing paranchymal zones where cells had very low active β-catenin levels confined at membrane.

The ESC pluripotency is regulated by the Wnt/β-catenin and β-catenin is transcriptionally active in parathyroid neoplasia: treatment of PDAs-derived cells (n=6) with 10-20 mM Lithium Chloride increased the Wnt gene targets AXIN2, DKK1, ZEB1, and modulated the expression of POUSF1/OCT4, SOX2 and NANOG mRNA levels depending on the time course of β-catenin activation [A-B]. Investigating samples from 25 PDAs, we observed that PDAs expressing AXIN2 (n=6) had abundant NANOG, SOX2 and WNT5A transcripts [C].

Conclusions
We firstly identified an embryonic pattern of gene expression in parathyroid tumours, where β-catenin signalling might be involved in regulating the expression of the core stem genes. SOX2, in particular, was associated with a more severe presentation of primary hyperparathyroidism.