Hypoxia-Inducible Factor-1 (HIF-1) Up-Regulates Adrenomedullin Expression in Human Tumour Cell Lines during Oxygen Deprivation: A Possible Promotion Mechanism of Carcinogenesis

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Little is known about the molecular mechanisms that control adrenomedullin (AM) production in human cancers. We demonstrate here that the expression of AM mRNA in a variety of human tumour cell lines is highly induced in a time-dependent manner by reduced oxygen tension (1% O_2) or exposure to hypoxia mimetics such as desferrioxamine mesylate (DFX) or $CoCl_2$. This AM expression seems to be under hypoxia-inducible factor-1 (HIF-1) transcriptional regulation, since HIF-1 α and HIF-1β knockout mouse cell lines had an ablated or greatly reduced hypoxia AM mRNA induction. Similarly, inhibition or enhancement of HIF-1 activity in human tumor cells showed an analogous modulation of AM mRNA. Under hypoxic conditions, immuno-histochemical analysis of tumour cell lines revealed elevated levels of AM and HIF-1 as compared with normoxia, and we also found an increase of immunoreactive AM in the conditioned medium of tumor cells analyzed by RIA. AM mRNA stabilization was shown to be partially responsible for the hypoxic up-regulated expression of AM. In addition, we have identified several putative hypoxia response elements (HREs) in the human AM gene, and reported studies with selected HREs were capable of enhancing luciferase expression after exposure to DFX. Furthermore, transient co-expression of HIF-1 α resulted in an augmented transactivation of the reporter gene after DFX treatment. Given that most solid human tumours have focal hypoxic areas and that AM functions as a mitogen, angiogenic factor, and apoptosis-survival factor, our findings implicate the HIF-1/AM link as a possible promotion mechanism of carcinogenesis.

Characterization of Pancreatic Endocrine Cells of the European Common Frog Rana temporaria

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To characterize the endocrine cell types of the pancreas of Rana temporaria, conventional staining, silver impregnation, and immunocytochemical methods for light and electron microscopy have been applied to paraffin, thin and semithin sections, many of them serial pairs. Quantitative data on the frequency and distribution (insular, extrainsular among the exocrine cells, or within the pancreatic ducts) of each endocrine cell type are also reported. Four distinct endocrine cell types have been identified: insulin (B) cells, which are also immunoreactive for [Met] enkephalin; glucagon/PP (A/PP) cells, also immunoreactive for GLP1; somatostatin (D) cells; and a fourth endocrine-like cell type (X cells) of unknown content and function. X cells display characteristic ultrastructure and tinctorial traits but are nonimmunoreactive for all of the 37 antisera tested. The presence of [Met] enkephalin in amphibian pancreatic endocrine cells is now reported for the first time. Almost half (44.9 ± 7.9) of the total endocrine cell population lies outside the islets, mainly spread among the exocrine cells. Approximately 37.2 ± 4.6% of the total endocrine cell population was immunoreactive for insulin, 48.8 + 6.9% was immunoreactive for somatostain; 79.2 + 6.4% of glucagon/PP cells are found within the exocrine parenchyma, representing the majority (86.4 ± 4.3%) of extrainsular endocrine component. On the contrary, most B cells (94.2 + 2.1%) are located within the islets; 30.8 ± 12.9% of D cells are found outside the islets.