

## Loss of Succinate Dehydrogenase (SDHB) Expression in Midgut Carcinoids as Prognostic Factor: A New Marker of Personalized Cancer Medicine in Neuroendocrine Tumors?

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**Background:** Gene mutations of SDH complex have been involved in the pathogenesis of cancer cells. These mutations are often associated with loss of activity of SDH subunit B and overexpression of HIF-1 $\alpha$ , which play a central role in angiogenesis.

**Aims:** To investigate the expression of SDHB levels in carcinoids as prognostic marker.

**Methods:** 31 carcinoid tumors were analyzed. Immunohistochemical (IHC) results for SDHB were assessed according to the staining intensity scored as 1 (low) or 2 (high).

**Results:** The IHC loss of SDHB expression has been reported to be a surrogate marker of malignancy in pheochromocytomas and paragangliomas, via activation of hypoxia signals. All patients had G1 tumors with stage IV for synchronous liver metastases. 25/31 patients underwent primary surgery. IHC evaluation of the SDHB and MIB1 expression was carried out in 19 primary tumors (T) and 19 liver metastases (M). In 11 patients, SDHB and MIB1 were tested in both T and M. High (2+) positivity for SDHB, with clear cytoplasmic mitochondrial reactivity, was found in 14/19 (77%) T, while loss of SDHB expression (1+) was detected in 17/19 (90%) M. The combined analysis (T+M) confirmed the loss of SDHB expression in 9/11 (82%) M compared to 2/11 (18%) T. These findings were inversely proportional to MIB1 distribution, that was 1,5% in the metastatic sites and 0.7% in the primary ones, respectively. The intensity of SDHB staining in tumor cells was associated significantly with the site of tumors and Ki67 labeling index, as primary lesions bearing a proliferative activity  $\leq 1.3\%$  showed over 50% immunoreactive tumor cells. Likewise, significant associations were found among the site of tumors ( $p < 0.0001$ ) or Ki-67 labeling index ( $p < 0.0001$ ) and SDHB intensity. No further associations were found.

**Conclusions:** This analysis suggests a possible correlation among SDHB expression loss, MIB1 increase and biological aggressiveness of advanced midgut carcinoids.