Succinate Dehydrogenase Deficiency in Sporadic Pituitary Adenomas: A Potential Mechanism for Tumorigenesis

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ABSTRACT

In order to determine whether succinate dehydrogenase (SDH) deficiency plays a role in sporadic, non-familial pituitary adenomas, we analyzed 80 pituitary adenomas for SDH deficiency from patients without familial tumor syndromes or without known SDH deficiency-associated neoplasms. SDH deficiency was determined by immunohistochemical (IHC) stains for SDHB since the loss of any of the four SDH subunits results in the loss of SDHB expression. Three pituitary adenomas showed complete loss of SDHB staining, and of these two also showed loss of SDHA staining. We further characterized these adenomas by looking at Ki67, 5-hmC, and 5-lactate levels via IHC. SDH-deficient (non-SDHA deficient) tumors had a Ki67 proliferation index higher than non-SDH deficient pituitary tumors while SDHA-deficient tumors had Ki67 indices similar to non-SDH deficient tumors. Ki67 IHC staining was similar across all subtypes. All SDH-deficient subtypes showed a loss of 5-hydroxymethylcytosine nuclear IHC staining. These findings suggest that SDH deficiency promotes tumorigenesis of pituitary adenomas through accumulation of succinate resulting in changes in the epigenome, specifically resulting in a hypermethylated state.

INTRODUCTION

Pituitary adenomas are relatively common neoplasms of the central nervous system found in approximately 16% of the population. Among all intracranial neoplasms, pituitary adenomas account for 10% of pathologically new growths and are the most common neoplasms within the sella. These tumors are categorized based on size, invasiveness, secretory capacity and specificity, and are almost invariably derived from the adenohypophysis. Treatment is primarily surgical.

The genesis of pituitary adenoma is still largely unresolved despite the association of these tumors with syndromes that have known progenitor mutations. Several families with germline mutations in the genes encoding SDH subunits have been associated with pituitary adenomas and SDH deficiency is pro-oncogenic in a variety of other tumors, including extra-adrenal paragangliomas, a subset of gastrointestinal stromal tumors, phaeochromocytomas, and renal cancers. Familial and genetic pituitary adenomas, however, account for only a small percentage of all pituitary adenomas (~5%). While SDH-deficient tumors typically occur in the setting of germline mutations, SDH-deficient tumors can occur sporadically.

The proposed mechanisms for tumorigenesis in SDH deficiency are loss-of-function mutations in or epigenetic silencing of SDH subunits that then cause the intermediate metabolite succinate to accumulate. Succinate build-up can result in a pseudohypoxic state within the cell which, through HIFs, upregulates expression of angiogenic factors and enzymes that aid in cell survival. Another possible mechanism of tumorigenesis related to succinate accumulation is inhibition of cell cycle-dependent enzymes, particularly the ten eleven translocation (TET) family of 5-methylcytosine (5mC) hydroxylases, which produces epigenetic alterations. In particular, SDH-deficient tumors have elevated hypermethylation compared to non-SDH deficient counterparts, suggested by the lower levels of 5-hydroxymethylcytosine (5-hmC).

METHODS

Pituitary adenomas analyzed were from patients without familial tumor syndromes or without known SDH deficiency-associated neoplasms. Of the 80 cases, 40 were females and 40 were males. The mean age was 52.3 years old (range 14-85).

RESULTS

Indeed, SDH deficiency was found in 12% of pituitary adenomas, with Ki67 indices similar to other non-SDH deficient pituitary adenomas. Ki67 proliferation indices similar to other non-SDH deficient pituitary adenomas.

CONCLUSIONS

1. SDH deficiency may account for tumorigenesis in approximately 1.3% of sporadic pituitary adenomas.
2. Analysis of additional cases and molecular analysis will be a necessary next step to determine clinical differences and intact SDH.
3. Accumulation of cellular succinate resulting from SDH deficiency may cause pituitary adenomas due to abnormal DNA methylation, in particular hypermethylation.
4. Increased understanding of how SDH deficiency leads to pituitary adenomas may lead to development of targeted therapy for this subtype of pituitary adenoma with the ultimate goal of replacing surgical treatment.

REFERENCES

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