Re: Mitochondria and Tumor Progression in Ulcerative Colitis

We read with interest the paper from Ussakli et al., which concludes that cytochrome c oxidase (CCO) loss precedes tumor progression in ulcerative colitis (UC) and may be a biomarker in UC cancer progression (1). They suggest that loss of CCO represents a reduction of the number of mitochondria in preneoplasia; in cancer, COX expression is maintained due to an increase in the number of mitochondria, and they detect this by quantification of mitochondrial DNA (mtDNA). We are surprised at the minor consideration given to the possibility that some of the changes found are due to clonal expansion of CCO-deficient colonic stem cells.

Previous studies have shown that such somatic mtDNA mutations increase with age and indicate clonal expansions in human tissues, including the colon (2,3), small intestine, stomach, liver, hair follicle, pancreas, and prostate (4). Such clonal mtDNA mutations, which are largely neutral (5), can be used to locate stem cell niches and in lineage tracing in normal and neoplastic human tissues (4).

The suggestion made by Ussakli et al. that CCO deficiency is causative in the development of dysplasia/carcinoma in inflammatory bowel disease is unsubstantiated. The data could equally be explained by a series of passenger mutations, which have been repeatedly confirmed: Such passenger mutations have been proposed as markers of clonal cell lineages in emerging neoplasia.

CCO deficiency marks clonal expansions; this provides an alternative explanation of why CCO deficiency predicts the emergence of dysplasia. A critical technical limitation of the Ussakli et al. study is that there have been no clonal or mutational analyses performed; they observed higher CCO expression in cancer than in surrounding mucosa, suggestive of no clonal link between the CCO deficient clone and the cancer. Moreover, that CCO deficiency occurs stochastically and is probably selectively neutral goes some way to explaining the observed limited specificity of CCO as a biomarker: if indeed it is mainly marking a clonal expansion, that expansion may or may not be of a carcinogenic clone.

It is always preferable to show CCO expression in frozen sections with double enzyme histochemistry (2). Regarding the immunohistochemical patterns of CCO expression in their Figure 1 (1), a single section is insufficient to interpret CCO distribution within a crypt; instead serial sectioning and reconstruction is required (7). Several panels in their Figure 1 appear to show nonspecific staining, including nonspecific granule staining in possible Paneth cell metaplasia (Figure 1H). There was antigen retrieval and no mention of absorption controls in the Supplementary Methods.

An investigation of clonal expansion may provide additional insight on this topic.

References

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