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The response to Dr. Yang

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TO THE EDITOR: We appreciate the comments of Dr. Yang regarding the problems in the evaluation of autophagy related proteins (Atg) by immunohistochemistry (IHC) or microarray in tissues and their correlation with autophagy activation. In our study entitled “The decreased expression of Beclin-1 correlates with progression to esophageal adenocarcinoma: the role of deoxycholic acid” we found that Beclin-1 expression is decreased in biopsies from patients with dysplastic Barrett’s esophagus (BE) and esophageal cancer (5).

We are aware of the studies by Liang et al. (2) showing that Beclin-1 has a leucine-rich nuclear export sequence. The mutation in this sequence leads to inhibition of autophagy and decreased tumor suppressor function of Beclin-1. In our recent studies Beclin-1 appears to be nuclear in epithelial cells in tissue biopsies; however, immunofluorescence reveals far more generalized expression (5). We compared the pattern of Beclin-1 localization in CP-A cells (BE cells) using confocal microscopy and fluorescent microscopy. Although Beclin-1 seemed to be nuclear by fluorescent microscopy, confocal microscopy revealed that Beclin-1 is localized primarily in perinuclear region (5). This finding is in agreement with study by Liang et al. showing that Beclin-1 expression is perinuclear (2). This could be the reason why the staining seems to be in the nucleus in patients’ tissue biopsies when we used bright-field microscopy; however, we agree that more detailed studies should be performed. Furthermore, it is not clear whether this perinuclear localization of Beclin-1 indicates that Beclin-1 has a different role other than a regulation of autophagy/apoptosis.

Perhaps confocal microscopy is a better method for evaluation of proteins that are expressed in the perinuclear region. The disadvantage of this method is that the details in the tissue morphology are not apparent. In the previous studies immunoblotting was used to evaluate the expression of Beclin-1 in patient tissues (4). This method is not suitable for heterogenous tissue and does to answer the question at what cellular compartments the protein is expressed. We believe that at this point there are no better techniques than immunohistochemistry to evaluate the expression of Beclin-1 and other autophagy-related proteins in clinical samples, especially if the tissue is very heterogenous as is Barrett’s esophagus.

We agree that it is important to consider the interplay between autophagy and apoptosis since these two processes are interconnected and the both are important in prevention of tumorgenesis. Hydrophobic bile acids, such as deoxycholic acid (DCA, model bile acid), induce apoptosis after acute exposure (3). In contrast, chronic exposure of epithelial cells to bile acids leads to the selection of clones with an apoptosis-resistant phenotype (1). Similarly, we reported in our recent paper, the acute exposure to relatively low concentrations of DCA leads to normal cellular response, the induction of autophagy, and increased Beclin-1 expression, but chronic exposure to DCA does not affect Beclin-1 expression and results in defective autophagy (5). Our current studies are now focused on the determination of the mechanism of autophagy/apoptosis resistance in the CP-A cells that are chronically exposed to DCA. At this point we have found that Mcl-1 and Bcl-xL, two antiapoptotic proteins that interact with Beclin-1, are increased in the DCA-resistant cells compared to parental CP-A cells.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES