TO THE EDITOR: In a recent issue of Am J Physiol Gastrointest Liver Physiol, Roesly et al. (10) examined samples of human and murine models of Barrett’s esophagus (BE) and esophageal adenocarcinoma (EAC) to characterize the expression of Beclin 1. Specifically, Roesly et al. found that the expression of Beclin 1 follows a decreasing trend along the continuum from nondysplastic BE to dysplastic BE to EAC. This observation was followed up with ex vivo testing of BE cell lines demonstrating that acute exposure of deoxycholic acid (DCA) was associated with Beclin 1 expression and autophagy activation, whereas chronic DCA exposure leads to decreased Beclin 1 expression with blunted autophagy. Corroborating these data together, Roesly et al. went on to suggest that autophagy is initially activated in response to bile acid, whereas prolonged exposure leads to autophagy resistance with reduced Beclin 1 expression.

Autophagy is an evolutionary conserved cellular process regulating the bulk catabolism of intracellular contents, a process involving the sequestration of cytoplasmic proteins and organelles within double-membrane vesicles followed by their fusion and degradation by lysosomes (3). Together with the proteasome-ubiquitin system, they form the two major protein degradation pathways. Among its many roles in cancer, Beclin 1 is critical in mediating the initiation of autophagy. Beclin 1 and Vps34 serve as a scaffold for the recruitment of other autophagy-related proteins (Atgs) that are critical in the formation of autophagosomes (8).

In measuring the expression of Beclin 1 to correlate with autophagy, it would be important to characterize its subcellular location, particularly whether there is a predominance of cytoplasmic vs. nuclear localization. Because autophagy occurs within the cytoplasm, it may be postulated that, depending on its localization, Beclin 1 may serve different roles. Therefore, nuclear Beclin 1 may not entirely reflect autophagic activity. Beclin 1 has a leucine-rich nuclear export signal required for cytosolic localization to activate autophagy, and the mutation of Beclin 1 nuclear export motif results in nuclear localization that renders the cell autophagy incompetent (5). Although cytosolic Beclin 1 is crucial for autophagy, the nuclear functions of Beclin 1 remain uncertain. It appears that the degree of nuclear Beclin 1 localization is cell type specific (5). Given that Beclin 1 and Vps34 serve as a scaffold for the recruitment of other Atgs, the colocalization of these proteins may more accurately reflect their autophagy-related roles. However, they may remain inadequate for demonstrating the state of autophagy, whether it is increased or decreased. This is because autophagy is a dynamic, multistep process and the accurate measurement of autophagy involves the quantification of autophagic flux (2). Therefore, the measurement of proteins associated with autophagy or those that are cleared by autophagy through quantitative methods such as immunohistochemistry (IHC)/tissue microarray (TMA) can be problematic. These methods provide a snapshot of the measured proteins at a specific point in time and are unable to reflect the state of autophagy. Their accumulation may represent either accelerated autophagy or a blockade, leading to accumulation that would otherwise be cleared within autophagosomes. Current data indicate that LC3/Atg8, a constituent of the inner autophagosomal membrane, and p62/SQSTM1, a multifunctional scaffold protein, are marker proteins that are cleared by autophagy (1, 7). Accordingly, their clearance has been utilized to demonstrate autophagic flux. However, their staining by IHC/TMA to measure autophagy is likely to be of limited utility on their own.

Another observation to consider would be the interplay between the autophagy and apoptosis process. Beclin 1 was first identified to form an interacting complex with the anti-apoptotic protein Bcl-2 (4), and Bcl-2/Bcl-XL have been shown to interact with Beclin 1 through its BH3 domain to reduce autophagy (6, 9), representing one of the “cross talks” between these two pathways. The staining for Beclin 1 alone does not account for such a potential interplay.

REFERENCES


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