



Autophagy Beyond Homeostasis: Does Autophagy Dysregulation Drive Colorectal Cancer? Comment on Shawn Gurwara *et al*; Altered Expression of Autophagy-related Genes in Human Colon Cancer

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Autophagy is an evolutionarily conserved and regulated catabolic process that ensures the degradation of damaged organelles and excessive or misfolded proteins in lysosomes for the recycling of essential amino acids and energy.¹ Autophagy is constitutively active at basal level in a majority of cell types and plays an important role in cellular homeostasis via maintaining cell organelles' and proteins' turnover as well as their functions. In addition to the homeostatic function, autophagy also acts as a pro-survival pathway and can be activated in response to different stress conditions, such as nutrient starvation, organelle damage, metabolic stress, endoplasmic reticulum stress, accumulation of non-functional proteins, and radiation or chemotherapy treatment. Recent studies have demonstrated that dysregulation of autophagy pathways may be involved in the pathogenesis of diverse diseases, such as myopathy, neurodegeneration, aging, microbial infection, inflammatory bowel disease, and cancer.²

In cancer, the role of autophagy is quite complicated and depends on tumor type and stage. During the early stage of tumorigenesis, autophagy usually acts as a tumor suppressor by clearing the damaged cellular content, reducing reactive oxygen species' level and thereby DNA damage. Whereas in established tumors or an advanced stage of the tumor, it may act as a tumor promoter, as tumor cells utilize enhanced autophagy to survive under low oxygen and low nutrient conditions. The core machinery of autophagy is encoded by autophagy-related genes (ATGs). As of now, 36 ATG genes have been identified. Recent studies have revealed that modulation of such autophagy genes as *BECN1 (ATG6)*, *ATG5*, *ATG7*, *ATG16L1*, *etc.* are associated with the pathogenesis of various cancers.^{1,3}

In the current issue of *Exploratory Research and Hypothesis in Medicine*, Shawn Gurwara *et al.* has reported that dysregulation of autophagy pathways could be a leading mechanism in the carcinogenesis of human colorectal cancer. In their study, it was observed that ATGs were downregulated in both early- and late-stage colon cancer compared to normal colon mucosa. Although

the sample size of this study was small, 17 ATGs were found to be significantly downregulated in human colon cancer; these include *ATG4A*, *ATG4C*, *ATG4D*, *CTSD*, *CTSS*, *ESR1*, *GAA*, and *GABARAP*. Further, the authors confirmed the similar mRNA expression profile for *ATG4A*, *ATG4C*, *ATG4D*, *GAA*, *GABARAP*, *CTSD*, and *CTSS* in a large TCGA dataset of colon adenocarcinoma and rectum adenocarcinoma (known as COAD/READ) patients. Though this study claims the possible role of ATGs in colon cancer, the limitations of this study are its small cohort, which includes only six tumor specimens, three for each early and late colon cancers, and the lack of protein expression data for the dysregulated ATGs.

The autophagy pathway is mediated by many ATGs, among which the proteases of ATG4 family play an important role in the conjugation of ATG8 to lipid membranes and the deconjugation of ATG8 from the autophagosome. The activity of ATG4 family genes is critical and highly specific for targeting and autophagic vacuole formation. Recent studies by others have demonstrated the antitumor role of ATG4C and ATG4D in fibrosarcoma and breast cancer.^{4,5} In agreement with previous studies, the findings by Gurwara *et al.* provide new insights into the pathogenesis of colon cancer and suggest the tumor suppressor role of autophagy in colon cancer. In the future, it will be interesting to study the role of these dysregulated ATGs in *in vitro* systems as well as *in vivo* colon cancer models for the development of new therapeutic regimens.

Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

Manuscript writing (AS).

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