Expression analysis of LC3B and p62 indicates intact activated autophagy is associated with an unfavorable prognosis in colon cancer.

Abstract:
Autophagy is a lysosomal degradation and recycling process implicated in cancer progression and therapy resistance. We assessed the impact of basal autophagy in colon cancer (CC) in vitro and ex vivo. Functional autophagy was demonstrated in CC cell lines (LoVo; HT-29) showing a dose-dependent increase of the autophagy markers LC3B, p62 and autophagic vesciles upon increasing concentrations of the autophagy inhibitor chloroquine, which was demonstrated by immunoblotting, immunofluorescence and electron microscopy. Next, tissue microarrays with 292 primary resected CC, with cores from different tumor regions, and normal mucosa were analyzed by immunohistochemistry for LC3B and p62. CC tissue showed LC3B dot-like, p62 dot-like, cytoplasmic and nuclear staining in various levels without significant intratumoral heterogeneity. Tumoral LC3B and p62 expression was significantly higher than in normal tissue (p<0.001). No associations between staining patterns and pathological features (e.g. TNM categories; grading) were observed. Both low LC3B dot-like and low p62 dot-like-cytoplasmic staining were associated with worse overall survival (p=0.005 and p=0.002). The best prognostic discrimination, however, was seen for a combination of LC3B...
dot-like/p62 dot-like-cytoplasmic staining: high expression of both markers, indicative of impaired activated autophagy, was associated with the best overall survival. In contrast, high LC3B dot-like/low p62 dot-like-cytoplasmic expression, indicative of intact activated autophagy, was associated with the worst outcome (p<0.001 in univariate and HR=0.751; CI=0.607-0.928; p=0.008 in multivariate analysis). These specific expression patterns of LC3B and p62 pointing to different states of autophagy associated with diverging clinical outcomes highlight the potential significance of basal autophagy in CC biology.