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Knockdown of p62/sequestosome 1 attenuates autophagy and inhibits colorectal cancer cell growth

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Abstract p62/sequestosome-1 is a multifunctional adapter protein implicated in selective autophagy, cell signaling pathways, and tumorigenesis, and plays an important role at the crossroad between autophagy and cancer. But, the connection between autophagy and cancer is complex and in some cases contradictory. Human colorectal cancer tissues from patients were analyzed for expression of p62 and Microtubule-associated protein light chain 3 (LC3, an autophagosome marker) using immunostaining, western blotting, real-time PCR, and confocal microscopy. To study the effects of p62 on autophagy and cell growth, shRNA for p62 was applied and cell growth curve was monitored in human colorectal cancer cell. In vivo experiments were done using the mouse xenograft model. We showed that up-regulated expression of p62 and LC3 in colorectal cancer tissues. We also demonstrated that specifically knockdown the expression of p62 showed significantly inhibitory effects not only on autophagy activation, but also on tumor growth both in vitro and xenograft tumors model. The ectopic overexpression of p62 and autophagy activation contributes to colorectal tumorigenesis. p62 and autophagy will be therapy targets for the treatment of colorectal cancer.

Keywords Colorectal cancer · p62/sequestosome 1 · Autophagy · Knockdown

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Background

Autophagy is a cellular degradation pathway for the clearance of cytoplasmic materials, damaged organelles, and aggregate-prone proteins in lysosomes. In tumor cells with defects in apoptosis, autophagy contributes to prolonged survival. Intriguingly, autophagy defect is also reported to play a critical role in tumorigenesis. There was much evidence suggesting that autophagy selectively targets signaling proteins and regulates cancer cell signaling. An adaptor protein-p62 (also known as sequestosome-1), plays critical roles in a number of cellular functions, including bone remodeling, obesity, and cancer. p62 is a ubiquitously expressed cellular protein and is localized at the autophagosome formation site and directly interacts with LC3, an autophagosome localizing protein, and it is incorporated subsequently into the autophagosome [1]. p62 is a multifunctional adapter protein implicated in selective autophagy, cell signaling pathways, and tumorigenesis [2]. p62 maybe play an important role at the crossroad between autophagy and cancer. The p62 structure containing important interaction domains attests to the ability of this protein to regulate and modulate the activation of these signaling pathways during tumor formation and propagation. The anther very important function of this protein is to act as a molecular adaptor between the autophagic machinery and its substrates [3]. However, the connection between autophagy and cancer is complex and in some cases contradictory. The analysis of autophagy-deficient mice revealed that the autophagy plays a tumor-suppressor role through eliminating p62 [4]. Abnormal p62 accumulation has been detected in gastrointestinal, prostate, liver, lung adenocarcinoma, and breast cancer cases [5–9], suggesting the presence of functional relationship between p62 accumulation and cancer progression. However, it remains