Autophagy: New Insights into Its Roles in Cancer Progression and Drug Resistance

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Simple Summary: Autophagy is a mechanism of lysosomal proteolysis that is utilized to degrade damaged organelles, proteins, and other cellular components. Although key studies demonstrate that autophagy functions as a mechanism of tumor suppression via the degradation of defective pre-malignant cells, autophagy can also be used as a mechanism to break down cellular components under stress conditions to generate the required metabolic materials for cell survival. Autophagy has emerged as an important mediator of resistance to radiation, chemotherapy, and targeted agents. This series of articles highlight the role of autophagy in cancer progression and drug resistance and underscores the need for new and more effective agents that target this process.

Keywords: autophagy; drug resistance; cancer; ROC-325; lysosome
In addition to these research articles, several excellent reviews summarizing key aspects of the field were published in this Special Issue. It has been well established that autophagy is an important mediator of therapeutic resistance to diverse classes of anticancer agents. Two outstanding articles discuss the mechanisms underlying autophagy-mediated treatment resistance and strategies to enhance chemosensitization through inhibition of autophagy [11,12]. An additional article specifically focuses on autophagy-driven resistance to histone deacetylase (HDAC) inhibitors [13]. Indeed, autophagy has been demonstrated to be a key resistance mechanism to HDAC inhibitor therapy, which has prompted the clinical evaluation of this therapeutic approach [14–16]. Taken together, these articles provide a comprehensive review of autophagy as a drug resistance factor and summarize the robust evidence in the literature that demonstrates that targeting autophagy can improve the anticancer activity of many chemotherapeutic agents.

Besides being a facilitator of drug resistance, upregulation of autophagy has been identified as a contributing factor that accelerates disease progression and metastasis in a multitude of tumor types. Saxena et al. review the roles of autophagy in esophageal squamous cell carcinoma and esophageal adenocarcinoma pathogenesis [17]. They also conclude that the development of novel agents that specifically activate or inhibit autophagy is essential to better understand the role of autophagy in malignant biology and to improve the clinical targeting of this pathway. In addition to disrupting the lysosome with agents such as HCQ, CQ, and ROC-325, upstream components of the autophagy machinery may prove to be viable therapeutic targets [4,18,19]. Some of the potential upstream targets in the cascade include the aforementioned PIK3C3 or vacuolar protein sorting 34 (VPS34) as well as UNC-51-like kinase 1 (ULK1) and autophagy-related gene 4 (ATG4). A particularly interesting target is ATG4, which is reviewed in this issue by Fu et al [20]. ATG4 is required for autophagosome formation and studies have suggested that ATG4 may be a potential anticancer target due to its elevated expression in some cancer types [21]. Another interesting review describes the role of actin during autophagy and the development of drug resistance [22]. Actin has previously been demonstrated to be involved in the formation and maturation of autophagic vesicles during the autophagy process [23,24]. They describe how actin manipulation affects autophagy and highlight potential therapeutic targets in this pathway. These reviews illuminate the complexity of autophagy and underscore the need for...
new agents to innovatively modulate this pathway by targeting previously unexplored regulators of the process.

The articles in this Special Issue mesh perfectly with each other to highlight the significance of autophagy as a key mechanism that cancer cells utilize to drive malignant progression and drug resistance. The articles comprehensively discuss the rationale for developing novel autophagy-modulating agents and combining them with standard therapeutic regimens to improve clinical outcomes. They also establish the framework for further studies aimed at delineating the differences between inhibiting autophagy at proximal vs. distal (lysosomal) points. Hopefully, the development of specific and more potent compounds will enable optimized precision targeting of autophagy in future clinical studies.

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