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AUTOPHAGIC PUNCTUM

UVRAG in autophagy, inflammation, and cancer

Ying Song, Christine Quach, and Chengyu Liang

Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

ABSTRACT

Macroautophagy/autophagy deregulation has been observed in perpetuated inflammation and the proliferation of tumor cells. However, the mechanisms underlying these changes have yet to be well-identified. UVRAG is one of the key players of autophagy, but its role in vivo remained puzzling. Our recent study utilized a mouse model with inducible expression of a cancer-derived frameshift (FS) mutation in *UVRAG* that dominant-negatively inhibits wild-type UVRAG, resulting in impaired stimulus-induced autophagy. The systemically compromised autophagy, particularly mitophagy, notably increases inflammation and associated pathologies. Furthermore, our discovery indicates that time-dependent autophagy suppression and ensuing CTNNB1/β-catenin activation may serve as one tumor-promoting mechanism underpinning age-related cancer susceptibility.

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Autophagy is a fundamental biological process that regulates homeostasis and participates in damage control. A complex network of proteins detects intracellular disorders, signals this detection, and clears cytosolic abnormalities through the autophagosome-lysosome pathway for degradation and recycling. This machinery is particularly crucial in cells stressed by endogenous and environmental stimuli, conditions that can go awry in various pathological disorders including cancers. But the exact mechanisms by which impaired functions of autophagy affect tissue homeostasis and their implications in disease, are far from understood, despite the key role of this process in cell physiology and pathology. Our recent study sheds new light on the matter, providing the molecular basis for inadequate autophagy in the propensity of inflammation and cancer by utilizing an inducible mouse model expressing a dominant-negative inhibitor of UVRAG (UV radiation resistance associated).

The initial description of UVRAG focused on its regulation of autophagic membrane remodeling as a binding partner and promoter of the BECN1/Beclin1-associated lipid kinase PIK3C3/Vps34. Paradoxically, a later study reported that suppressing UVRAG in cancer cells had limited effects on autophagosome biogenesis or flux. Particularly, genetic knockout of the mammalian *UVRAG* ortholog in yeast or *Arabidopsis* showed mixed results and controversial effects on autophagy induced by nutrient deprivation, leading to a debate as to whether UVRAG indeed functions in autophagy in vivo. Given that the loss of UVRAG results in embryonic lethality, the exact in vivo role for mammalian UVRAG in autophagy regulation remained unaddressed. Our recent work settled this debate by demonstrating that specific inhibition of UVRAG through an induced expression of a truncated UVRAG (UVRAG[FS]) impairs starvation-induced autophagy activation by more than 50% in different tissues of mice [1]. The reduced production of autophagosomes and suppressed autophagic flux observed with the UVRAG[FS] mutant are associated with disassembly of the UVRAG-BECN1-PIK3C3/Vps34 autophagy-promoting complex. Particularly intriguing is the interaction between autophagy and the turnover of lipid droplets (LDs), intracellular organelles that store neutral lipids, during prolonged nutrient deprivation. We found that LDs are primarily surrounded by autophagic vesicles in hepatocytes of starved control mice and are in the process of being degraded. By contrast, in starved UVRAG[FS] mice, massively enlarged LDs are found free in the cytoplasm, suggesting a failure of their turnover. Although starvation-induced autophagy is generally considered to be nonselective, starvation-induced lipophagy may represent a selective event that requires full functionality of UVRAG.

The compromised autophagy observed with the UVRAG[FS] mutation also aggravates sepsis-related pathologies, evidenced by increased vulnerability to septic shock and increased inflammatory response, which is associated with aberrant activation of the NLRP3 inflammasome. To gain further insight into the function of autophagy in combating inflammation, we used bone marrow-derived macrophages from UVRAG[FS] mice and observed that these cells are impaired in mitochondrial homeostasis after septic shock, including increased mitochondrial membrane potential loss, cytosolic mitochondrial DNA (mtDNA) release, and mtROS production. Reassuringly, these defects can be remedied by treating cells with MitoQ, a mtROS scavenger, to reduce CASP1 activation and resultant IL1B secretion. These results indicate that the autophagy pathway, particularly mitophagy, exerts a cytoprotective role during inflammation by restricting CASP1 overactivation and resultant cytotoxicity.

Encouraged by these results, we found that the role for UVRAG in inflammasome regulation could be extended to

CONTACT Chengyu Liang chengyu.liang@med.usc.edu Department of Molecular Microbiology and Immunology, University of Southern California, Room 5517, MC NRT 9605, 1450 Biggy Street, Los Angeles, CA 90033, USA

other inflammatory disorders. UVRAG[FS] mice presented with enhanced susceptibility to dextran sodium sulfate (DSS)-colitis with increased NLRP3 activation and IL1B secretion in colonic tissues. In accord, selective pharmacological blockade of NLRP3 offsets the genetic predispositions of UVRAG[FS] mice to acute colitis, which is consistent with a model in which failure of UVRAG-mediated autophagy results in hyperactivation of NLRP3 and enhanced IL1B secretion in DSS-colitis. We further show that both hematopoietic and nonhematopoietic UVRAG[FS] plays a proinflammatory role in inflamed colons, and that uncontrolled inflammation in UVRAG[FS] mice is associated with increased tumor growth and de-differentiation in the azoxymethane (AOM)-DSS-induced model of colitis-associated colon cancer. These studies suggest that UVRAG-mediated autophagy plays an important role in inflammatory signaling and promotes anti-inflammatory processes and tumor surveillance in the intestinal microenvironment.

As if the discovery of an anti-inflammatory function for UVRAG, and by extension autophagy, was not surprising enough, we further show that inhibition of autophagy is associated with age-related spontaneous cancers through a mechanism that involves aberrant activation of CTNNB1/β-catenin. Although loss-of-functions of several essential autophagy genes results in spontaneous cancers, the precise mechanisms underlying autophagy-related tumor prevention at a molecular level remain elusive. UVRAG was considered as a haploinsufficient tumor suppressor, yet in vivo evidence for its tumor-suppressing role was lacking. We expand upon these findings by demonstrating that inducible expression of UVRAG[FS] accelerates age-associated decline in autophagic capacity, leading to impaired autophagic turnover of oncogenic CTNNB1/β-catenin. Notably, increased WNT-CTNNB1/β-catenin has been implicated in inhibiting autophagic clearance. This interrelationship may trap cells in a deleterious cycle, whereby decreased autophagy promotes CTNNB1/β-catenin accumulation that then further suppresses autophagy in oncogenically primed cells, thereby additionally increasing CTNNB1/β-catenin retention. This sequence of events ultimately enhances cell proliferation and may accelerate oncogenic transformation through the deregulation of CTNNB1/β-catenin target oncogene products such as CCND1 (cyclin D1) and MYC/c-Myc. More studies are needed to determine whether this age-dependent regulation of CTNNB1/β-catenin in UVRAG[FS] mice can be generalized to other autophagy-related tumor models. As observed in vitro, UVRAG[FS] tumors also exhibited centrosome amplification and chromosomal instability, providing additional evidence that sustained UVRAG inhibition significantly promotes the onset and the progression of age-related malignancies.

Collectively, by generating mice with inducible expression of UVRAG[FS], we have clarified the in vivo roles for UVRAG in autophagy and its importance in combating inflammation and cancer by restricting uncontrolled cytokine production and oncogenic signaling, respectively. Of note, it remains to be tested whether this mutant might also possess activities of its own, in addition to the antagonism of its normal counterpart, which can contribute to various aspects of inflammation- and/or cancer-related pathologies. It is also of interest how different oncogenic mechanisms of UVRAG[FS] are spatio-temporally cross-regulated to engage in different pathologies. The challenge ahead is to test whether these preclinical findings in UVRAG[FS] mice can be translated into more effective anti-inflammation and/or anti-cancer treatments.

Disclosure statement

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Reference

[1] Quach C, Song Y, Guo H, et al. A truncating mutation in the autophagy gene UVRAG drives inflammation and tumorigenesis in mice. Nat Commun. 2019 Dec 12;10(1):5681. doi:10.1038/s41467-019-13475-w.