Asian Journal of Andrology (2011) 13, 610–611

www.nature.com/aja

RESEARCH HIGHLIGHT

# Interplay between autophagy and metabolism in Ras mutation-induced tumorigenesis

**Ming Jiang**

*Asian Journal of Andrology* (2011) **13,** 610–611; doi:10.1038/aja.2011.31; Published online: 18 April 2011

Macroautophagy (hereafter referred to as autophagy) or 'self-eating' is a lysosomal degradation pathway and plays a role in the breakdown of disordered intracellular organelles, such as peroxisomes (pexophagy), mitochondria (mitophagy), endoplasmic reticula (reticulophagy) and ribosomes (ribophagy), as well as providing for controlled recycling of macromolecules during cellular adaption and pathogenesis.[1,2] Mitophagy serves to remove mitochondria containing damaged components and also to eliminate subsets of mitochondria producing reactive oxygen species.[3] The lysosomal compartment is responsible for the controlled recycling of cellular organelles and macromolecules. These dynamic organelles contain hydrolytic enzymes (proteases, lipases and glycosidases) capable of degrading proteins, proteoglycans, nucleic acids and lipids. Both heterophagic and autophagic cargos find their final destiny in lysosomes, where they are broken down by numerous hydrolyses.[4] Certain environmental cues (such as starvation, high temperature, low oxygen and hormonal stimulation) or intracellular stress (damaged organelles, accumulation of mutant proteins and microbial invasion) activate signaling pathways that increase autophagy.[1,2,5] When the cell receives an appropriate signal, autophagy-execution proteins trigger a cascade of reactions that result in the formation of double membrane-bound vesicles called autophagosomes. The vesicles then fuse with lysosomes followed by a release of lysosomal digestive enzymes into the lumen of the resulting autolysosomes. The sequestered cytoplasmic contents are degraded inside the autolysosome into free nucleotides, amino acids and fatty acids, which are reused by the cell to maintain macromolecular synthesis and to fuel energy production.[6] Autophagy is induced *in vivo* in tumors in hypoxic regions and contributes to tumor cell survival.[7] Accumulated defective lysosomes and autophagic vacuoles were detected in both nuclear receptor PPARγ- and PPARγ2-deficient prostatic carcinogenesis.[8,9] Autophagy is also frequently activated in different tumor cells treated with chemotherapy or irradiation. Short-term inhibition of autophagy along with radiotherapy leads to enhanced cytotoxicity of radiotherapy in resistant cancer cells. Autophagy acts either to destroy defective cells, or as a survival mechanism for damaged cells putting them in a position to accumulate further genetic damage, suggestive of 'a double-edged of sword' reported in different types of cancer.[10] Whether autophagy is 'protective' for the organism by promoting effective 'self-eating and self-digesting' and/or 'self-killing' of damaged cells or alternatively, acts as an 'oncogenic' survival response in cancer is not yet determined. Recently in an original research paper published in *Genes & Development*, Guo *et al.* hypothesized that autophagy plays opposing roles in tumor initiation and in established human tumors.[11] They suggested that, whereas damage mitigation resulting from autophagy may be important for suppressing tumor initiation, in aggressive cancers, growth in a stressed microenvironment may instead result in dependency on autophagy for survival. The intriguing work reported by Guo *et al.* impacts on the interplay between autophagy/mitophagy and mitochondrially oxidative metabolism in a model of Ras mutations (H-ras$^{V12}$ or K-ras$^{V12}$)-induced tumorigenesis. The authors have established an integrated *in vitro* and *in vivo* system to investigate the biological functions of autophagy in maintaining oxidative metabolism in active Ras-mediated tumorigenesis.

Guo *et al.* first delineated the functional roles and biopathological consequences of active autophagy in Ras mutation-mediated tumorigenesis. Using an immortal non-tumorigenic baby mouse kidney epithelial line iBMK, they tested the hypothesis that activation of a strong cell growth-promoting oncogene such as H-ras$^{V12}$ or K-ras$^{V12}$ would alter the requirement for autophagy. They found that isogenic iBMK cell lines deficient for the essential autophagy genes *atg5* or *atg7* are completely defective for autophagy. Interestingly, allelic loss of the essential autophagy gene *beclin1* produces a partial autophagy defect. Activated Ras-expressing iBMK cells are dependent on autophagy creating 'autophagy addiction' to survive starvation involving elevated p62 (an autophagy cargo receptor) expression. They demonstrated that autophagy supports activated Ras-mediated tumorigenesis in iBMK cells. The authors also detected a high level of basal autophagy in a number of human cancer cell lines with Ras mutations and determined that autophagy facilitates growth and survival of a subset of human cancer cell lines with active Ras.

Then, Guo *et al.* investigated the mechanism of interactions between autophagy and oxidative metabolism to support cancer cell survival. They found that Ras-expressing isogenic iBMK tumors (*atg5*$^{-/-}$, *atg7*$^{-/-}$, *beclin1*$^{+/-}$ and *p62*$^{-/-}$) showed a striking accumulation of abnormal, swollen mitochondria consistent with defective mitophagy. These cells displayed autophagy defects and impaired mitochondrial function, maintenance of mitochondrial membrane potential, mitochondrial respiration and oxygen consumption. Autophagy deficiency depletes mitochondrially produced tricarboxylic acid cycle metabolites, likely by impairing mitochondrial conversion of pyruvate and/or fatty acid into acetyl-CoA and citrate under Ras expression. Finally, Guo *et al.* found that in autophagy-defective cells, the metabolic insufficiency in starvation produces an acute energy crisis, leading to cell death and suggested that development of specific autophagy inhibitors

Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, USA
Correspondence: Dr M Jiang (ming.jiang.1@vanderbilt.edu)

and determination of the optimal point in the autophagy pathway to compromise cancer survival is clearly warranted.

Lysosome alterations are common in cancer. Cancer invasion and metastasis are associated with altered lysosomal trafficking and increased expression of cathepsins.[4] Disordered lysosomes lead to defective autolysosome formation, a late stage of autophagy including mitophagy, which may also promote tumorigenesis. In order to integrate these ideas, it is important to explore the connections between mitophagy and lysosomal biogenesis and functions in Ras mutation-induced tumorigenesis.

Molecular mechanisms defining the interplay between autophagy and metabolism during tumorigenesis are not yet well understood. It has been reported that dysregulation of cellular energetic metabolism decreases lipid β-oxidation in favor of *de novo* fatty acid synthesis and glutaminolysis in mitochondria and glycolysis in the cytosol, driving cell transformation and carcinogenesis.[6,12] It is important to determine how the major enzymes controlling lipid oxidation, *de novo* fatty acid synthesis, glutaminolysis and glycolysis in Ras mutation-induced tumorigenesis are regulated.

The activation or suppression of autophagy as a route to cancer prevention or therapy is a potential paradox, given that encouraging cancer cell death is considered a positive response while allowing survival and the accumulation of further mutations is clearly undesirable. These recent findings suggest that autophagy stimulation and preventing cellular damage and mutation may be an important strategy to prevent cancer initiation. Alternatively, aggressive cancers apparently can rely on autophagy for survival. As such, autophagy inhibition may be an appropriate approach to treating aggressive cancers and may augment the efficacy of cancer therapy.

1 Kondo Y, Kanzawa T, Sawaya R, Kondo S. The role of autophagy in cancer development and response to therapy. *Nat Rev Cancer* 2005; **5**: 726–34.
2 Levine B. Cell biology: autophagy and cancer. *Nature* 2007; **446**: 745–7.
3 Tolkovsky AM. Mitophagy. *Biochim Biophys Acta* 2009; **1793**: 1508–15.
4 Kroemer G, Jaattela M. Lysosomes and autophagy in cell death control. *Nat Rev Cancer* 2005; **5**: 886–97.
5 Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. *Nat Rev Mol Cell Biol* 2007; **8**: 741–52.
6 Rabinowitz JD, White E. Autophagy and metabolism. *Science* 2010; **330**: 1344–8.
7 Degenhardt K, Mathew R, Beaudoin B, Bray K, Anderson D *et al*. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell* 2006; **10**: 51–64.
8 Jiang M, Fernandez S, Jerome WG, He Y, Yu X *et al*. Disruption of PPARgamma signaling results in mouse prostatic intraepithelial neoplasia involving active autophagy. *Cell Death Differ* 2010; **17**: 469–81.
9 Jiang M, Jerome WG, Hayward SW. Autophagy in nuclear receptor PPARgamma-deficient mouse prostatic carcinogenesis. *Autophagy* 2010; **6**: 175–6.
10 White E, DiPaola RS. The double-edged sword of autophagy modulation in cancer. *Clin Cancer Res* 2009; **15**: 5308–16.
11 Guo JY, Chen HY, Mathew R, Fan J, Strohecker AM *et al*. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. *Genes Dev* 2011; **25**: 460–70.
12 Levine AJ, Puzio-Kuter AM. The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. *Science* 2010; **330**: 1340–4.