AUTOPHAGY
2017, VOL. 13, NO. 5, 987–988
http://dx.doi.org/10.1080/15548627.2017.1280223

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AUTOPHAGIC PUNCTUM

Tumor cell-intrinsic CD274/PD-L1: A novel metabolic balancing act with clinical potential

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ABSTRACT

Tumor expression of the immune co-signaling molecule CD274/PD-L1 was originally described as impeding antitumor immunity by direct engagement of its receptor, PDCD1/PD-1, on antitumor T cells. Melanoma-intrinsic PDCD1 was recently shown to promote tumor growth and MTOR signals in cooperation with tumor CD274, and sarcoma-intrinsic CD274 signaling promotes glucose metabolism to impede antitumor immunity. Our recent report shows that tumor cell-intrinsic CD274 promotes MTORC1 signaling in mouse melanoma and mouse and human ovarian cancer, inhibits autophagy and sensitizes some tumors to clinically available pharmacological autophagy inhibitors and confers resistance to MTOR inhibitors. Tumor CD274 could be a biomarker of autophagy or MTOR inhibitor response in selected tumors, and these inhibitors could improve anti-CD274 or anti-PDCD1 cancer immunotherapy. As we found that distinct tumor types exhibit this CD274-driven phenotype, it could be widely applicable.

ARTICLE HISTORY
Received 23 December 2016
Revised 4 January 2017
Accepted 4 January 2017

KEYWORDS
autophagy; B7-H1; cancer immunotherapy; CD274; melanoma; MTOR; ovarian cancer; PD-1; PD-L1; PDCD1; unfolded protein response

CD274/PD-L1/B7-H1 is an immune co-signaling molecule commonly upregulated in many different cancer types. Antibodies blocking CD274 or its receptor, PDCD1/PD-1, are revolutionizing cancer immunotherapy by effecting meaningful clinical responses in many cancer types. However, understanding mechanisms of these agents and consequences of tumor CD274 expression remain incomplete. A recent paper found that tumor cell-intrinsic CD274 promotes glucose metabolism in sarcoma cells that inhibits antitumor T cells by outcompeting them for local glucose. Another paper showed that in melanoma cells, intrinsic PDCD1 cooperates with intrinsic CD274 to promote immune-independent tumor growth and MTOR signals. Thus, the tumor CD274-T cell PDCD1 signaling axis paradigm is incomplete. Using RNAi technology to silence CD274 expression in melanoma and ovarian cancer cells to study mechanistic targets of anti-CD274 immunotherapy, we found that tumor-intrinsic CD274 signals elicit immune-independent growth, promote tumor MTORC1 and inhibit MTORC2.

RNA-seq data further suggested that tumor cell CD274 significantly alters major mediators of canonical and noncanonical autophagy pathways, among other important signaling effects. To test functional consequences, we showed that tumor CD274 significantly inhibits tumor cell autophagic flux (western blots for LC3-II/LC3-I and autophagosome formation by confocal imaging). To assess clinical effects of CD274-dependent autophagy modulation, we used the pharmacological autophagy inhibitors chloroquine and 3-methyladenine. Tumor cell-intrinsic CD274 sensitizes B16 melanoma and ID8agg ovarian cancer cells to growth suppression in vitro by either autophagy inhibitor. By contrast, melanoma cells are also sensitive to growth suppression by both autophagy inhibitors in vivo whereas ovarian cancer cells are sensitive to neither. Tumor CD274 confers resistance to metabolic inhibition by the MTORC1 inhibitor rapamycin in both tumor cell types. Basal autophagic flux and CD274-driven autophagy suppression are greater in B16 cells versus ID8agg cells. Thus, CD274-dependent sensitization to pharmacological autophagy inhibitors could reflect differential CD274-mediated autophagy requirements of B16 versus ID8agg cells, which could further reflect CD274-driven MTORC1 signals. Human ES2 ovarian cancer cells exhibit similar CD274-driven MTOR and autophagy effects in vitro. Thus, tumor CD274 expression, perhaps in conjunction with MTORC1 signaling or autophagic flux, could be a biomarker for tumors particularly responsive to autophagy (or MTOR) inhibitors.

Further investigation is required to determine if elevated CD274-driven MTORC1 underlies increased tumor cell proliferation, or alters sensitivity to autophagy or MTOR inhibitors. Alternatively, endoplasmic reticulum (ER) stress from elevated MTOR signals could also explain how tumor CD274 alters tumor cell sensitivity to autophagy or MTORC1 inhibition. MTORC1 stimulates protein synthesis that could activate the unfolded protein response (UPR) and induce ER stress. In support, we used RNA-seq to show that tumor-intrinsic CD274 altered the UPR signaling proteins ERN1/IRE1, EIF2AK3/PERK, and ATF4. Furthermore, autophagy

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Punctum to: Clark CA, Gupta HB, Sareddy G, Pandeswara S, Lao S, Yuan B, Drerup JM, Padron A, Conejo-Garcia J, Murthy K, Liu Y, Turk MJ, Thedieck K, Hurez V, Li R, Vadlamudi R, Curiel TJ. Tumor-intrinsic PD-L1 signals regulate cell growth, pathogenesis, and autophagy in ovarian cancer and melanoma. Cancer Res 2016; 76: 6964-6974; http://dx.doi.org/10.1158/0008-5472.CAN-16-0258

is stimulated by ER stress but inhibited by MTORC1. Thus, tumor cells with elevated CD274 appear to balance growth and stress stimuli finely, whereby even slight pharmacological reductions in autophagy or MTORC1 signals could be therapeutic. Conversely, tumor cells with decreased CD274 might have reduced autophagy requirements from lower metabolic demands and/or ER stress and therefore decreased susceptibility to pharmacological autophagy inhibition or increased susceptibility to MTOR inhibition despite elevated autophagic flux and reduced MTORC1 signaling. Furthermore, tumor CD274 expression can be constitutive or induced by antitumor immunity, and can be heterogeneous in one host. These variables require further study for optimal clinical applications of autophagy or MTOR inhibitors.

The LC3-II/LC3-I ratio and autophagosome formation we studied as autophagic flux readouts could indicate upstream events resulting from defects in downstream autolysosome function. Mechanistic studies identifying specific CD274-induced perturbations of autophagy are therefore needed. For instance, whereas CD274-induced MTORC1 signaling could directly inhibit autophagy, CD274 also appears to alter noncanonical autophagy signaling. Thus, CD274 could affect MTORC1 and autophagy by divergent mechanisms. PDCD1 signaling in observed CD274 effects also deserves further investigation based on a recent report and our unpublished.

We and others have reported that tumor CD274 influences cell viability after other specific insults, such as chemotherapy or immune mediators. Hydroxychloroquine to inhibit autophagy, and MTOR inhibitors are in clinical trials as adjuncts to other cancer therapies, including chemotherapy. Our work suggests that autophagy or MTORC1 inhibition plus anti-CD274 or anti-PDCD1 are attractive combinations for further investigations, particularly for tumors with reduced CD274 expression that are least likely to respond to anti-CD274 or anti-PDCD1, and provides potential biomarkers and mechanisms to assess clinical efficacy. As we noted effects in distinct tumor types, these various approaches could be widely applicable. However, we also identified tumors with poor response to autophagy inhibition despite relatively elevated CD274 expression, suggesting that additional factors (such as the distinct mutational landscape of individual tumors) must also be considered.

In summary, we found that mouse melanoma, and mouse and human ovarian cancer cells with high CD274 exhibit relatively reduced basal autophagy, high MTORC1 activity, and heightened sensitivity to autophagy inhibitor-mediated, but resistance to MTOR inhibitor-mediated, growth reduction compared with cancer cells with lower CD274 expression. We postulate that autophagy inhibition in cancer cells with elevated MTORC1 activity and reduced autophagic activity is catastrophic. Some of these cells could be identified by CD274 expression. Our data further the understanding of CD274 signals, initially studied as immune co-signaling molecules, in cancer immunopathogenesis and treatment responses, and define CD274 as a novel autophagy regulator. Data are also clinically exploitable in novel treatment combinations and as potential biomarkers.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.