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Commentary | *Open Access*

Commentary: The Role of Reactive Oxygen Species in Lysosome-Induced Immunogenic Cell Death

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Ever since deDuve discovered the lysosome [1], its potential for causing cell death has been recognized [2,3]. We have recently suggested that the lysosome may be the Achilles' Heel of Cancer – by way of its crucial role in initiating selective tumor cell death [4]. Lysosome-Induced Immunogenic Cell Death (LIICD) is a cascade of events that begins when immune cells, specifically macrophages and NK cells, release a respiratory burst of superoxide and produce cytokines involved in anti-tumor T-cell activity. These cytokines include TNF-alpha and IL-2 [5-9]. Reactive oxygen species (ROS) are highly reactive, unstable, and short-lived molecules of oxygen that include peroxides, superoxide, and hydroxyl radicals. When ROS interacts with low density lipoprotein (LDL), an oxidized LDL (ox-LDL) is created as an oxidation product. We have shown in earlier studies that treatment with TNF-alpha and IL-2 in animals and in patients results in higher levels of oxidized low-density lipoprotein in the plasma [8]. There is a direct connection between ox-LDL and apoptotic cell death [10,11]. We have also shown that when cultured cells are treated with bovine xanthine oxidase and hypoxanthine, lysosome-induced immunogenic cell death is initiated as evidenced by the appearance of the well-established markers of immunogenic cell death. Namely, these hallmark signs include extracellular ATP, HMGB-1 and ecto-calreticulin [12]. The induction of immunogenic cell death under these circumstances is presumed to result from ox-LDL [13].

Studies show evidence of ROS production during immune surveillance, a monitoring process of the immune system to identify and destroy virally-infected and malignantly transformed cells [14,15]. ROS has many physiologic and pathologic functions, but here we focus on their role in immune surveillance and LIICD. Several reports show that the plasma of patients with cancer have more oxidized lipids than control subjects. Specifically, ox-LDL is found in plasma at substantially higher levels than controls in subjects with breast, prostate, ovarian, colon and other cancers than controls [9,16-19]. We have shown that subjects with breast cancer had more ox-LDL than

controls [9]. Rapidly growing cancer cells have a much higher requirement for cholesterol than benign cells. This is reflected by a higher level of LDL receptors on the surface of cancer cells, including breast cancer, colorectal cancer, and glioblastoma cells [16,17,20,21]. We have shown that ox-LDL is taken up through the LDL receptor and is incorporated into the lysosomes of cells [10]. In patients and animals, the visualization of ox-LDL reflects ongoing immune surveillance (Figure 1).

Further evidence of the role of ox-LDL in immune surveillance is found in three large placebo-controlled studies showing that the use of antioxidants in at-risk populations raised cancer incidence significantly. The findings suggest that eradicating ROS hinders cancer cell killing. In the first of these studies, Vitamin E and Beta Carotene were given to male smokers with the hypothesis that these antioxidants would prevent cancer occurrence. The research team found that, contrary to their hypothesis, there was an 18% increase of cancer incidence in the group receiving antioxidants (n=7282) compared to placebo (n=7287) (p=0.01). Average follow up was 6.1 years [22]. In the second study, antioxidants Vitamin A and Beta Carotene (n=9420) or placebo (n=8894) were given to subjects exposed to asbestos and subjects who were heavy smokers. With 73,137 person-years of follow-up there was a 28% increased incidence of lung cancer in the group receiving antioxidants compared to the placebo group (p=0.02) [23]. Finally, In the third study, Vitamin E was given to men and incidence of prostate cancer was observed. The result was not statistically significant when the monitoring group stopped the trial (p=0.06). In continued follow-up for approximately three years, the group receiving antioxidants (n=8,737) had a 17% increased incidence of prostate cancer compared to the group receiving placebo (n=8,696) which was statistically significant (p=0.02) [24].

The results of these three antioxidant studies can be understood through the paradigm of tumor development and surveillance described by Dunn et al. That is, early in tumor development the immune system can kill most malignant cells through immune surveillance. Dunn et al. proposed that this process can be characterized into three stages: elimination, equilibrium, and escape [25]. In the elimination stage, the tumor burden is controlled. This is in part due to high ROS levels. In contrast, equilibrium takes place in an environment of intermediate levels of ROS and medium cell growth. In escape, tumor cells proliferate unchecked by the immune system and ROS in the environment is low (Figure 2).

The addition of antioxidants in the cited studies suppress elimination and equilibrium and tipped the balance in favor of escape (Figure 3). Antioxidants such as Vitamin E, Beta Carotene and Vitamin A interact with free radicals such as ROS and inactivate them. These results strongly suggest that ROS plays a key role in the natural defense against tumor development.

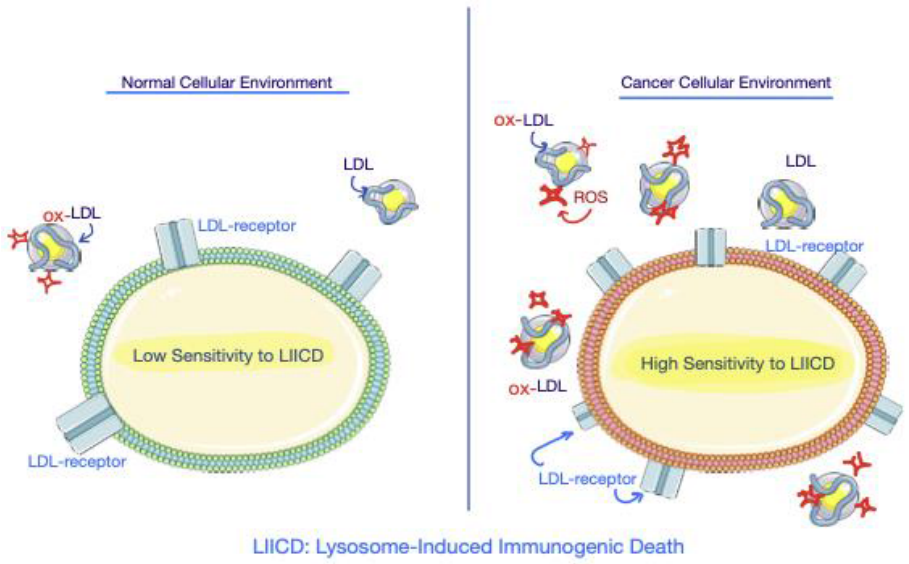

Figure 1: Susceptibility of cancer cells to reactive oxygen species (ROS)-mediated lysosome-induced immunogenic cell death (LIICD). LDL is taken up by LDL receptors on the cancer cell surface. Malignant cells have substantially more LDL receptors than normal cells [16,17,20,21].

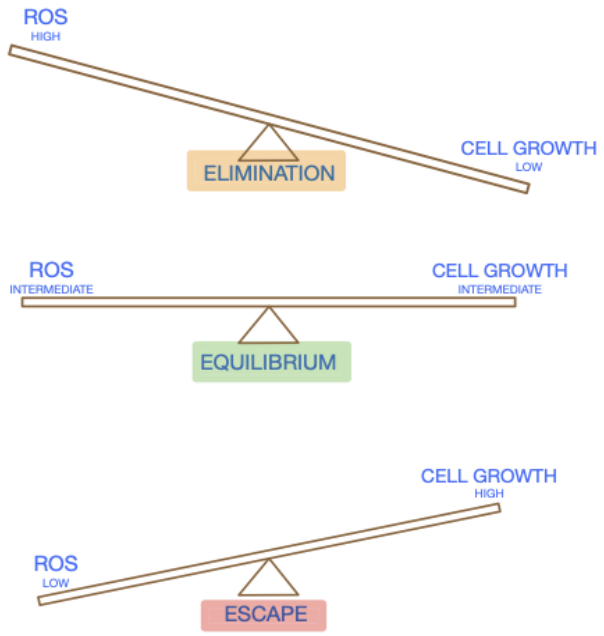

Figure 2: The Three E's paradigm as proposed by Dunn et al. The ability of the immune system to control cell death can be seen as largely three states: Elimination, Equilibrium, and Escape. Each can understood in terms of varying levels of ROS and malignant cell proliferation [25].

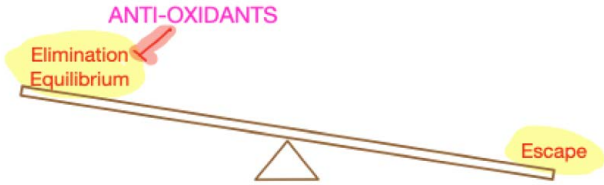

Figure 3: The effect of antioxidants on facilitating tumor escape from immune surveillance. Antioxidants such as Vitamin A, Vitamin E, and Beta Carotene have the observed effect of suppressing immune elimination of cancer cells and tipping the balance in favor of cancer escape [22-24].

Treatment modalities are surfacing that take advantage of the susceptibility of cancer cells to reactive oxygen species. For example, statins are agents known to upregulate the LDL receptor which have been shown to improve outcomes in clinical trials of a variety of cancer therapies. The upregulation of the LDL receptor helps sensitize cancer cells more fully to local upregulation of ROS. Dietary polyunsaturated fatty acids have also been shown to improve outcomes in clinical trials against cancer when combined with a variety of cytotoxic agents because these fatty acids are effective enabling lipid peroxidation in the tumor microenvironment [26,27].

The role of ROS in cancer cell death and the role of lysosomal leakage in immunogenic cell death, can and should be more directly linked via the concept of LIICD [4]. Growing awareness of ROS and the lysosome for mediating cancer cell death can lead to the development of new cancer therapies. Selectively producing superoxide in the tumor micro-environment and not elsewhere could be an important step in the treatment of cancer.

1. Conflict of Interest

All authors listed are affiliated with ViskaBio of Cambridge MA.

2. References

1. Duve D, Pressman BC, Gianetto R, Wattiaux R, Appelmans F. Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. Biochemical journal 60, 604-617, doi:10.1042/bj0600604 (1955).
2. Guicciardi ME, Leist M, Gores GJ. Lysosomes in cell death. Oncogene 23, 2881-2890, doi:10.1038/sj.onc.1207512 (2004).
3. Kroemer G, Jäättelä M. Lysosomes and autophagy in cell death control. Nature reviews. Cancer 5, 886-897, doi:10.1038/nrc1738 (2005).
4. Iulianna T, Kuldeep N, Eric F. The Achilles' heel of cancer: targeting tumors via lysosome-induced immunogenic cell death. Cell death & disease 13, 509-509, doi:10.1038/s41419-022-04912-8 (2022).
5. Tsujimoto M, Yokota S, Vilcek J, Weissmann G. Tumor necrosis factor provokes superoxide anion generation from neutrophils. Biochem Biophys Res Commun 137, 1094-1100, doi:10.1016/0006-291x(86)90337-2 (1986).
6. Larrick JW, Graham D, Toy K, Lin LS, Senyk G, Fendly BM. Recombinant tumor necrosis factor causes activation of human granulocytes. Blood 69, 640-644 (1987).
7. Figari IS, Mori NA, Palladino MA. Regulation of Neutrophil Migration and Superoxide Production by Recombinant Tumor Necrosis Factors-α and -β: Comparison to Recombinant Interferon-γ and Interleukin-1 α. Blood 70, 979-984, doi:10.1182/blood.V70.4.979.979 (1987).
8. McDonagh J, Fossel ET, Kradin RL, Dubinett SM, Laposata M, Hallaq YA. Effects of Tumor Necrosis Factor-α on Peroxidation of Plasma Lipoprotein Lipids in Experimental Animals and Patients. Blood 80, 3217-3226, doi:10.1182/blood.V80.12.3217.3217 (1992).
9. Fossel ET, Hall FM, McDonagh J. C-13 NMR spectroscopy of plasma reduces interference of hypertriglyceridemia in the H-1 NMR detection of malignancy. Application in patients with breast lesions. Breast cancer research and treatment 18, 99-110, doi:10.1007/BF01980972 (1991).
10. Fossel ET, Zanella CL, Fletcher JG, Hui KKS. Cell DeathInduced by Peroxidized Low-Density Lipoprotein: Endopepsis. Cancer Research 54, 1240-1248 (1994).
11. Salvayre R, Auge N, Benoist H, Negre-Salvayre A. Oxidized low-density lipoprotein-induced apoptosis. BBA - Molecular and Cell Biology of Lipids 1585, 213-221, doi:10.1016/S1388-1981(02)00343-8 (2002).
12. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB. et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer. (2020) 8.

13. Taritsa I, Fossel E, Neote K. Abstract 4244: Using lysosomal immunogenic cell death to target cancer via xanthine oxidase. Cancer research (Chicago, Ill.) 82, 4244-4244, doi:10.1158/1538-7445.AM2022-4244 (2022).

14. Wang L, Kuang Z, Zhang D, Gao Y, Ying M, Wang T. Reactive oxygen species in immune cells: A new antitumor target. Biomedicine & pharmacotherapy 133, 110978-110978, doi:10.1016/j.biopha.2020.110978 (2021).

15. Kotsafti A, Scarpa M, Castagliuolo I, Scarpa M. Reactive Oxygen Species and Antitumor Immunity-From Surveillance to Evasion. Cancers 12, 1748, doi:10.3390/cancers12071748 (2020).

16. Delimaris I, Faviou E, Antonakos G, Stathopoulou E, Zachari A, Dionyssiou-Asteriou A. Oxidized LDL, serum oxidizability and serum lipid levels in patients with breast or ovarian cancer. Clinical biochemistry 40, 1129-1134, doi:10.1016/j.clinbiochem.2007.06.007 (2007).

17. Diakowska D, Grabowski K, Nienartowicz M, Zarębski P, Fudalej K, Markocka-Mączka K. Circulating Oxidized Low-Density Lipoproteins and Antibodies against Oxidized Low-Density Lipoproteins as Potential Biomarkers of Colorectal Cancer. Gastroenterology research and practice 2015, 146819-146817, doi:10.1155/2015/146819 (2015).

18. Wan F, Qin X, Zhang G, Lu X, Zhu Y, Zhang H. et al. Oxidized low-density lipoprotein is associated with advanced-stage prostate cancer. Tumor biology 36, 3573-3582, doi:10.1007/s13277-014-2994-6 (2015).

19. Minciullo PL, Inferrera A, Navarra M, Calapai G, Carlo Magno G. et al. Oxidative stress in benign prostatic hyperplasia and prostate cancer. Urol Int 85, 328-333, doi:10.1159/000315064 (2010).

20. Peterson, C. et al. Hypocholesterolemia in cancer patients may be caused by elevated LDL receptor activities in malignant cells. Med Oncol Tumor Pharmacother 2, 143-147, doi:10.1007/bf02934541 (1985).

21. Maletínská L, Blakely EA, Bjornstad KA, Deen DF, Knoff LJ, Forte TM. Human glioblastoma cell lines : Levels of low-density lipoprotein receptor and low-density lipoprotein receptor-related protein. Cancer research (Chicago, Ill.) 60, 2300-2303 (2000).

22. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330, 1029-1035, doi:10.1056/nejm199404143301501 (1994).

23. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334, 1150-1155, doi:10.1056/nejm199605023341802 (1996).

24. Klein EA, Thompson Jr IM, Tangen CM, Crowley JJ, Scott Lucia M, Goodman PJ. et al. Vitamin E and the risk of prostate cancer: Updated results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Journal of clinical oncology 30, 7-7, doi:10.1200/jco.2012.30.5_suppl.7 (2012).

25. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annual review of immunology 22, 329-360, doi:10.1146/annurev.immunol.22.012703.104803 (2004).

26. Minden MD, Dimitroulakos J, Nohynek D, Penn LZ. Lovastatin Induced Control of Blast Cell Growth in an Elderly Patient with Acute Myeloblastic Leukemia. Leukemia & lymphoma 40, 659-662, doi:10.3109/10428190109097663 (2001).

27. Katz MS, Minsky BD, Saltz LB, Riedel E, Chessin DB, Guillem JG. Association of statin use with a pathologic complete response to neoadjuvant chemoradiation for rectal cancer. International journal of radiation oncology, biology, physics 62, 1363-1370, doi:10.1016/j.ijrobp.2004.12.033 (2005).