



Editorial: Endoplasmic Reticulum and Its Role in Tumor Immunity

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Cancer cells express surface proteins and display antigens that differ from the “norm.” These differences can be exploited to promote a therapeutic antitumor immune response. Specifically, components within the endoplasmic reticulum (ER) play a critical role in deciding which antigenic peptides are presented on the cancer cell surface to immune cells. Furthermore, under stress conditions, certain ER-resident proteins can exit the ER and translocate to the surface. The translocation of such ER proteins to the outside of the cell (1, 2) can lead to modulation of immune responses in cancer (3, 4), autoimmunity (5) and other diseases (6, 7). Normally, proteins undergo a number of ER stress checks for correct folding and, e.g., ability to resist inappropriate oxidation and reduction before secretion. Failing these quality controls leads to ER stress and triggers a series of unfolded protein responses (UPRs) to restore order. In cancer cells, these pathways can be dysregulated opening up the possibility of developing potential therapeutics to target cancer cells (8). In this topic, these various aspects of the ER in tumor immunity are explored in a series of focused review and research articles.

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BEHIND THE “ION” CURTAIN

Within the Ca²⁺-ion rich confines of the ER, chaperones, oxidoreductases, aminopeptidases (ERAPs) work industriously for the benefit of the cellular state, regulating signaling to the “outside world.” The calcium channels linking the ER lumen and cytosol act as ER stress gates and chaperones, such as GRP78, act as gate keepers deciding the fate of the cell by their ability to control Ca²⁺ release (9). Alterations in Ca²⁺ homeostasis in the ER can provoke cell stress and trigger one or more UPR coping mechanism pathways, which normally leads to either recovery of a stressed cell or non-inflammatory cell death. However, solid tumors typically thrive in a low oxygen and nutrient environment that usually triggers ER stress. Dicks and coworkers describe corrective UPR strategies that aid malignant cells to survive in this environment, with a focus on GRP78 (10). In brief, GRP78 transcription triggered by ER stress facilitates chromatin remodeling and DNA damage repair and in certain types of malignancies aids survival.

One of the best known immune-regulatory functions occurring within the ER is the assembly of the major histocompatibility complex (MHC)-I/antigen peptide complex. Stratikos and colleagues report on the role of the ER aminopeptidases (ERAP1 and 2) in generating mature antigenic epitopes for loading onto the MHC class I molecules, prior to their transport to the cell surface (11). The authors suggest that both ERAP 1/2 are required for natural killer and T cell-mediated immunity

against tumors. These highly polymorphic ERAPs contain many single nucleotide polymorphisms (SNPs) associated with diseases, including cancer (12). These SNPs can influence aminopeptidase expression, enzymatic activity, and antitumor cytokine expression. Such ERAP mutations may aid tumor cells to avoid immune surveillance and eradication (13).

THE GREAT ESCAPE

Endoplasmic reticulum chaperones and oxidoreductases can serve as “eat-me” signals on the surface of tumors cells, while promoting tumor growth on others. How ER chaperones escape retention from the ER and move to the plasma membrane remains contentious (14). Several articles within this e-book describe mechanisms to prevent and allow escape of chaperones from the ER and how this influences tumor recognition. Gutiérrez and Simmen describe the regulatory processes involved in retaining or recapturing ER proteins as they attempt to leave the ER (15). Gutiérrez and Simmen describe the conditions by which ER chaperones and oxidoreductases (calreticulin, ERp57, PDI, and GRP94) escape retention and enhance tumor elimination by the immune system. Conversely, other ER proteins (BiP/GRP78) are expressed on many cancer cell surfaces and enhance proliferation, angiogenesis, and therapeutic resistance (16). Undoubtedly, if the “escape” and retention of ER proteins to and from the cell surface can be controlled, the process could be exploited for specific cancer therapies. However, methods to trigger escape of potentially immunogenic regulatory proteins from the ER will have to be strictly regulated, given their ability to modulate tumor growth and induce unwanted adaptive immunity in other diseases. Wiersma and coworkers (5) highlight the fact that in autoimmune diseases, cell stress provokes extracellular release of some ER proteins, which can affect innate and adaptive immune systems and trigger inflammation (17–19).

The idiom “That which hath been is now; and that which is to be hath already been” (*King James Bible, Ecclesiastes 3:15*) is no better illustrated by the fact that parasites have been secreting chaperones for thousands of years as a defense mechanism against the human immune system (20, 21). Ramirez-Tolosa et al. (22) describe how surface calreticulin on the Chagas disease causing parasite *Trypanosoma cruzi* blocks activation of complement and aids immune escape of the parasite. Moreover, people with Chagas disease appear less susceptible to certain malignancies (23), and Ramirez-Tolosa et al. identify segments of calreticulin that can inhibit tumor angiogenesis.

WAR AND PEACE

Several papers in this e-book describe immune properties of ER proteins capable of raging “war” against tumors. Wang and colleagues describe the adjuvant properties of the stress inducible glucose-regulated protein 170 (GRP170). Previously, they showed an isoform of GRP170 was secreted in melanoma, prostate, and

colorectal cancer cells (24–26). GRP170 associates with tumor antigens both intracellularly and extracellularly, acting like a double agent, inducing potent anticancer immunity when outside the cells, but aiding the survival of cancer cells when within the ER. The authors have exploited GRP170 to develop an immune adjuvant for cancer vaccines to trigger a number of adaptive immune processes. An alternative means of delivering antitumor chaperones to the cell surface is by inducing cell stress using photodynamic therapy (PDT) to generate localized production of reactive oxygen species by transfer of light energy from the photosensitizer chlorin C6. This strategy induces surface exposure of calreticulin within minutes of treatment in squamous carcinoma cells (27). Tumoricidal activity is enhanced when PDT treated cells are supplemented with additional recombinant calreticulin. In a similar manner, de Bruyn and coworkers describe that tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) recruits CRT to its TRAIL-receptor 2 DISC complex and dissociate CRT from CD47 on the cell surface of cancer cells (28), whereby it may or may not facilitate phagocytic uptake by dendritic cells.

A major aspect of ER protein stimulation of anticancer immunity is to activate specific cytotoxic T cells to provide long lasting immunity against developing tumors. Løset et al. illustrate how tumor-specific T cells armed with specific T-cell receptors (TCRs) could eradicate tumors by interacting with MHC class I containing tumor and/or chaperone peptides (29). Løset and coworkers highlight an alternative therapeutic approach that exploits soluble TCRs that engage peptide/MHC (pMHC) complexes, some of which are now in clinical trials. As an alternative to the stealth-like cancer eradication by TCR-transduced T cells, Graner and colleagues have proposed a more “blanket-bombing” approach. They describe the development of a vaccination rationale comprising of chaperone-rich cell lysates (CRCL) purified from solid tumors designed to induce a plethora of immune responses (30).

SUMMARY

The ER and its specialized proteins do play a major role in tumor immunity both indirectly and directly. Clearly, there is much more to understand but the potential role and therapeutic options of ER proteins, as described herein, will aid further research into this fascinating topic.

AUTHOR CONTRIBUTIONS

Dr. MM, Dr. PE, and Dr. EB have discussed/written the editorial content and approved it.

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REFERENCES

1. Tarr JM, Young PJ, Morse R, Shaw DJ, Haigh R, Petrov PG, et al. A mechanism of release of calreticulin from cells during apoptosis. *J Mol Biol* (2010) **401**(5):799–812. doi:10.1016/j.jmb.2010.06.064
2. Kepp O, Gdoura A, Martins I, Panaretakis T, Schlemmer F, Tesniere A, et al. Lysyl tRNA synthetase is required for the translocation of calreticulin to the cell surface in immunogenic death. *Cell Cycle* (2010) **9**(15):3072–7. doi:10.4161/cc.9.15.12459
3. Kim H, Bhattacharya A, Qi L. Endoplasmic reticulum quality control in cancer: friend or foe. *Semin Cancer Biol* (2015) **33**:25–33. doi:10.1016/j.semcancer.2015.02.003
4. Wang WA, Groenendyk J, Michalak M. Endoplasmic reticulum stress associated responses in cancer. *Biochim Biophys Acta* (2014) **1843**(10):2143–9. doi:10.1016/j.bbamcr.2014.01.012
5. Wiersma VR, Michalak M, Abdullah TM, Bremer E, Eggleton P. Mechanisms of translocation of ER chaperones to the cell surface and immunomodulatory roles in cancer and autoimmunity. *Front Oncol* (2015) **5**:7. doi:10.3389/fonc.2015.00007
6. Gold L, Williams D, Groenendyk J, Michalak M, Eggleton P. Unfolding the complexities of ER chaperones in health and disease: report on the 11th international calreticulin workshop. *Cell Stress Chaperones* (2015) **20**(6):875–83. doi:10.1007/s12192-015-0638-4
7. Eggleton P, Michalak M. Calreticulin for better or for worse, in sickness and in health, until death do us part. *Cell Calcium* (2013) **54**(2):126–31. doi:10.1016/j.ceca.2013.05.006
8. Kato H, Nishitoh H. Stress responses from the endoplasmic reticulum in cancer. *Front Oncol* (2015) **5**:93. doi:10.3389/fonc.2015.00093
9. Hammadi M, Oulidi A, Gackiere F, Katsogiannou M, Slomianny C, Roudbaraki M, et al. Modulation of ER stress and apoptosis by endoplasmic reticulum calcium leak via translocon during unfolded protein response: involvement of GRP78. *FASEB J* (2013) **27**(4):1600–9. doi:10.1096/fj.12-218875
10. Dicks N, Gutierrez K, Michalak M, Bordignon V, Agellon LB. Endoplasmic reticulum stress, genome damage, and cancer. *Front Oncol* (2015) **5**:11. doi:10.3389/fonc.2015.00011
11. Stratikos E, Stamogiannos A, Zervoudi E, Fruci D. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer pre-disposition. *Front Oncol* (2014) **4**:363. doi:10.3389/fonc.2014.00363
12. Fruci D, Romania P, D'Alicandro V, Locatelli F. Endoplasmic reticulum aminopeptidase 1 function and its pathogenic role in regulating innate and adaptive immunity in cancer and major histocompatibility complex class I-associated autoimmune diseases. *Tissue Antigens* (2014) **84**(2):177–86. doi:10.1111/tan.12410
13. Mehta AM, Spaans VM, Mahendra NB, Osse EM, Vet JN, Purwoto G, et al. Differences in genetic variation in antigen-processing machinery components and association with cervical carcinoma risk in two Indonesian populations. *Immunogenetics* (2015) **67**(5–6):267–75. doi:10.1007/s00251-015-0834-5
14. Johnson S, Michalak M, Opas M, Eggleton P. The ins and outs of calreticulin: from the ER lumen to the extracellular space. *Trends Cell Biol* (2001) **11**(3):122–9. doi:10.1016/S0962-8924(01)01926-2
15. Gutierrez T, Simmen T. Endoplasmic reticulum chaperones and oxidoreductases: critical regulators of tumor cell survival and immunorecognition. *Front Oncol* (2014) **4**:291. doi:10.3389/fonc.2014.00291
16. Lee AS. Glucose-regulated proteins in cancer: molecular mechanisms and therapeutic potential. *Nat Rev Cancer* (2014) **14**(4):263–76. doi:10.1038/nrc3701
17. Tarr JM, Winyard PG, Ryan B, Harries LW, Haigh R, Viner N, et al. Extracellular calreticulin is present in the joints of patients with rheumatoid arthritis and inhibits FasL (CD95L)-mediated apoptosis of T cells. *Arthritis Rheum* (2010) **62**(10):2919–29. doi:10.1002/art.27602
18. Donnelly S, Roake W, Brown S, Young P, Naik H, Wordsworth P, et al. Impaired recognition of apoptotic neutrophils by the C1q/calreticulin and CD91 pathway in systemic lupus erythematosus. *Arthritis Rheum* (2006) **54**(5):1543–56. doi:10.1002/art.21783
19. Kovacs H, Campbell ID, Strong P, Johnson S, Ward FJ, Reid KB, et al. Evidence that C1q binds specifically to CH2-like immunoglobulin gamma motifs present in the autoantigen calreticulin and interferes with complement activation. *Biochemistry* (1998) **37**(51):17865–74. doi:10.1021/bi973197p
20. Kasper G, Brown A, Eberl M, Vallar L, Kieffer N, Berry C, et al. A calreticulin-like molecule from the human hookworm *Necator americanus* interacts with C1q and the cytoplasmic signalling domains of some integrins. *Parasite Immunol* (2001) **23**(3):141–52. doi:10.1046/j.1365-3024.2001.00366.x
21. Ferreira V, Valck C, Sanchez G, Gingras A, Tzima S, Molina MC, et al. The classical activation pathway of the human complement system is specifically inhibited by calreticulin from *Trypanosoma cruzi*. *J Immunol* (2004) **172**(5):3042–50. doi:10.4049/jimmunol.172.5.3042
22. Ramirez-Tolosa G, Aguilar-Guzman L, Valck C, Abello P, Ferreira A. Is it all that bad when living with an intracellular protozoan? The role of *Trypanosoma cruzi* calreticulin in angiogenesis and tumor growth. *Front Oncol* (2014) **4**:382. doi:10.3389/fonc.2014.00382
23. Roskin G. Toxin therapy of experimental cancer; the influence of protozoan infections upon transplanted cancer. *Cancer Res* (1946) **6**:363–5.
24. Wang XY, Arnouk H, Chen X, Kazim L, Repasky EA, Subjeck JR. Extracellular targeting of endoplasmic reticulum chaperone glucose-regulated protein 170 enhances tumor immunity to a poorly immunogenic melanoma. *J Immunol* (2006) **177**(3):1543–51. doi:10.4049/jimmunol.177.3.1543
25. Gao P, Sun X, Chen X, Subjeck J, Wang XY. Secretion of stress protein grp170 promotes immune-mediated inhibition of murine prostate tumor. *Cancer Immunol Immunother* (2009) **58**(8):1319–28. doi:10.1007/s00262-008-0647-6
26. Arnouk H, Zynda ER, Wang XY, Hylander BL, Manjili MH, Repasky EA, et al. Tumour secreted grp170 chaperones full-length protein substrates and induces an adaptive anti-tumour immune response in vivo. *Int J Hyperthermia* (2010) **26**(4):366–75. doi:10.3109/02656730903485910
27. Korbek M, Banath J, Saw KM, Zhang W, Ciplys E. Calreticulin as cancer treatment adjuvant: combination with photodynamic therapy and photodynamic therapy-generated vaccines. *Front Oncol* (2015) **5**:15. doi:10.3389/fonc.2015.00015
28. de Bruyn M, Wiersma VR, Helfrich W, Eggleton P, Bremer E. The ever-expanding immunomodulatory role of calreticulin in cancer immunity. *Front Oncol* (2015) **5**:35. doi:10.3389/fonc.2015.00035
29. Loset GA, Berntzen G, Frigstad T, Pollmann S, Gunnarsen KS, Sandlie I. Phage display engineered T cell receptors as tools for the study of tumor peptide-MHC interactions. *Front Oncol* (2014) **4**:378. doi:10.3389/fonc.2014.00378
30. Graner MW, Lillehei KO, Katsanis E. Endoplasmic reticulum chaperones and their roles in the immunogenicity of cancer vaccines. *Front Oncol* (2014) **4**:379. doi:10.3389/fonc.2014.00379

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