Lupus (2017) 0, 1–6
journals.sagepub.com/home/lup

REVIEW

Can killers be saviors?

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Autoimmunity and cancer have a multifarious epidemiology. Often, it is because of an impaired genome, culminating in functional aberrations in the human system. Systemic lupus erythematosus (SLE) is a heterogeneous complex disease which ensues due to the failure of the immune system to distinguish between self and non-self antigens, thus producing autoantibodies against DNA, RNA and proteins. Cancer, the other side of the same coin, results from an excessive proliferation of cells that evade immune regulation as a result of incompetent defense by T-cells, B-cells and macrophages. Recent findings have indicated that lupus autoantibodies could be used as an effective weapon to kill cancerous cells. This is an attempt to take an account of malicious 'lupus autoantibodies' and their role in neutralizing cancerous cells which may help in enhancing the survival rate of cancer patients, hence, killers can be saviors. *Lupus* (2017) **0,** 1–6.

Key words: Systemic lupus erythematosus (SLE); lupus; autoantibodies; cancer; protective autoimmunity

Introduction

Cancer is an obstinate enemy that originates from a combination of genetic and epigenetic mutations which can be either sporadic or familial.[1] The nidus of cancer cells harbors the heterogeneous cell population with altered characteristics and metabolic properties. Decades of research have led us to an interim conclusion that the natural humoral immunity as well as cytotoxic T-lymphocytes can detect the tumor associated antigens (TAAs) or neoantigens; however, the autoantibodies generated to react with mutated proteins in cancer were also seen to react with wild-type proteins.[2] Hence the manifestation of malignancy can mark an advent of autoimmune disease and vice-versa. Therefore, a chronic autoimmune disease has now been logically linked with cancer.[3] In autoimmune disease, the host fails to distinguish between foreign and self antigens and begins to produce autoantibodies. The anti-dsDNA, ANA (antinuclear antibody), anti-histone, anti-La and other anti-blood cell autoantibodies are generated during rheumatic diseases (autoimmune diseases) such as scleroderma, and systemic lupus erythematosus (SLE),[4] while the natural autoantibodies like IgM detect altered self antigens in cancer.[5] There are instances where immunosuppressive drugs in autoimmunity (e.g. cyclophosphamide, methotrexate) can predispose patients to cancer and increased risk of infections.[6]

This review will summarize the previously established link between these two maladies. The content will also throw light on the potential therapeutic roles of prime players, the autoantibodies, generated inside the host during the systemic autoimmune diseases (SAIDs) and malignancy.

Lupus and cancer synchronized

Autoimmunity and cancer have long been identified as leading causes of an increased rate of mortality and morbidity throughout the world. Both these maladies converge at the aberrant immune system. SLE is a heterogeneous, chronic autoimmune disease with ambiguous etiology. The hallmark of this disease is the loss of immune regulation, characterized by the generation of autoantibodies against the nuclear antigens primarily, thereby producing antigen–antibody complexes

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Received 30 March 2016; accepted 15 December 2016

10.1177/0961203316688783

(immune complexes, ICs) which induce an inflammatory response, resulting in end-organ damage like lupus nephritis (Figure 1).

Cancer is also an outcome of a compromised immune system. When there is an uncontrolled multiplication of cells due to a genetic or epigenetic defect within the genome of the cell, malignancy emanates.[7] The immune surveillance system generates antibodies against the tumor-specific antigens but fails to wrestle with the rapidly dividing cells and in the end the tumor overwhelms the surveillance system. But in cancer, protective autoimmunity[8] also exists, within which natural polyreactive autoantibodies, IgM isotypes, are targeted against altered self-antigens expressed by tumor cells. Thus, overlapping pathways persist for cancer immunity and autoimmunity.

Several cohort studies have hinted at the coexistence of lupus and cancer,[9] but the molecular link is yet to be discerned. A cohort study estimated an increased risk of non-Hodgkin's lymphoma (NHL),[10] cancer of vulva, lung, thyroid and liver in SLE patients while there was a decreased risk of breast, endometrial and ovarian cancers.[11] The low standard incidence ratio of these cancers in women having SLE can be due to premenopausal-associated reproductive factors. The higher risk of cervical, vulva and hepatic cancer in SLE patients can be due to defective elimination of viruses like human papilloma virus and vulnerability to infections because of the use of immunosuppressive regimens for treatment. The hypothesis governing this discordance can well be stated as SLE patients are at low risk for hormone-sensitive cancers like breast and ovary due to altered estrogen metabolism while at high risk for vulva, prostate and hepatic cancers because of altered viral clearance and exogenous medications that predispose them to these cancers.

There is also evidence from cohort studies that posit the triggering of autoimmunity in cancer. In a study, patients with coexistent scleroderma and cancer were observed to have autoantibodies anti-RPC1 against wild-type as well as mutated fragment of RPC-1 generated due to mutation in the POL3A gene (polymerase III polypeptide A gene encoding RPC-1).[12] Thus the beneficial autoimmunity against altered self proteins turns out to

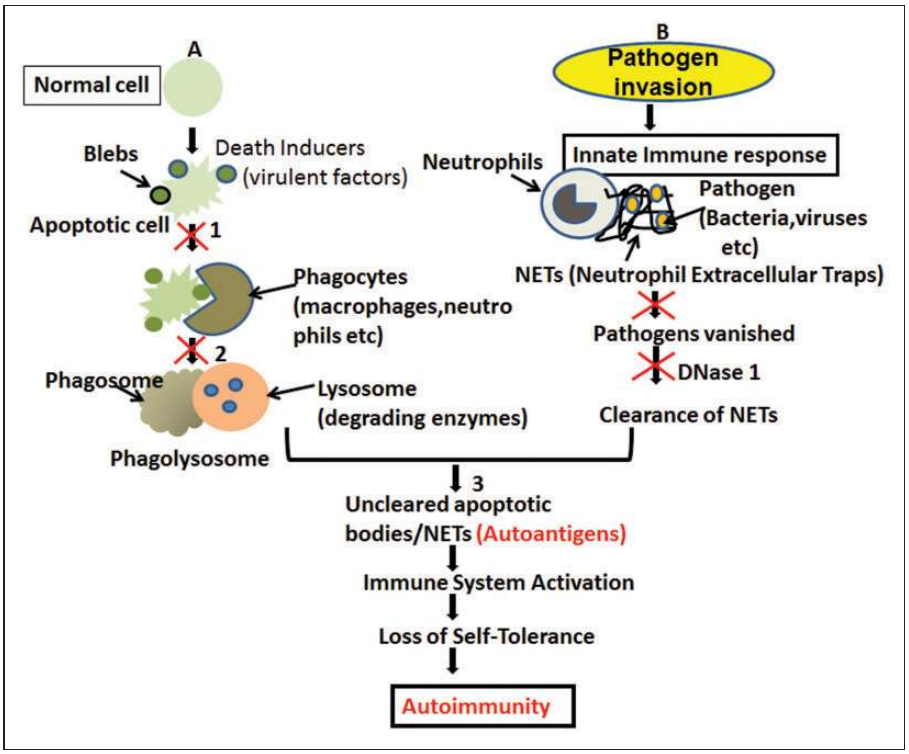

Figure 1 The obstructed program cell death (PCD) mechanisms including apoptosis and netosis (formation of NETs; neutrophil extracellular traps) that lead to loss of self-tolerance by the immune system and drive autoimmunity. (A) Death-inducers initiate apoptosis in normal cells, thereby forming blebs in apoptotic cells. (1) Phagocytes (macrophages, neutrophils etc.) migrate towards apoptotic cells thereby forming phagosome. (2) Phagosome maturation and fusion with lysosome to form phagolysosome. (B) Similarly, the pathogen invasion leads to formation of NETs in order to eliminate pathogen. (3) Thus, when the downstream process of phagosome maturation or formation of NETs is blocked then uncleared dead cells lead immune system activation and autoimmunity.

be disastrous when it targets the wild-type self proteins. The clinical studies revealed the coexistence of both these diseases and the researchers postulated that both can trigger each other.

Autoantibodies, the protagonists

B-lymphocytes are the primary leaders of the immune system that generate antibodies against potentially invasive antigens.[13] Autoreactive B-cells are negatively excluded in the developmental process only by receptor editing.[14] Low affinity autoreactive naïve B-cells in bone marrow escape deletion[15] and enter in the maturation phase in secondary lymphoid organs, forming an immune-competent B-cell repertoire.[16]

Sometimes, the editing fails and leads to manifestation of autoimmunity which can be either disastrous (causing grave autoimmune disorders) or beneficial (killing cancer). Autoreactive B-cells produce autoantibodies[17] (catalytic antibodies/abzymes) like anti-dsDNA, anti-Ro, anti-La, anti-thyroglobulin, anti- proliferating cell nuclear antigen (PCNA), anti-Sm, anti-histone, anti-C1q and anti-phospholipid.[18] Lupus serum has been shown to have an elevated level of anti-nuclear antibodies (anti-DNA, anti-RNP), complexed with proteins having DNase activity.

These abzymes (Abzs) have a remarkable property of penetrating healthy cells[19] and hydrolyzing their nuclear material, a clinical feature of SLE like lupus nephritis. After internalization, Abzs interact with DNase1 in the cytoplasm and target the nuclear antigens (dsDNA) having a pentapeptide DWEYS as a mimetope of immunogenic dsDNA recognized by these catalytic antibodies. Additionally, the nucleic acid cytoplasmic receptors like DNA-dependent activator of interferon-regulatory factors (DAI), absent in melanoma 2 (AIM2) and interferon-gamma inducible protein-16 (IFI16) are upregulated in lupus due to stimulation by chromatin material spilled from the dysregulated PCD (programmed cell death) pathway.[20] Besides, the recently studied Trex1 gene[21], coding for an exonuclease, responsible for extracellular gratuitous genomic DNA digestion, as well as the TRIM21 gene that degrades the RNA/DNA biosensors (self-antigens) on the antigen presenting lymphocytes, were observed to be deficient in SLE patients linked to fatal autoimmunity and malignancy. Thus, these inducible factors trigger loss of self-tolerance in B-cells thereby generating autoantibodies both in cancer and SAIDs.

In a systemic autoimmune disease, the reason behind the immunogenicity of autoantigens is still cryptic but the presence of autoantibodies against autoepitopes in cancer is lucid. The genetic mutations in cancer generate neoantigens which can be truncated proteins or completely new proteins defined as TAAs.[22] These altered genes or proteins become pathogenic and trigger an immune response. In a study, elicited levels of IgG autoantibodies in the serum of hepatocellular carcinoma (HCC) patients were identified against TAAs such as gankyrin, and cyclin B1.[23]

Whether this presence of 'autoimmunity' in cancer is 'protective' or 'destructive', has long been an inquisitive question among scientists.

Epitopes, the therapeutic targets

Epitope definition of the autoantigens is remarkably essential to elucidate the pathway behind autoantibodies generation and their target identification (Figure 2). In a study of PCNA protein, the autoepitopes on PCNA protein recognized by the autoantibodies in lupus sera have a higher ordered conformational structure as compared with the autoantibodies against PCNA from cancer sera.[24] Recently, anti-p53 autoantibodies were identified in lung cancer patients which depend on the type of mutation in p53 (the missense product due to a point mutation in p53 was highly immunogenic).[25] These observations deduced that native antigens harbor autoepitopes (chimeric peptides) that are 'conformationally' compatible (immunoediting) to be targeted by autoantibodies.

The conventional therapies for lupus include antimalarial drugs, immunosuppressive medications like cyclophosphamide, non-steroidal anti-inflammatory drugs and steroids like prednisolone, which are non-specific and feature numerous adverse side effects throughout the life of a patient. On the other hand, cancer can be controlled by treatments like chemotherapy, radiation therapy, and surgery, which still lack specificity. Recent breakthroughs in research have given us a new insight of treating cancer by autoantibodies generated in lupus. In-vitro studies revealed that anti-dsDNA antibodies produced in autoimmune diseases were toxic to cancer cells.[26] The lupus autoantibody 3E10, a single chain variable fragment (scFv) was observed to be a potential therapeutic target for cancers involving mutations in DNA repair mechanisms.[27] Similarly, an anti-nuclear IgG2a-k lupus autoantibody 5C6 was proved to

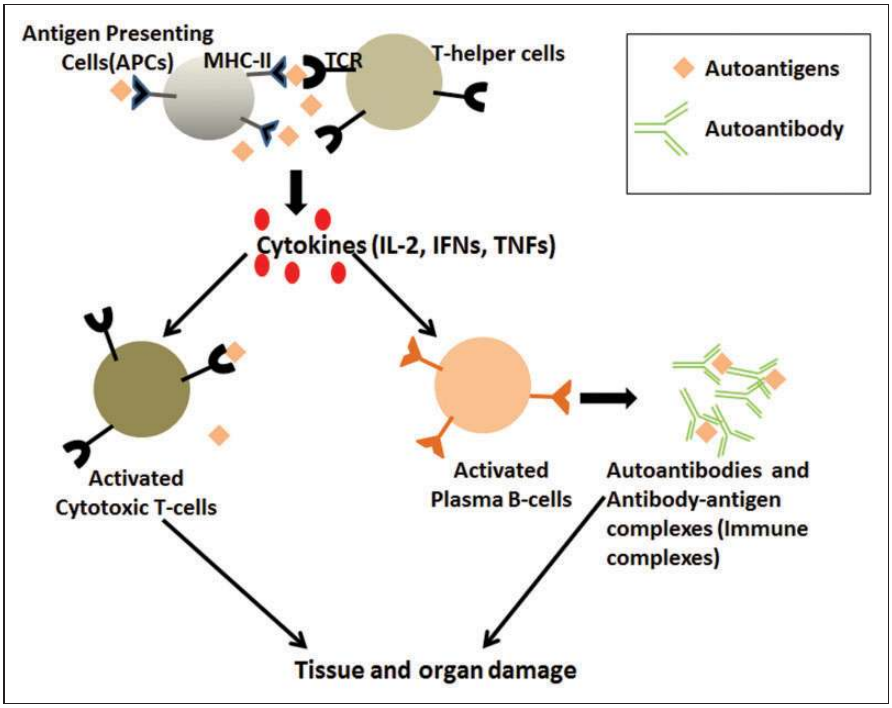

Figure 2 Loss of self-tolerance. Self-antigens (autoantigens) recognized by APCs (antigen presenting cells) like dendritic cells are presented by MHC-II to T-helper cells (Th1 and Th17). Activated Th-cells release cytokines like interleukins (IL-1, IL-3, IL-4), interferons (IFNs) and tumor necrosis factor (TNF). These stimulants trigger activation of cytotoxic T-lymphocytes and proliferation of B-cells (plasma cells). Plasma cells produce autoantibodies and antibody–antigen complexes (ICs) generated and deposited on organs like the kidney, causing inflammation (lupus nephritis). Autoreactive cytotoxic T-cells also get recruited to tissues and damage them.

be toxic to BRCA2-deficient cancer cells.[28] These autoantibodies make cancer cells more prone to chemotherapeutic drugs because they damage nuclear material in malignant cells, which cannot be further repaired (i.e. aberration of the DNA repair mechanism). Thus, the killers (lupus autoantibodies) can be hypothesized as saviors in cancer. These findings have hinted upon the analeptic use of 'lupus autoantibodies' in cancer. These studies till now have nucleated the plethora of questions boggling the mind of scientists. Why are the immunogenic autoepitopes not edited or aberrant self-antigens degraded? Why do autoantibodies against altered proteins cross-react with the wild-type determinants? The specificity of the autoantibodies is yet to be carved out at the molecular level to alleviate chronic autoimmunity and stimulate the beneficial autoimmunity in cancer.

Discussion

The association between cancer and SLE is a baffling question. The cohort studies have revealed the predisposition of SLE patients to develop malignancies like lymphoma, hepatocellular carcinoma but reduced risk of breast, ovarian and prostate cancers. Paradoxically, scientists have also shown the development of autoimmunity during cancer. The rationale behind this paradigm has been vexing scientists for over a decade. The genome-wide analyses have speculated the link between these two chronic diseases, but the clinical significance and the prognostic markers that can define the predisposition of one disease in the presence of other remains unexplored. The hypothesis so far proposed is: (1) loss of immune tolerance; (2) altered self-antigens due to mutagenesis leading to the production of autoantibodies during SAIDs, thereby killing the cancer cells surfacing altered self-receptors. Therefore, there is a need to study the heterogeneity of cancer cells to develop autoantibodies against the exposed surface antigens. Hence, the remarkable studies on autoantibodies killing cancer cells have opened new avenues in the field of developing therapeutics for cancer. In the near future, nanomolecules and autoantibodies (as monoclonal antibodies,) from SLE patients could potentially be used to kill cancer cells in patients. The advancement in immunotherapeutic

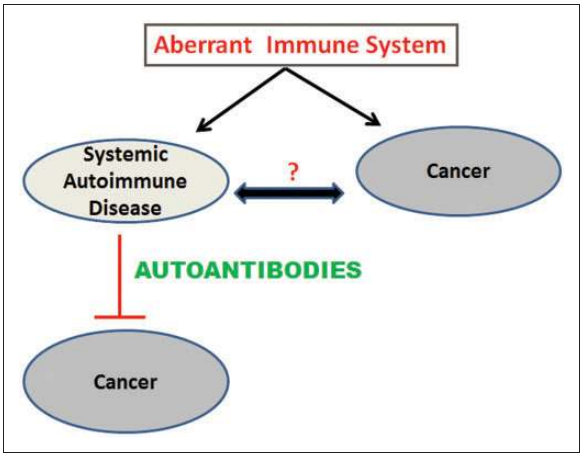

Figure 3 The animated figure depicts the interrelationship between SAIDs (systemic autoimmune diseases) like SLE (systemic lupus erythematosus) and cancer via unknown mechanisms. Whether the autoantibodies generated in lupus can target cancer or not, is still an unanswered question.

approaches to fight cancer by the impaired host machinery during autoimmunity could be groundbreaking in the clinical management of cancer.

There are still many intriguing questions that need to be answered related to the decreased incidence ratio of cancers in SLE patients, the molecular mechanisms governing this link to identify neotargets for treating cancer and other impregnable theories (Figure 3). Darwinian principles dictate the 'survival of the fittest'; this unambiguously complies with the initiative of using lupus autoantibodies to abrogate cancer. Nature is leaving its imprints in the form of one disease, to cure another. It can be perceived as 'rigorously using the host machinery to heal host malignancy'.

Acknowledgment

We thank Brad H Rovin from Ohio State University, Columbus, USA for his helpful comments and suggestions in organizing the manuscript. AS is also thankful to the Vice Chancellor Shiv Nadar University for providing all the necessary support to perform this study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: AS acknowledges financial support from Shiv Nadar University, India.

References

1 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144: 646–674.
2 Bernatsky S, Ramsey-Goldman R, Labrecque J, *et al*. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun* 2013; 42: 130–135.
3 Chang SH, Park JK, Lee YJ, *et al*. Comparison of cancer incidence among patients with rheumatic disease: a retrospective cohort study. *Arthritis Res Ther* 2014; 16: 428.
4 Rekvig OP, Putterman C, Casu C, *et al*. Autoantibodies in lupus: culprits or passive bystanders? *Autoimmun Rev* 2012; 11: 596–603.
5 Toubi E, Shoenfeld Y. Protective autoimmunity in cancer (review). *Oncol Rep* 2007; 17: 245–251.
6 Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. *Int J Mol Sci* 2014; 15: 16043–16056.
7 Martinez-Outschoorn UE, Balliet RM, Rivadeneira DB, *et al*. Oxidative stress in cancer associated fibroblasts drives tumor-stroma co-evolution: a new paradigm for understanding tumor metabolism, the field effect and genomic instability in cancer cells. *Cell Cycle* 2010; 9: 3256–3276.
8 Dalessandri T, Strid J. Beneficial autoimmunity at body surfaces - immune surveillance and rapid type 2 immunity regulate tissue homeostasis and cancer. *Front Immunol* 2014; 5: 347.
9 Lane PJ, McConnell FM, Anderson G, *et al*. Evolving strategies for cancer and autoimmunity: back to the future. *Front Immunol* 2014; 5: 154.
10 Fallah M, Liu X, Ji J, et al. Autoimmune diseases associated with non-Hodgkin lymphoma: A nationwide cohort study. *AnnOncol* 2014; 25(10): 2025–2030.
11 Bernatsky S, Easton DF, Dunning A, *et al*. Decreased breast cancer risk in systemic lupus erythematosus: the search for a genetic basis continues. *Lupus* 2012; 21: 896–899.
12 Joseph CG, Darrah E, Shah AA, *et al*. Association of the autoimmune disease scleroderma with an immunologic response to cancer. *Science* 2014; 343: 152–157.
13 Schneider P, Takatsuka H, Wilson A, et al. Maturation of Marginal Zone and Follicular B Cells Requires B Cell Activating Factor of the Tumor Necrosis Factor Family and Is Independent of B Cell Maturation Antigen. *J Exp Med* 2001; 194: 1691–1697.
14 Wilson PC, Wilson K, Liu YJ, et al. Receptor Revision of Immunoglobulin Heavy Chain Variable Region Genes in Normal Human B Lymphocytes. *J Exp Med* 2000; 191: 1881–1894.
15 Luning Prak ET, Monestier M, Eisenberg RA. B-cell receptor editing in tolerance and autoimmunity. *Ann NY Acad Sci* 2011; 1217: 96–121.
16 Wang YH, Diamond B. B-cell receptor revision diminishes the autoreactive B-cell response after antigen activation in mice. *J Clin Invest* 2008; 118: 2896–2907.
17 Zaenker P, Gray ES, Ziman MR. Autoantibody production in cancer - the humoral immune response toward autologous antigens in cancer patients. *Autoimmun Rev* 2016; 15: 477–483.
18 Tan EM. Autoantibodies, autoimmune disease, and the birth of immune diagnostics. *J Clin Invest* 2012; 122: 3835–3836.
19 Yanase K, Smith RM, Puccetti A, *et al*. Receptor-mediated cellular entry of nuclear localizing anti-DNA antibodies via myosin 1. *J Clin Invest* 1997; 100: 25–31.
20 Pieterse E, van der Vlag J. Breaking immunological tolerance in systemic lupus erythematosus. *Front Immunol* 2014; 5: 164.

21 Lee-Kirsch MA, Gong M, Chowdhury D, et al. Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 are associated with systemic lupus erythematosus. *Nature genetics* 2007; 39: 1065–1067.
22 Tan EM, Shi FD. Relative paradigms between autoantibodies in lupus and autoantibodies in cancer. *Clin Exp Immunol* 2003; 134: 169–177.
23 Middleton CH, Irving W, Robertson JF, *et al*. Serum autoantibody measurement for the detection of hepatocellular carcinoma. *PLoS One* 2014; 9: e103867.
24 Chan EK, Hamel JC, Buyon JP, *et al*. Molecular definition and sequence motifs of the 52-kD component of human SS-A/Ro autoantigen. *J Clin Invest* 1991; 87: 68–76.
25 Winter SF, Minna JD, Johnson BE, et al. Development of antibodies against p53 in lung cancer patients appears to be dependent on the type of p53 mutation. *Cancer Res* 1992; 52: 4168–4174.
26 Kozyr AV, Sashchenko LP, Kolesnikov AV, et al. Anti-DNA autoantibodies reveal toxicity to tumor cell lines. *Immunol Lett* 2002; 80: 41–47.
27 Hansen JE, Chan G, Liu Y, *et al*. Targeting cancer with a lupus autoantibody. *Sci Transl Med* 2012; 4: 157ra42.
28 Noble PW, Young MR, Bernatsky S, *et al*. A nucleolytic lupus autoantibody is toxic to BRCA2-deficient cancer cells. *Sci Rep* 2014; 4: 5958.