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Staphylococcal enterotoxins as good candidates for cancer immunotherapy: a systematic review

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Key words: Staphylococcus aureus, Enterotoxin, Cancer, Immunotherapy, Superantigen
Parole chiave: Staphylococcus aureus, Enterotossina, Cancro, Immunoterapia, Superantigeni

Abstract

Background. *Cancer is considered as one of the leading causes of death today. The wrong lifestyles have led to an increase in the incidence rate of this deadly disease. There are many complications associated with common treatments of this disease. Immunotherapy is one of the new approaches taken recently. The purpose of this systematic review was to evaluate the studies on Staphylococcus aureus enterotoxins as a treatment of cancer worldwide.*

Study design. *We conducted a systematic review of articles published in PubMed, Cochrane, Scopus and Google scholar databases from 1995 to 2016 to evaluate the effects of Staphylococci enterotoxins on cancer.*

Methods. *Eligible studies were evaluated qualitatively based on a checklist prepared by two independent reviewers, and they were subsequently matched.*

Results. *Our review identified 97 records through searching PubMed and Cochrane database and 1306 records through searching Google scholar and Scopus. Forty six studies were excluded from PubMed and Cochrane database and 1281 studies were excluded from Google scholar and Scopus after screening abstracts and titles. Therefore, our systematic review was based on 51 publications on PubMed and Cochrane, and 25 publications on Google scholar and Scopus, which met our criteria. Staphylococcal enterotoxin A was the most commonly used toxin in these studies. The side effects of using this toxin in immunotherapy have been reported to be low and all studies have identified this toxin as a suitable option for immunotherapy*

Conclusions. *The data obtained from these studies showed that due to the low rates of complications, Staphylococcal enterotoxins have the potential to induce immune system against various cancers as superantigens. Therefore, they can be considered as a suitable candidate for immunotherapy of cancer.*

Introduction

Cancer is considered as one of the leading causes of death all over the world. With increase in population, especially in developing countries, cancer is expected to grow further. Selecting an inappropriate lifestyle including smoking, tobacco use, malnutrition, physical inactivity, and cultural shifts in the role of women in society can be associated with the risk of cancer (1, 2). Unfortunately, there are several complications following common treatments for cancer such as chemotherapy, radiotherapy which urges studies to find new effective therapeutic approaches as a substitution for these treatments.

Immunotherapy is generally associated with the treatment of cancer and many immune interventions are being developed for

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the treatment of various cancers and infectious diseases (principles of immunotherapy: implications for treatment strategies in cancer and infectious diseases). The immunotherapy of tumors is based on the presence of tumor-associated antigens (TAAs) that can be identified by the immune system. These antigens are often endogenously expressed and different mutations can lead to their overexpression. Since most of these TAAs are located inside the cells, it is believed that the immunity generated by cytotoxic T lymphocyte cells (CTLs) against the TAAs is the most effective (3, 4). At the end of the nineteenth century, William Cali was the first researcher to discover bacterial potential for cancer immunotherapy. By investigating on cancer patients who had an acute bacterial infection, Cali found that the size of tumors decreased. Furthermore, in collaboration with Robert Koch, he combined a mixture of bacterial toxins for cancer patients who could not undergo surgery. However, safety concerns regarding these toxins as well as their limited effectiveness led to a decrease in their use for cancer treatment (5). However, the application of bacteria in cancer treatment such as the use of Bacillus Calmette-Guerin (BCG) in the treatment of bladder cancer after tumor removal was still controversial. Weekly intraperitoneal administration of BCG to the bladder can prevent tumor recurrence in 60% of patients (6). Toxin administration for the reduction of tumor size is rooted from the fact that bacteria can induce an early inflammatory immune response by activating the pathogenic molecular pattern (PAMPs) (7). Therefore, pathogen-based immunotherapy has been widely used for cancer treatment. *Staphylococcus aureus* is one of the most studied bacteria in immunotherapy owing to possessing various enterotoxins which account for its high antigenic property. Today, bacterial toxins and their specific properties have been employed to fight cancer (8). *Staphylococcus aureus* is an opportunistic pathogen that can repeatedly colonize human and animal skin and mucus leading to wide range of diseases. This bacterium is capable of producing various toxins that can contribute to the disease (9). Among them, exfoliative toxin A, B, Toxic Shock Syndrome Toxin 1 (TSST1), enterotoxins A to E and G to O are the most common (10-12). The immune system is normally activated by antigen presenting cells through T lymphocytes. In fact, the antigens are taken up, hydrolyzed and presented as peptides to their complements on T lymphocytes. These peptides are expressed on the small groove of major histocompatibility complex II (MHC II) on the surface of antigen presenting cells (APCs). Then, the receptor of these antigens on T lymphocyte cells can detect the MHC II peptide complex with a specific bond between the five-dimer variants of α and β chains (vβ, Dβ, Jβ, Vα, Jα). However, super-antigens can interfere with this particular interaction and bind the external part of the Vβ domain and establish a direct bind to the MHC II. Normally, 1/10,000 of T cells are activated during antigen presentation, however, the super-antigens activate up to 25% of all existing T cells, resulting in cytokine release and the following consequences (13, 14). Recent studies have shown that these super-antigens can be used to induce immune system against cancer. So far, the use of these super-antigens, such as Staphylococcal enterotoxins (SE), as agents for apoptosis, has been confirmed in studies. Super-antigens of *S. aureus*, commonly known as *S. aureus* super-antigens (SAgs) are classified in different types including staphylococcal enterotoxins (SEs), staphylococcal enterotoxin-like proteins (SELS), and toxic shock syndrome toxin-1 (TSST-1). Staphylococcal enterotoxins are essentially defined as toxins that can produce staphylococcal food poisoning (SFP) and typically include SEs A, B, C, D, E, G, H, I, R, and T (15-18). In this systematic review, all of the studies conducted on the

effect of SE on cancer treatment have been investigated in order to scientifically and precisely assess their effect on the treatment of different cancer types.

Materials and Methods

1. Search strategy and study selection

Searching in databases including PubMed, Cochrane, Google Scholar, and Scopus was done with the keywords: (*Staphylococcus aureus*) or (Staphylococcal) and (enterotoxins) or (enterotoxin) and (super-antigen) and (neoplasms) or (cancer) or and ('+All fields) or (treatment) or (therapeutics). With a time limit of 1995 to 2016 for obtaining articles related to the selected keywords, articles were selected in 3 steps: (1) reviewing the title of the article, (2) reviewing the summary of the article, and (3) finally, a full review of the article. Review articles, case reports, editorials, and articles that were summarized or not published, the abstracts of articles from congresses and meetings in languages other than English were not included. Only the original research papers that studied the role of staphylococcal enterotoxins in cancer treatment by standard methods were included. Moreover, bibliography of the selected papers were examined for additional studies (Figure 1).

2. Data extraction

The selected papers and the following information were extracted from all databases: The names of the authors, the year of the

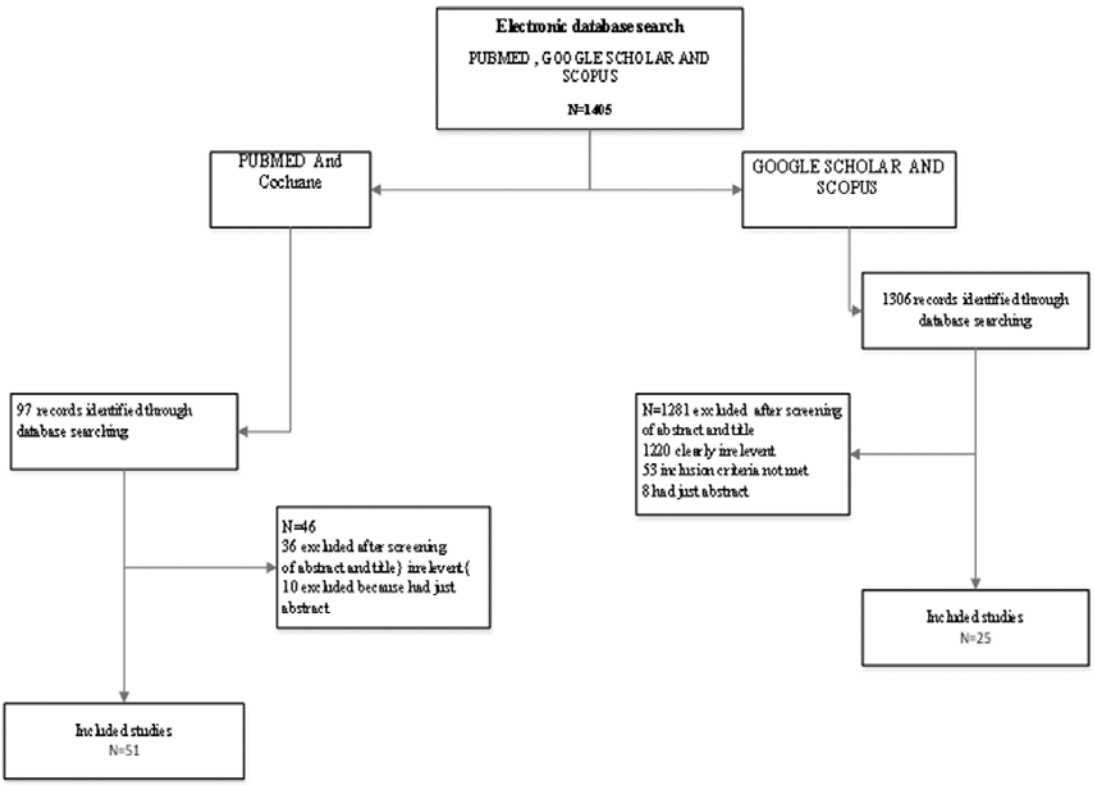

Figure 1 - Flow diagram of literature search and study selection

publication, the model designed for testing, the studied animals, toxin type, the cancer cells, and the study results. A summary of these studies are presented in Table 1 (See Results). These data were added to the form provided by the Authors and disputed independently without regarding the study setting and study design by two Authors (Shivaee A, Sedighi M) and disagreements were resolved by the Authors.

3. Study quality assessment

We assessed the methodological quality of the included studies using the criteria based on a checklist described in Table 2.

The quality of studies was assessed independently by A. Shivaee and M. Sedighi and difference in opinions was resolved by all the Authors.

4. Statistical analysis

Statistical analysis was performed with Microsoft Excel (version 2016 for windows). Since the outputs of the studies included in this systematic review are all qualitative and lack any quantitative data, we were not able to use meta-analysis for data analysis and the analysis was therefore descriptive.

Results

1. Study Selection

Our review identified 99 records through searching PubMed and Cochrane database; and then 97 records were obtained and screened for possible inclusions. Forty six studies were excluded, 36 of which were excluded after screening the abstract and title (irrelevant) and 10 were excluded due to the mere presence of abstract. Searching Google scholar and Scopus databases yielded 1306 records of which 1281 were excluded after screening their abstracts and titles; 1220 of these articles were clearly irrelevant, 53 did not meet inclusion criteria and eight of them only possessed abstract. Therefore, our systematic review was based on 56 publications of PubMed and Cochrane and 25 publications of Google scholar and Scopus all of which met our criteria.

2. Description of Studies

The characteristics of the included studies are shown in Table 1. A large variation was present in the characteristics of the included studies. In total, 61.84%) N=47) of the included studies used Staphylococcal Enterotoxin A (1) to treat different cancer types, while 35.52 % (N=27), 10.52% (N=8) and 2.63% (N=2) of the studies used Staphylococcal Enterotoxins B (SEB), C2 (SEC2) and E (SEE), respectively. Among various cancer types examined in the included studies, B16 melanoma was the most studied cancer type (N=14) and SEA was used as a therapeutic method in studies conducted on B16 melanoma cancer. In all of these studies, SEA had a positive effect on cancer treatment and inhibited the progression of malignancy. Other studied cancers included breast cancer (N= 4), bladder cancer (N=3), bile duct cancer (N=4) and other cancer types presented in Table 1. The studied toxin in breast and bladder cancer was SEB, while SEA was applied in studies on colon cancer and bile duct cancer. An animal model was used in most of the studies (N=61, 80.3%), with C57BL/6 and BALB/C (N=38, 50%) being the most studied animal models, respectively. Other animal models and cell lines are indicated in Table 1. In the current review, few studies (N=4, 5.3%) were conducted on human cases as clinical trials among which three studies used SEA and one study used SEB. In clinical trials, enterotoxin immunotherapy was taken against four different types of human cancers including glioma, head and neck carcinoma, renal cell cancer and myeloma. All clinical trials concluded that the SEs or their derivate such as enterotoxin recombinant vaccines could boost human immune system and induce immune responses against different

Table 1 - Characteristics of the included studies

First author	Publication year	Study population	Method of study	Type of toxin	Type of cancer	Effect	Study quality
M.J. Litton et al(19)	1997	Mice C57BL/6	conjugation of Fab-SEA	SEA	Lung Melanoma micrometastasis	+	A
W. Ma et al(20)	2004	Mice C57BL/6	conjugation of B16-SEA	SEA	B16 Melanoma	+	A
C. Gidlöf et al(21)	1997	Mice SCID	conjugation of anti-CD19-fab-SEAm	SEA	B-cell lymphoma	+	A
A. Rosendahl et al(22)	1999	f Mice C57BL/6	conjugation of SEA-Fab/Fab-IL2	SEA	B16 Melanoma	+	A
A. Rosenda et al(23)	1996	f Mice C57BL/6	conjugation of C215fab-SEA	SEA	B16 Melanoma lung metastases	+	B
S-i Takemura et al(18)	2002	F SCID	conjugation of (SEA D227A M×3 diabody	SEA	Bile duct cancer	+	A
H. Mahmoodzadeh Hosseini et al(24)	2015		conjugation of Texosom-SEB	SEB	Ovarian cancer cells	+	A
Q. Wang et al(25)	2001	F C57BL/6	conjugation of C215fab-SEA	SEA	B16 Melanoma	+	A
G. Jeudy et al(26)	2008	F C57BL/6	conjugation of pSEA-TM/PEI	SEA	B16 Melanoma	+	A
S. Shu et al(17)	1993	C57BL/6	conjugation of SEA/SEB/SEC2 - MHC II	SEA/SEB/SEC2	Pulmonary Metastases	+	A
M. Shimizu et al (27)	2003	F Balb/C	conjugation of SEA/SEB-Meth A cell	SEA/B	Fibrosarcoma Meth A cells	+	A
K-G. Jie et al(28)	2007	C57BL/6	Effect of SEC on T cell and B cell	SEC	liver tumor cell line BEL-7402	+	A
S.L. Kominsky et al(29)	2001	C57BL/6	conjugation of B16 F10-SEA/B	SEA/SEB	B16 F10 melanoma	+	A
G.E. Plautz et al(30)	2000	human	LN cells in presence of SEA	SEA	Glioma cancers	+	A
B.A. Pulaski et al(31)	2000	F Balb/C&Nu/ Nu 4T1	conjugation of MHC II & CD80 -SEB	SEB	Breast Cancer in mice with SCID	+	A
M. Shinoda et al(32)	1998	SCID mice	conjugation of SEA-MUSE11 mAB&SEA-fab2(of MUSE 11 mAB	SEA	Bile duct cancer(BDC)	+	A
F.G.E. Perabo et al(33)	2005	human cell line	use of SEB	SEB	Bladder Cancer	+	B
M. Shimizu et al (34)	1996	BALB/ C&human cell line	conjugation of SEA/SEB-Meth A cell	SEB	Sarcoma & Meth A & Hepatoma MH134	+	A
M. Inoue et al(35)	1996	C57BL/6J(B6)	SEs-Activated LN cells	SEA&C2&E&SSSS	Intracranial Tumors	C2&A P/ E N	A
S. Si et al(36)	2006	C57BL/6	create a conjugation of SEA-TM CD80 -α Fetoprotein (AFP)(AFP enhancer/promoter to reduce toxicity and to improve safety)by adenovirus	SEA	Hepatoma	+	A
F. Xiu et al(37)	2007	F C57BL/6	create a conjugation of SEA-TM anchored Exosome(EXO/SEA-TM)	SEA	Murine lymphoma	+	A
M. Dohlsten et al(38)	1995	F SCID	conjugation of C242fab-SEA	SEA	colon carcinoma	+	A

L. Gu et al(39)	2013	C57BL/6 & New Zealand rabbit R&SCID mouse	conjugation of MHC II-SEB-TCR and comparison between wild and mutant	SEB&SEB-H32Q/K	Hepatoma&BGC823/Hela	+	A
H-J Hao et al(40)	2005		conjugation of (scdsFv-SEA(D227A)	SEA	Hepatoma(SMMC-&7721)	+	B
G. Hedlund et al(41)	1993	C57BL/6	direct injection of SEA	SEA	Raji/MHC II Tumor	+	A
C. Huang et al(42)	2005	C57BL/6	gene engineering by HSP70 vector and anchored that cell with TM-SEA(B16-TM-SEA)	SEA	B16 Melanoma	+	A
L. Peng et al(43)	2006	HLA-A2/12b Tran	SEA	SEA	M.W.Melanoma-associat Ag	+	A
C. Huang et al(44)	2003	C57BL/6	B16-TM-SEA	SEA	B16 Melanoma	+	A
H. Belfrage et al(45)	1997	F BALB/ C&C57BL/6	SEA-IL2	SEA	Human lymphoma Raji	+	A
H. Kodama et al(46)	2001	rabbits	mSEA-D227A conjugated with Ab	SEA	Bile duct carcinoma	+	A
P.A. Lando et al(47)	1993		mAb-SEA	SEA	Colon carcinoma	+	A
L. Wang et al(48)	2009	F Balb/C	SEB-bFGF	SEB	Colorectal adenocarcinoma HT-29	+	A
M.J. Litton et al(49)	1996	SCID mice	C242Fab-SEA	SEA	Colon carcinoma	+	A
E.J. McConnell et al(50)	2002	MET mouse	conjugation of Dendritic/Tumor cell-SEB	SEB	Pancreatic cancer	+	A
B-P. Miao et al(51)	2015	C3H/HEN	conjugation of SEB+SqC	SEB	Squamous cell carcinoma	+	A
W.C. To et al(52)	2000	human	direct injection of SEA	SEA	SCCH N	+	B
G.E. Plautz et al(53)	1997	C57BL/6	T cell activated with SEC2	SEC2	intracranial Fibrosarcoma(GL261 glioma)	+	A
G.E. Plautz et al(54)	1999	human	IL2&anti CD3-SEA	SEA	renal cell	+	B
K.A. Newell et al(55)	1991	C3H/HEN	direct injection of SEB	SEB	Skin Tumor	+	A
L. Ragnarsson et al(56)	2001		conjugation of PA-SEAm	SEA	multiple melanoma(4)	+	B
L.O. Reis et al(57)	2012	F fisher	conjugation of BCG-SEB	SEB	Bladder Cancer	+	A
A.P. Rapoport et al(58)	2005	human	direct injection of SEB	SEB	myloma	+	B
D.C. Rice et al(59)	1999	F C3H/HeN	create a conjugation of anti CD3-αnti P97-SEB	SEB	Syngeneic P97 Murine Melanoma CL62	+	A
N. Sakurai et al(60)	1999	TFK-1	SEA-antibody single chain fv (SEA-scFv)	SEA	Bile duck carcinoma	+	A
D.P. Schrayer et al(61)	2002	C57BL/6	conjugation of IL2+SEA	SEA	B700 Melanoma	+	A
Q. Sun et al(62)	2012	Male ICR mice	conjugation of SEA(D227A)-VEGF	SEA	Solid tumor (S180)	+	A
A. Sundstedt et al(63)	2007	C57BL/6	conjugation of TTS C215fab-SEA)+IFNα	SEA	B16 Melanoma	+	A
A. Sundstedt et al(64)	2009	C57BL/6	conjugation of TTS+docetaxel -C215fab-SEA	SEA	B16 Melanoma lung metastases	+	A

D.H. Thamm et al(65)	2003	Dogs	create a conjugation of Lip-SEA -canine IL2	SEA	STS(soft tissue sarcoma)	+	A
J.M. Tordsson et al(66)	2000	F CB17	conjugation of (HMW-MAA)K305fab-SEA(D227A)	SEA		+	B
X. Wang et al (67)	2009	F BALB/C	direct effect of mutant SEC2(T20L/G22E) &SEC2	SEC2	Cell line (Hepa1-6&H22)	+	B
Q. Xu et al (68)	2010	C57BL/6	TGFβL3-SEA(D227A)	SEA		+	B
M. Xu et al (69)	2011	BALB/C	SEC2(SAM-3)	SEC2	cell line (Hepa1-6&H22)&colon cancer in animal	+	A
J. Zhou et al(70)	2013	BALB/C	direct mutant of SEC2(14-128)	SEC2	cell line(hepa1-6)	+	A
M.F. Heidary et al (71)	2015	cell line	Direct effect of SEB on Mir-10&Mir335	SEB	Breast Cancer(MDA-MB231)	+	A
H. Mahmoodzadeh Hosseini et al (72)	2014	cell line	create a structure of EXO-SEB	SEB	Pancreatic cancer	+	A
A.A. Imani Fooladi et al (73)	2008	WEHI-168-&balb/c	IV injection of SEB	SEB	Fibrosarcoma	+	A
A.A. Imani Fooladi et al(74)	2015	Balb/c	create a structure of SEB-TEX	SEB	Breast Cancer	+	A
H. Mahmoodzadeh Hosseini et al(75)	2014	cell line	create a structure of EXO-SEB	SEB	Breast Cancer	+	A
A.A. Imani Fooladi et al(76)	2014		create a structure TGFβL3-SEB	SEB	various human carcinomas	+	B
A.A. Imani Fooladi et al(77)	2009	BALB/C	Monophosphoryl lipid A and SEB (MPL + SEB)	SEB	Fibrosarcoma	+	A
F. Yousefiet al(78)	2015	4T1(NCBIC604)	create a conjugation of TGFβL3-SEB	SEB	Breast Cancer	+	A
E. Erlandsson et al(79)	2003	cell line	direct effect of mutant SEA/E(SEA/E-120)	SEA/E	Colo 205	+	A
P.A. Lando et al(80)	1991	cell line	create a structure of SEA-MHC II	SEA	K562&Raji/Colo205	+	A
D.W. Newton et al(81)	1997	CHO	conjugation of SEA mutant (D227A&F47)-C215fab/C242fab	SEA	B16(lung metastas)	+	A
F.G.E. Perabo et al(82)	2005	Balb/c	direct effect of SEB on PBMC	SEB	Bladder Cancer	+	A
J. Hui et al(83)	2008	cell line	direct effect of SEC2 mutant	SEC2	colorectal cancer	+	A
T.N. Brodin et al(84)	1998	C57BL/6	conjugation of SEA-fab	SEA	B16	+	A
M. Kato et al(85)	2011	C57BL/6	a conjugation of SEB&A+Tumor Ag(57A257-264)-Pulsed DC	SEB/A	EGV-2LL-B16	+	A
W. Ma et al(86)	2003	C57BL/6	gene engineering by pET-28a vector and create a conjugation of pET-28a-TM-SEA)	SEA	ovarian cancer	+	A
T.K. Mondal et al(87)	2002	male swiss albino	Use of SEA+PA	SEA	Ehrlish ascites tumore	+	A

D.P. Shrayer et al(88)	1997	C57BL/6	gene engineering and creating a conjugation of SEA-secreting B16 cell	SEA	B16	+	A
J. Yang et al(89)	2001	Balb/c	create a structure of mAb HAb18(ab')2-SEA	SEA	Hepatocellular carsinoma(HCC)	+	A
B.T. Renno et al(90)	1996	Balb/ c&C57BL/6	investigation of role of SEB on fas	SEB		+	B
U. Holzer et al(91)	1995	mice	create tow conjugative structure ch14018-SEA & protein A-SEA	SEA	Neuroblastoma	+	A
J. Ihle et al(92)	1995	mice	protein A and SEA binding to the mAbs CD7 or CD38	SEA	leukemias	+	A

Table 2 - Checklist for the quality assessment of the study

(1) Was the sample representative of the target population?
(2) Were the study participants recruited in an appropriate way?
(3) Was the sample size adequate?
(4) Were the study subjects and the setting described in detail?
(5) Were objective, standard criteria used for the measurement of the condition?
(6) Was the condition measured reliably?
(7) Was the statistical analysis appropriate?
(8) Are all important confounding factors/subgroups/ differences identified and accounted for?
(9) Was the research question specified and clear?
(10) Were the outcome measures relevant to cancer research?
(11) Are the characteristics (species, background, and sex) of the study population clear?
(12) Was the correct control group present?
(13) Was the experiment non-randomized?
(14) Was the type of toxin mentioned?
(15) Was the method used for immunotherapy clear?
(16) Was the mechanism of toxin function in the immune system clear and specified?
(17) Was the type of cancer mentioned?
(18) Was the administration route specified?
(19) Were the methods used for outcome assessment the same in both groups?
(20) Was the outcome assessment blinded?
(21) Was the outcome assessment non-randomized across the groups?
(22) Was the outcome of animal experiments included in studies and mentioned clearly?
(23) What was the effect of *staphylococcal* enterotoxin on cancer in vitro and in vivo (positive or negative effect)?

cancer types through the production of cytokines and anticancer factors by immune cells especially active T lymphocytes. In all studies, the use of staphylococcal superantigenic enterotoxins have been reported with the least or without side effects, and all studies conducted on staphylococcal enterotoxins showed their effectiveness in

inducing immune system against various cancer types (Table 1).

3. Quality assessment

Included studies were evaluated based on the criteria checklist described in Table 2, which was categorized into three categories: A (high) B (median), and C. The average quality score was 10 items out of the 15 items listed on the checklist. The majority of the included studies failed to clearly report items such as age and number of animal models studied for the effect of the toxins, and the age at which the animals were sacrificed.

Discussion

Cancer treatment is one of the major priorities of global health system due to high prevalence and mortality rate of various cancer types (93, 94). Unfortunately, common treatments for this deadly disease have various complications that have urged the scientists to focus on finding novel treatments with less complications (95). One of the novel treatments with a low rate of complication is inducing body immune system against cancer cells by bacterial super-antigenic products. Super-antigen molecule binds the outer part of the peptide binding cleft of MHCs II with high affinity and subsequently interacts with T cells expressing particular sequences in the variable (3) region of the TCR β chain (TCR V β, in the outer portion of the T cell specific receptor). Both CD4+ and CD8+T cells respond to staphylococcal super-antigens by proliferation, production of various cytokines such as interleukin-2, interferon gamma, and tumor necrosis factor α (TNFα), and generation of strong T-cell cytotoxicity(96, 97). Super-antiges have the ability to direct T-cell cytotoxicity against HLA-DR–positive (HLA-DR+) cells including B cells, dendritic cells, and monocytes (98).

In this systematic review, 76 reliable and valid studies were included. All of them aimed at immunological cancer treatment using *S. aureus* super-antigens. Most commonly studied super-antigens were SEA (47 paper) and SEB (27 paper) enterotoxins, however, a few studies have also examined the effects of SEC (8 paper) and SEE (2 paper) super-antigens on cancer.

Studied cases included different classes of laboratory mice (most cases), laboratory rabbits, cell lines of various human tissues and, in few cases, human beings. These researches investigated several cancer types including lymphoma, bile duct cancer, fibrosarcoma, liver tumor, glioma cancers, breast cancer, bladder cancer, sarcoma, hepatoma, intracranial tumors, colon carcinoma, colorectal adenocarcinoma, pancreatic cancer, squamous cell carcinoma, skin tumor, myeloma, ovarian cancer, neuroblastoma, leukemia and renal cell cancer. Their findings indicate high therapeutic effects of super-antigenic staphylococcal products, including enterotoxin-containing recombinant vaccines against these malignancies and a satisfactory response to treatment. A summary of these studies (1995-2016) covering super-antigenic products, toxin types, and cancer types is presented in Table 1. Most of the studied super-antigens included SEA and SEB and few studies investigated the effects of SEC and SEE on several cancer types. Except a study by Mamoru Inoue *et al*. in 1996 (35), the results of all included qualitative studies indicate the positive effects of these SEs on cancer treatment using different laboratory methods and various laboratory animals, cell lines or even human model. The study by Mamoru Inoue *et al*. (35) on the effect of SEA, SEC2 and SEE for the treatment of intracranial tumors in rat (C57BL/6J) revealed the positive effects of SEA and SEC2 toxins on cancer treatment; however, SEE had no positive effect on tumor treatment. Hence, immune cells activated by

SEE probably have no therapeutic effects on intracranial tumors.

In other studies, there is not even one negative effect of super-antigens on different malignancies. Therefore, it can be concluded that according to several studies conducted on the effects of staphylococcal super-antigenic enterotoxins on different cancer types, the products of these toxins certainly have a potent effect on cancer treatment.

Although the difference in laboratory methods and models as well as differences in the details of the methodology employed by researchers may challenge the discussion section in the present study, what is important is to confirm the positive effect of the staphylococcal super-antigens on different cancer types.

Most studies have evaluated the effects of SEA and SEB on a variety of animal and human models or cell lines through different methods. Generally, these studies have shown the similar effects of these enterotoxins on different genders with different races, confirming that factors such as sex and race do not interfere with employing enterotoxins for cancer treatment. Similarly, studies conducted by Thamm et al. (2003) (65), Rapoport et al. (2005) (58), Perabo et al. (2005) (82), Plautz et al. (1999, 2000) (30, 54), Hui et al. (2008) (83), Kato et al. (2011) (85), Wang et al. (2009) (48), Huang et al. (2005) (42), Yang et al. (2001) (89), Rosendahl et al. (1999) (22), Sundstedt et al. (2008, 2009) (63, 64) and several other studies show that demographic indicators such as age, sex, weight, and race of the participants did not influence the effects of enterotoxins on the surveyed cancer types.

In this systematic review, we performed a comprehensive search of the literature, including 76 articles and reporting four clinical trials. These clinical trials were conducted by To et al. (2000, 17 patients with head and neck carcinoma) (52), Plautz et al. (2000, 12 patients with glioma) (30), Plautz et al. (1999, 20 patients with renal cell carcinoma) (54) and Rapoport et al. (2005, 54 patients with myeloma) (58), who evaluated the clinical efficacy and safety of specific immunotherapy by staphylococcal enterotoxins in 103 cancer patients. All of these studies suggested positive and promising effects of staphylococcal super-antigens on cancer treatment.

Although specific immunotherapies have not recently been the focus of research, there are currently few studies about clinical effectiveness of specific immunotherapies by bacterial super-antigens in cancer patients. Based on the available literature, the results of this systematic review suggest that some specific immunotherapies such as SEA-anchored vaccine, B16-TM-SEA tumor vaccine, SEA-modified tumor vaccine, SEB transfected tumor vaccines, SEA/SEB vaccine and enterotoxin recombinant vaccine therapy could be beneficiary for cancer treatment. In addition, most studies reported a positive outcome (although not significant) from treatment with super-antigenic immunotherapy. Therefore, further studies are essential to evaluate short-term as well as long-term effects of enterotoxins immunotherapy in patients with different malignancies.

Overall, the results of our review effort strongly suggest applying a new immunotherapy strategy using various staphylococcal super-antigenic products, including the development of various vaccines, and active and "passive" immunization to induce, or to offer, an anti-tumor immune response for cancer treatment.

Limitations

This systematic review has some limitations. One of the limitations is reliance on published results rather than clinical data. Secondly, there was a considerable heterogeneity in designs, interventions and populations of the studies included in this systematic review. To try to overcome this

limitation, we rated the quality of studies. Third, the sample size of the included trials concerned with immunotherapy interventions were relatively small, which limited the studies to detect a significant difference. Fourth, the number of clinical trials conducted on humans is small, therefore, generalizing the results to human cases can be challenging. Fifth, some data and outcomes in some studies were not reported properly, therefore, we could not include them in our systematic review. Finally, the risk of bias was high in some cases and enough evidence was not provided to allow the judgment of bias in some particular areas.

Conclusions

According to the immunological studies, super-antigens of *S. aureus*, especially SEA and SEB, have a high potential for activating immune T cells, providing a strong antigen, stimulating other immune cells through cytokine production, activating them, increasing the anti-toxicity of immune cells, improving the invasive properties of macrophages and dendritic cells and secreting multiple antitumor factors in tumor region. Data revealed that treatment with the staphylococcal super-antigenic products can result in massive cytokine production (i.e., IL-2, IFN-γ and TNF-α), T-cell proliferation and strong CTL activity, which can eventually induce significant tumor growth inhibition. Although most studies have been conducted on animal models and cell lines and only a few clinical studies are present, a high percentage of positive effects of tumor therapy and the success of cancer treatment using recombinant vaccines containing staphylococcal super-antigenic products have been reported. The results of our review study demonstrate that staphylococcal enterotoxins-derived vaccine therapy prolongs the immune response in vivo and induces long-term survival of the humans and animals carrying different tumors. Therefore, the production of staphylococcal super-antigenic vaccines, especially vaccines containing enterotoxins of this bacterium, can be a valid step towards inducing strong immunological responses and developing a reassuring cancer treatment in human models.

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Riassunto

Le tossine stafilococciche, valide candidate per l'immunoterapia dei tumori: una revisione sistematica

Premessa. Il cancro è considerato oggi come una delle principali cause di morte e gli stili di vita scorretti sono alla base della sua aumentata incidenza. Sono molte le implicazioni negative degli attuali trattamenti terapeutici, la chemio- e la radio-terapia. La immunotereapia è una delle modalità terapeutiche di più recente adozione. Lo scopo della presente revisione sistematica è stato quello di valutare gli studi sin qui effettuati nel mondo sull'uso delle enterotossine dello *S aureus* come modalità di trattamento del cancro.

Disegno dello studio. Pubblicazioni selezionate secondo criteri predeterminati sono state valutate qualitativamente sulla base di una serie di quesiti predisposti in modo indipendente da due revisori, e le valutazioni confrontate tra loro.

Risultati. La nostra ricerca effettuata su Pub Med e Cochrane database ha identificato 97 pubblicazioni, mentre altre 1.306 sono stati identificate attraverso Google Scholar e Scopus. In base all'analisi dei riassunti e dei titoli, ne sono state scartate 46 di Pub Med e Cochrane database e ben 1281 di Google Scholar e Scopus. Pertanto, la nostra revisione sistematica è stata effettuata su 76 pubblicazioni che rispettavano i nostri criteri, appartenenti, rispettivamente, 51 al primo e 25 al secondo gruppo. L'enterotossina A dello *S aureus* è risultata la tossina più frequentemente usata in questi studi. Gli ef-

fetti collaterali del suo impiego nell'immunoterapia sono stati giudicati modesti e tutti gli studi l'hanno identificata come un'opzione terapeutica adeguata.

Conclusioni. Le informazioni ricavate dagli studi considerati hanno mostrato che le enterotossine stafilococciche, grazie alla bassa frequenza di effetti collaterali, sono utilizzabili come induttori del sistema immunitario contro diversi tipi di tumori, comportandosi come super-antigeni. Pertanto sono da considerare adatte per l'immunoterapia dei tumori.

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