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OPINION ARTICLE

Should safety of the flu vaccine for cancer patients be reexamined? [version 1; peer review: 2 approved with reservations]

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Abstract

Seasonal flu vaccine is recommended as the best protection for cancer patients against influenza infection. Recent *in silico* and experimental data suggest that antibodies elicited with influenza vaccine could activate bradykinin receptor B2-associated signaling pathway, which is also involved in cell proliferation and migration of tumor cells. These results point to an urgent need for the reexamination of safety of influenza vaccine(s) in cancer patients.

Keywords

breast cancer, influenza, vaccine

This article is included in the **Emerging Diseases and Outbreaks** gateway.

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

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Cancer and cancer treatment can weaken the immune system making cancer patients particularly vulnerable to complications of infections, especially from acute respiratory infections such as influenza. For this reason, seasonal flu vaccine is recommended for most people with cancer and cancer survivors as the best protection against the influenza infection¹.

Several epidemiological studies have suggested that vaccination against seasonal influenza virus(es) significantly reduces the risk of major cardio-vascular events in patients with acute coronary syndrome or coronary artery disease^{2,3}. The first clinical study on the effect of influenza vaccination after heart attack on future cardiovascular prognosis is underway. The molecular mechanism underlying protection of flu vaccine against cardiovascular diseases is unknown; however, this phenomenon is independent from vaccine efficacy against influenza A infections. Recently, it was suggested that the vaccine against influenza A viruses could elicit agonistic antibodies for bradykinin receptor B2 (BKB2R), which activates a BRB2R-associated signaling pathway that may contribute to the protection against cardiovascular diseases⁴. Moreover, it has been established that antibody activation of BKB2R is possible, with all biological activities associated with it⁵. Recently, a monoclonal antibody with agonistic BKB2R activity as well as anti-influenza A activity has been patented for multiple purposes⁶. Taken together, these data support the hypothesis of “molecular mimicry” between BKB2R and hemagglutinin (HA) of influenza A viruses that may allow for generation of cross reactive antibodies.

In addition, it was found that levels of kinins in biological fluids of cancer patients are increased and that activation of kinin receptors expressed on cancer cells produces an increase in cell proliferation and migration of tumor cells [reviewed in Ref. 7]. Additionally, it has been demonstrated that tumor growth is increased by stimulation of kinin receptors expressed on other

cells within the tumor microenvironment⁷, and that bradykinin and its receptors are involved in pathogenesis of numerous common cancers (gastric⁸, hepatocellular⁹, brain¹⁰, bladder¹¹, renal¹², prostate¹³ and breast¹⁴). These data point out that, because of possible activation of BKB2R with antibodies elicited by influenza vaccine, safety of this vaccine in cancer patients is an important issue.

Screening of the clinical trials database (clinicaltrials.gov) for trials that investigated safety of the influenza vaccine in cancer patients with solid tumors (literature data connect pathogenesis of this type of tumors with BKB2R-pathway) revealed only five completed studies (Table 1). Patients were monitored in the period between 21 days and 6 months following vaccination and results were released only for one study (NCT01666782 in Table 1) for the monitoring time frame of 21 days. These short-term studies suggest that influenza vaccination is effective and safe in cancer patients in general^{1,15–17}. However, long-term studies might be needed to test the hypothesis that if antibodies elicited by the seasonal flu vaccine may contribute to activation of BKB2R in cancer patients with potentially far-reaching consequences.

In conclusion, previously published results suggest that influenza vaccines could produce antibodies with BKB2R-agonistic activity. On the other hand, experimental and clinical data showed that activation of the bradykinin pathways plays an important role in pathogenesis of several common solid tumors. All these data suggest that until the role of the influenza vaccine in activation of BKB2R is clarified, vaccination of cancer patients against flu should be taken with some caution, and vaccines need to be monitored beyond the flu season. This especially concerns children with cancer, who represent the most vulnerable population of oncology patients. In addition, previous *in silico* analysis of informational properties of BKB2R and HAs from different

Table 1. Clinical trials of safety of influenza vaccine cancer patients.

Clinical study	ClinicalTrials.gov Identifier	Monitoring time frame
Clinical Trial to compare the Immunogenicity, Safety, and Tolerability of an Adjuvanted A(H1N1) Influenza Vaccine Versus Non-Adjuvanted A(H1N1) Influenza Vaccine in Patients With Invasive Solid Tumors	NCT01031719	3 months
Safety of a Flu Vaccine Spray, Called FluMist, in Children with Cancer	NCT00112112	42–180 days
A Study of a Live Intranasal Influenza Vaccine in Children With Cancer (FMRESP)	NCT00906750	6 months
Study Comparing High-Dose Flu Vaccine to Standard Vaccine in Cancer Patients Less Than 65 Receiving Chemotherapy (IMMUNE)	NCT01666782	28 days
Immunogenicity of Fluzone HD, A High Dose Flu Vaccine, In Children With Cancer or HIV	NCT01205581	21 days

influenza A viruses suggested that flu vaccines are not equally efficient in production of agonistic antibodies for BKB2R⁴. This opens the possibility for selection of antigens with low crossreactivity with BKB2R and design influenza vaccines incapable of inducing production of cross-reactive antibodies for safer use in cancer patients.

Competing interests

No competing interests were disclosed.

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This paper by Paessler and Veljkovic on the potential link between bradykinin-2 receptor (BKB2R) and influenza virus is an interesting, as well as a provocative follow-up of previous work by this group published in 2014¹. In that paper, sequence homology between influenza virus and human proteins was investigated by the informational spectrum method (ISM analysis). BKB2R, although it didn't get the highest amplitude or signal:noise values on the IS frequency, was studied in more detail because of its association with cardiovascular disease. It should be noted that conventional BLASTing of BKB2R with a range of influenza A strains (including A/Beijing/262/95 (H1N1), A/NewCaledonia/20/1999(H1N1)), shows very limited sequence homology. Thus far there is no direct evidence that influenza vaccination induces antibodies (agonistic or antagonistic) that would bind to BKB2R, but is interesting to speculate about possible consequences.

Bradykinin, signaling via BKB2R (as well as BKB1R) is an important regulator molecule in inflammatory and vascular processes including angioedema, tissue permeability, vascular dilation, and smooth muscle contraction. Bradykinin also has been shown to promote proliferation and invasion of cancer cells, as indicated in the manuscript.

Indeed, natural or experimental infection with influenza virus induces bradykinin secretion, which can be measured in nasal secretions during the first days after onset of symptoms (before specific antibodies are formed)². In the above context, this would argue in favor of vaccination to prevent influenza infection.

The immunogenicity and safety (including potentially negative effects) of influenza vaccination in (pediatric) patients with cancer have been published: NCT00112112³, NCT00906750⁴. In an accompanying editorial of latter study, the need for influenza vaccination of children with cancer is emphasized⁵. Most studies have limited follow-up, related to the seasonal nature of influenza

vaccination. Prolonged monitoring of vaccinees therefore is warranted. Patients with solid tumors are treated with chemotherapy and/or checkpoint inhibition therapy. From that perspective, BKB2R agonists have been investigated as adjuvant therapy. While being effective in animal models⁶, thus far it is not being used in patients. It could be concluded that the intricate relation between bradykinin and influenza, also in the context of vaccination of patients with cancer required further study. Current clinical and immunological data however would not support a safety concern.

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Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Partly

Are arguments sufficiently supported by evidence from the published literature?

Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: medical immunology (GTR), oncology (MW), influenza vaccination (both)

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have

significant reservations, as outlined above.

Author Response 21 Mar 2018

Veljko Veljkovic, Biomed Protection, Galveston, USA

Response to Referee 1

The Referee's statement: "In that paper, sequence homology between influenza virus and human proteins was investigated by the informational spectrum method (ISM analysis)." is wrong because ISM is the bioinformatics approach for analysis of the information encoded in the proteins. For this reason, results obtained by ISM and BLAST are incomparable. The same concerns the Referee's remark that immunological cross-reactivity between influenza antigens and BKB2R is unlikely because of "very limited sequence homology". The cross-reactivity between proteins with the common ISM frequency is experimentally proved, even in the absence of their sequence homology (Koma et al. Sci Rep 2018;8:1882).

Referee's conclusion that vaccine is beneficial for cancer patients because it prevents bradykinin secretion is correct, but it is not in contrast with conclusions in this article, which concern the different aspect the safety of influenza vaccine. It is important correctly assess positive and negative effects of vaccination for cancer patients taking into account a very low effectiveness of influenza vaccine.

Referee pointed out some positive anticancer effects of activation of BKB2R in animal model. It is hard to believe that this will be tested in humans, taking into account numerous harmful effects of activation of BKB2R in cancer patients.

Finally, Referee concluded "that the intricate relation between bradykinin and influenza, also in the context of vaccination of patients with cancer required further study." and that: "Most studies have limited follow-up, related to the seasonal nature of influenza vaccination. Prolonged monitoring of vaccinees therefore is warranted." It is exactly what we suggested in the conclusion of this article.

Competing Interests: No competing interest

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In this article, the authors suggest that flu vaccine could elicit antibodies against BKB2R. This, in turn, would lead to BKB2R activation and, therefore, activate/reinforce pro-tumoral pathways. The suggestion for the possible generation of anti-BKB2R antibodies comes from an in silico work of the authors and is supported by the observation that BKB2R monoclonal antibodies inhibit influenza virus replication in cell lines (data from a patent). These considerations are not solid enough to advise against the flu vaccination of cancer patients. Moreover, the authors should clearly state in the text that there are no experimental data yet supporting their suggestion for anti-BKB2R antibodies production upon flu vaccination.

The authors suggest that BKB2R antibodies would activate the receptor. However, reasoning in the same way, these antibodies should also inhibit BKB2R, or mediate immune response toward cells expressing this receptor, thus showing anti-cancer properties. This latter is another point of view that should be considered in the discussion.

Taking together, these considerations suggest that advise against the flu vaccination is premature, while further studies that aim to clarify if the vaccine against influenza A viruses could elicit agonistic antibodies for BKB2R are needed and could have an impact on flu vaccination choice as well as on cancer treatments.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Mar 2018

Veljko Veljkovic, Biomed Protection, Galveston, USA

Response to Referee 2

Referee stated following: "These considerations are not solid enough to advise against the

flu vaccination of cancer patients.” and “that advise against the flu vaccination is premature, while further studies that aim to clarify if the vaccine against influenza A viruses could elicit agonistic antibodies for BKB2R are needed and could have an impact on flu vaccination choice as well as on cancer treatments.”

In this article authors not advise against flu vaccination but suggested “that until the role of the influenza vaccine in activation of BKB2R is clarified, vaccination of cancer patients against flu should be taken with some caution, and vaccines need to be monitored beyond the flu season”. Referee 1 gives the similar suggestion: “Most studies have limited follow-up, related to the seasonal nature of influenza vaccination. Prolonged monitoring of vaccinees therefore is warranted.”

Antibodies directed against G-protein coupled receptors (GPCR) can act as receptor agonists or antagonists (see Dragun et al. *Thromb Haemost.* 2009;101:643). Taking into account (i) that activation of BKB2R pathway has cardioprotective effect and (ii) that influenza vaccine showed protection against cardiovascular disease, it was reasonable to hypothesize that antibodies elicited by influenza vaccine act as agonist of BKB2R. If these antibodies would act as antagonist of BKB2R than influenza vaccine should be harmful for CVD patients.

Competing Interests: No competing interest

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