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OPINION
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The PATHOGENesis of Food Allergy

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SUMMARY

The current paper suggests that egg allergy may arise due to microbial proteins that are homologous to egg allergens. These microbial proteins elicit an allergic response and lead to the development of specific microbial IgE molecules. These molecules cross-react with egg allergens and result in egg allergy. Some examples of microbial proteins that share similar sequences as egg allergens are presented in this paper.

Food allergy has a negative impact on the quality of life and nutrition. In addition, it can lead to life-threatening reactions. The pathogenesis of food allergy is still not fully understood. Many young children develop food allergy with no known prior ingestion of the food allergen in question. The strong connection between food allergy and atopic dermatitis has been well-documented. While the prevalence of food allergy in the general pediatric population is 4–5%, the prevalence of food allergy in atopic dermatitis is at least 20% (1). This connection between food allergy and atopic dermatitis has led to the suggestion that the skin may be the site of food IgE sensitization, leading to food allergy. The dual-allergen-exposure hypothesis suggests that food allergens are sensitized via eczema, whereas early gastro-intestinal exposure leads to tolerance (2). This hypothesis is supported by multiple basic studies that provide evidence for IgE sensitization via the skin [reviewed in (3)]. In addition, it has been shown that environmental level of peanut allergens is increased in children who developed peanut allergy (4). The early introduction of peanut has led to the prevention of peanut allergy (5). Likewise, early introduction of egg has also met with some success, although the results were not as consistent (3). It has been suggested that improvement in eczema, in addition to early introduction of egg, is needed for successful prevention of egg allergy (6). This suggestion further highlights the importance of skin in the pathogenesis of food allergy. A hypothesis is proposed here that the interaction between the neonatal skin and microbial proteins is important for the development of IgE sensitization and egg allergy.

The current hypothesis predicts the presence of microbial proteins that are homologous to egg allergens. **Table 1** shows the microbial proteins that share homology with the IgE-binding domains of Gal d 1 (ovomucoid) (7). Four out of the 6 microbial proteins share > 60 % identity with a clinically-relevant IgE-binding region of Gal d 1 (FNPVCGTDGVTYDN) (8). Significant homology was also found between microbial proteins and Gal d 2 (ovalbumin), but no homology was found in the IgE-binding domains of Gal d 2 (9) (data not shown). To further confirm the correlation between microbial proteins and Gal d 1, prospective studies may be carried out to look for these microbial pathogens in atopy-prone neonates and correlate with neonates who eventually develop allergy to Gal d 1. These microbial pathogens can also be inoculated in animal models to show the development of specific IgE that cross-react with Gal d 1. Atopy-prone neonates who are born to parent with atopic dermatitis, asthma or allergic rhinitis have inherent skin barrier defects that predispose them to develop atopic dermatitis. Microbial pathogens are capable of evading these barrier defects to interact with the cutaneous immune system in these children. The processing of microbial proteins by antigen-presenting cells and subsequent presentation of antigenic peptides to T helper type 2 cells leads to the production of IL-4 and IL-13, which induce B cells to express specific IgE molecules. Bacterial allergy has been described more than half a century ago (10). It is

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TABLE 1 | Microbial proteins that share similar sequences as the IgE-binding domains of Gal d 1.

Microbe	Microbial protein*	NCBI/GenBank ref. sequence	Homologous egg allergen*
Sphingobacteriales (bacteroidetes)	T9SS type A sorting domain-containing protein	WP_088748939.1	Gal d 1

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           190             200       210               220       230       240       250
Microbe FDCINPAQINP-----VAPCPAIYAPVCGCDGITYDNDC------VAQNMGVTTFVPGVCGEPTIFQPCLDPNAVNTNPC
        ..: . :. .      .. :   . :::: ::.::::.:      : :. .:     : : .  .    .: .      :
Gal d 1 MNCSSYANTTSEDGKVMVLCNRAFNPVCGTDGVTYDNECLLCAHKVEQGASVDKRHDGGC-RKELAAVSVDCSEYPKPDC
             100       110       120       130       140       150       160       170

            260       270             280       290       300       310       320
Microbe PVNYEPVCGCNGVTYVNSCYATRA-----GVLSYTA-GQCEITTYEVCADNAVEIGVPFVPNTIYIWSPATGLSCDNCPD
         .. .:.:: .. :: :.:     :     :.:. .  :.:
Gal d 1 TAEDRPLCGSDNKTYGNKCNFCNAVVESNGTLTLSHFGKC
              180       190       200       210
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Bacteroidetes bacterium (bacteroidetes)	T9SS C-terminal target domain-containing protein	RMG76445.1	Gal d 1

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                                                  420               430       440       450
Microbe CYDPQNVVNGGYTTVDPLTGIITMNCPADSSEPVCGCDGITYPSAC------VAEASGVTFYTAGQCGQCVEPAQMN---
        : .   .  ..:...    : . . :   . .:::: ::.:: . :       : ....:     : : . .  ....
Gal d 1 CKETVPMNCSSYANTTSEDGKVMVLC-NRAFNPVCGTDGVTYDNECLLCAHKVEQGASVDKRHDGGCRKELAAVSVDCSE
          90       100       110       120       130       140       150       160

            460       470             480       490       500       510       520
Microbe -PDTLCPYVYDPVCGCNDITYMNAC-----MAEAAGVVSYTP-GPCSGSSIWCDNATPIQCGDFLPYEKTTGLVNKISNY
         :   :     :.:: .. :: : :     ..:. :... .  : :
Gal d 1 YPKPDCTAEDRPLCGSDNKTYGNKCNFCNAVVESNGTLTLSHFGKC
          170       180       190       200       210
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Methanophagales archaeon (Archaea)	Kazal-type serine protease inhibitor domain-containing protein	RCV64500.1	Gal d 1

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                     70        80              90          100       110       120
Microbe -KQADMCTADYNPVCGDNGKTYANKCTACS-----SGEVNAWTVGECS---TAVWVNCTEEEKQAEVCTQEYDPVCGDDG
         :   .:.  .::::: .: :: :.:  :.     .. :.    : :    .:: :.:.:  :    :: :  :.::.:.
Gal d 1 GKVMVLCNRAFNPVCGTDGVTYDNECLLCAHKVEQGASVDKRHDGGCRKELAAVSVDCSEYPKPD--CTAEDRPLCGSDN
          110       120       130       140       150       160       170       180

           130             140       150       160       170       180       190       200
Microbe ITYGNKCTAC-----SSGNVNAWTAGECPINDSSEKIAREFIENSDWYNAGPTPFNLTFVGLKPGPCTSCWTFTYEYQVV
         ::::::. :     :.:...    :.:
Gal d 1 KTYGNKCNFCNAVVESNGTLTLSHFGKC
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Candidatus Nitrosopumilus sp. NM25 (Archaea)	DUF4377 domain-containing protein	WP_109876664.1	Gal d 1

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       290       300       310       320             330       340       350       360
Microbe AKSLKDRGWQTKYPNFACTLEYAPVCGVDGQTYGNKC-----MISSNHVAT-KHVGECTDMIEETKGIFENALDYTTSPP
        : :.      ..::.  :: :  :.:: :..:::::     .. :: . : .: :.:
Gal d 1 AVSVD----CSEYPKPDCTAEDRPLCGSDNKTYGNKCNFCNAVVESNGTLTLSHFGKC
        160           170       180       190       200       210
```

(Continued)

TABLE 1 | Continued

Microbe	Microbial protein*	NCBI/GenBank ref. sequence	Homologous egg allergen*
Nitrosopumilus maritimus SCM1 (Archaea)	Proteinase inhibitor I1 Kazal	ABX12911.1	Gal d 1

```
       290       300       310       320               330       340
Microbe KNLEQRGWQIPLPVFACTLEYAPVCGVDGKTYGNKC----AIASSH--VTIKHVGECTNDIP
         ...    . : :   :: :  :.:: :.:::::::    :.. :.  .:..: :.:
Gal d 1 VSVDCS--EYPKP--DCTAEDRPLCGSDNKTYGNKCNFCNAVVESNGTLTLSHFGKC
       160           170       180       190       200       210
```

Nitrosopumilus (Archaea)	MBL fold metallo-hydrolase	WP_014962656.1	Gal d 1

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             250       260             270       280       290       300       310
Microbe EKQPYLRPLQQGNAGIAASD--VICAESLQL---LFKSHDGS-PACVSNDAKKKLQERGWQTSIPLLACTLEYAPVCGVD
          :::.  :. :.. ..  ..:: :...   . : :::     :  . ..  .  . . .. .: :.  . :::::
Gal d 1 -----LRPIC-GTDGVTYTNDCLLCAYSIEFGTNISKEHDGECKETVPMNCSSYANTTSEDGKVMVL-CNRAFNPVCGTD
           50          60        70        80        90       100       110       120

           320       330             340       350       360       370       380
Microbe GKTYGNSCMINSNHVAT------KHIGECSSMVEDTKGIFEKTLDYTTQPAVVDEEKGYFVTEIADDVYWLVGNGYQTMF
        : :: : :.. ...:        .: : :
Gal d 1 GVTYDNECLLCAHKVEQGASVDKRHDGGCRKELAAVSVDCSEYPKPDCTAEDRPLCGSDNKTYGNKCNFCNAVVESNGTL
          130       140       150       160       170       180       190       200
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**The protein sequences of bacteria/archaea and egg allergen, ovomucoid (Gal d 1), were first screened in microbial protein BLAST database of National Center for Biotechnology Information (NCBI) (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Homology was searched using an 80-amino-acid sliding window alignment with a default threshold for at least 35% identical amino acids (www.allermatch.org) (Wageningen University and Research) (UnitProt allergen database). Identity was based on Full Fasta 36 (http://www.allergenonline.org/databasefasta.shtml) (University of Nebraska-Lincoln).*

also known that specific IgE to staphylococcal toxins can develop in young children with atopic dermatitis (11). Bacteria such as bacteroides can be acquired during birth or they can be part of neonates' microbiome (12). The skin also contains a wide array of microbial pathogens that can participate in the development of allergy (13). More recent data suggests that many microbial organisms (e.g., proteobacteria and archaea) previously thought to exist only in the environment such as soil, fresh or marine waters are now found to be part of the human skin microbiome (14, 15). Proteobacteria and bacteroides are also known to be present in atopic dermatitis lesions (16). The current proposal is conceptual that microbial proteins can be a sensitizing source in the development of food allergy in predisposed children. Preliminary data also suggests the presence of homologous proteins between microbes and other food allergens including peanut and cow's milk (unpublished data). Whether these microbial pathogens have a direct interaction with neonates, leading to the development of specific IgE, remains to be proven. It is possible that the prevention of egg allergy requires a different approach by targeting microbial pathogens.

AUTHOR CONTRIBUTIONS

PO conceived the idea, generated the data, and wrote the paper.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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