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Mini-Review

Protein cross-reactivity and blood cancer

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ABSTRACT

Atopy is a medical term for many allergies. When a person has many allergies, a diverse number of immunoglobulin-e antibodies eliminate harmless exogenous-proteins referred to as allergens. The immunoglobulin-e antibodies formed through humoral immunity can bind to endogenous proteins based on structure homology, a cross-react immune response. An over-expression of endogenous proteins is associated with aggressive blood cancer, including leukemia, lymphoma, and myeloma. Cancer immunotherapies seek to stop or inhibit the growth of blood cancer cells. This review proposes cancer immunotherapy involving allergen-specific proteins wherein a hyper-allergenic skin cream induces immunoglobulin-e antibodies that may cross-react with over-expressed proteins associated with acute myeloid leukemia.

KEYWORDS: atopy, maladaptive immunity, cross-reactive immunoglobulin-E (cIgE), blood cancer, acute myeloid leukemia (AML).

ABBREVIATIONS

cIgE, Cross-Reactive Immunoglobulin-E; AML, Acute Myeloid Leukemia.

INTRODUCTION

The Leukemia and Lymphoma Society® communicates that one person is diagnosed with a blood cancer every 3 minutes in the United States (US), and one person dies from a blood cancer every 9 minutes [1].

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An example of a rapidly progressing blood cancer is acute myeloid leukemia (AML); an increased number of myeloid cells interferes with the production of healthy white blood cells, red blood cells, and platelets. The five-year overall survival rate for AML is 27.4 percent, according to the National Cancer Institute [2].

Chemotherapy is successful at inducing remission of AML, although the disease has a high probability of relapse. Strategies to prevent relapse involve consolidation chemotherapy, stem cell transplantation, and immunotherapy [3].

Immunotherapies under evaluation to improve the outcomes of patients with AML include Car T-cell therapy, immune checkpoint inhibitors, bispecific antibodies, and monoclonal antibodies [4].

Immunotherapy that induces allergen-specific atopy may provide insight on survival rates and quality of life for patients with AML and other hematologic malignancies. In a meta-analysis to determine if there is an association between atopy and childhood/adolescent leukemia, the researchers stated, “No association was observed for leukemia overall or AML or for any of the specific atopic conditions and AML examined separately, although there were fewer studies of AML and fewer AML cases” [5].

In a case report that diagnosed AML-M4 with atopic dermatitis as a first manifestation, the researchers stated, “The patient had a long history of exposure to chemical substances and maybe this is the direct cause of the dermatitis. Perhaps this plays a role in the pathogenesis of leukemia. But it needs further confirmation” [6].

In other research, cutaneous complications are common in patients with leukemia. However, the cause is not always immediately apparent, as there are often numerous potential etiologies [7].

In a research article titled, Atopy and Specific Cancer Sites: A Review of Epidemiological Studies, the researchers disclose that a protective effect of atopic diseases against pancreatic cancer has been shown consistently in case-control studies, but not in cohort studies. Allergy of any type appears to be protective against glioma and adult acute lymphoblastic leukemia. Most studies on atopic diseases and non-Hodgkin lymphoma or colorectal cancer reported an inverse association. The other sites identified had different and non-significant outcomes. "Further research should be dedicated to carefully defined exposure assessments of atopy as well as the biological plausibility in the association between atopic diseases and cancer" [8].

Discussion

Multicellular eukaryotic organisms are known to express proteins having similar, but not identical, molecular structure and biological function. In humans, exposure to such proteins can trigger an immune response when recognized as foreign. The humoral immune system produces immunoglobulin-e antibodies that are bio-engineered to interact with effector cells and, after that, bind to foreign proteins to expedite their removal. Humoral immunity is considered a maladaptive immune process in that the foreign protein (allergens) is often harmless to the body. This maladaptive process can form immunoglobulin-e (cIgE) antibodies that bind to endogenous proteins having structure homology, a cross-react immune response. A medical hypothesis proposes that maladaptive immunity may inhibit metastatic cancer through cross-react immune responses [9].

In humans, the S100 protein family is composed of 21 members that exhibit a high degree of structural similarity but are not functionally interchangeable. This family of proteins modulates cellular responses by functioning both as intracellular Ca^{2+} sensors and as extracellular factors. Dysregulated expression of multiple members of the S100 family is a common feature of human cancers, with each type of cancer showing a unique S100 protein profile or signature [10]. S-100 proteins are frequently over-expressed in AML [11]. An investigative topical hyper-allergenic composition (e.g., skin cream) designed to inhibit the expression of S-100 proteins may propose the following allergens:

An allergen from *Timothy* (Grass Pollen) may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins. The polcalcin allergen rPhl p 7 (9 kDa) and the human S-100 proteins (9-13 kDa) are $Ca2^{+}$-binding proteins with helix-loop-helix conformation [12, 13].

An allergen from *Olea European* (Olive Tree Pollen) may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins (9-13 kDa). The polcalcin allergen Ole e 3 (9.2 kDa) secondary structure is composed of 52% α-helix, 10% β-strand, 29% β-turn and 9% non-regular conformation [14].

Allergens from *Petula Bendula* (European White Birch) may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins (9-13 kDa). The polcalcin-like allergen Bet v 3 (24 kDa) and the polcalcin allergen Bet v 4 (7-8 kDa) are proteins that belong to a novel class of Ca^{2+}-binding proteins [15, 16].

An allergen from *Juniperus Oxycedrus* (Prickly Juniper Tree) may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins (9-13 kDa). The polcalcin allergen rJun o 2 has sequence similarity to calmodulins (16.7 kDa) [17]. The inhibition of the calmodulin CaMKII results in growth arrest and differentiation in myeloid leukemia cells [18].

An allergen from Bermuda Grass pollen may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins (9-13 kDa). The polcalcin allergen Cyn d 7 has been identified as a 12 kDa protein [19].

An allergen from *Alnus glutinosa* (European Alder) may induce the humoral immune system to produce cIgE antibodies that inhibit the expression of human S-100 proteins (9-13 kDa). The polcalcin allergen rAln g 4 has been identified as a 9.4 kDa protein [20].

CONCLUSION

Skin creams formulated with polcalcin-like allergens may provide topical hyper-allergenic compositions that induce cIgE antibodies and inhibit S-100 proteins that are often over-expressed in acute myeloid leukemia.

AUTHOR DISCLOSURE

This review contains a discussion of an unapproved/ investigative hyper-allergenic skin cream designed to inhibit metastatic blood cancer.

CONFLICT OF INTEREST STATEMENT

Michael J. Dochniak is cofounder of Alleam, LLC, Minnesota, USA.

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