



## Review

## Allergies and childhood leukemia

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## ABSTRACT

A majority of studies to date have reported an inversed association between allergies and childhood leukemia. However, this association is likely an indirect one and may represent some shared underlying immune mechanisms that have been explained in the context of the “hygiene hypothesis”, which has been thought to play an important role in the development of both allergies and childhood leukemia. This review focuses on what we know so far about the role of various immune cells (Th1, Th2, T regulatory and Th17 cells) in the development of allergies and how they may potentially be related to the etiology of childhood leukemia. In addition, the utilities of genetic and molecular studies to disentangle the association between allergies and childhood leukemia and to elucidate the biological mechanisms are also discussed.

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## Epidemiology of childhood leukemia

Childhood leukemia is the most common cancer among children in the U.S. and accounts for 31% of all cancer cases occurring in children under the age of 15 (or approximately 3000 cases each year) [1]. The incidence of childhood leukemia in the U.S. increased an average of 0.7% per year between 1975 and 2002 with an average of 1.3% increase per year between 1975 and 1988 and 0.2% increase between 1988 and 2002 [2]. There are few established risk factors of childhood leukemia

including sex, age, race, exposure to ionizing radiation, and congenital diseases (e.g. Down syndrome, neurofibromatosis) [1]; however, these risk factors account for only 10% of the childhood leukemia cases [3].

## Current etiologic hypothesis of childhood leukemia

Chromosomal translocations are commonly present in childhood leukemia and many of the chromosomal translocations are present before birth [4]. The most frequent translocations associated with ALL and AML are *TEL-AML1* [t(12;21), 20% of ALL] and *AML1-ETO* [t(8;21), 15% of AML], respectively [4]. Although the prevalence of the *TEL-AML1* fusion gene is approximately 1% in the fetal cord blood sample, the lifetime occurrence of ALL with *TEL-AML1* is 1 in 10,000, meaning

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that only 1 out of 100 children born with the *TEL-AML1* translocation will develop leukemia [5]. *In vitro* and animal studies have shown that either expression of *TEL-AML1* or *AML1-ETO* fusion protein alone can establish a covert preleukemic clone [6,7] but the expression of these protein is not sufficient to transform hematopoietic cell lines into leukemic cells [8,9]. Other animal studies have shown that *TEL-AML1* or *AML1-ETO* together with a second mutation in other genes may induce acute leukemia [10–13]. These data strongly suggest that in addition to the prenatal initiating events, postnatal promoting events are required for the development of childhood leukemia.

Though many postnatal exposures have been assessed by studies of childhood leukemia, two major hypotheses, Greaves' "delayed infection" hypothesis [14] and Kinlen's "population mixing" hypothesis [15], have remained in the forefront. The "population mixing" hypothesis, states that the risk of childhood leukemia increases when populations from different geographic areas come together, increasing the contact level between susceptible and infected individuals [15]. The "delayed infection" hypothesis states that the infection early in life primes the children for normal immunological development and the lack of this "priming" by early-life infection would result in an abnormal immune response to infections later in life leading to the development of leukemia [14]. The difference between these two hypotheses is that "population mixing" hypothesis suggests the existence of a leukemia-causing agent(s) where as the "delayed infection" hypothesis does not. However, both hypotheses have a common theme which involves the abnormal host immune responses to infectious agents and such responses predispose a child to develop leukemia.

### Hygiene hypothesis

The "hygiene hypothesis" was first proposed by Strachan in 1989 to explain the rising prevalence of allergies in the western population [16]. In that study, Strachan reported that the number of older children in the household was inversely associated with having hay fever or eczema [16]. Strachan hypothesized that early childhood infection may be protective against allergies and that the declining family size and improved sanitation may have reduced the chance for early childhood infection and thus the rise in the prevalence of allergies [16]. Since then other epidemiologic studies have reported an inverse association between allergies and various proxy measures of early childhood infection including higher birth order [17–21], and early daycare attendance [22,23].

The "hygiene hypothesis" is also relevant to childhood leukemia. Similar to allergies, a reduced risk of childhood acute lymphoblastic leukemia has been observed with higher birth order [24,25] and early daycare attendance [26–29]. Studies of early childhood infection have yielded mixed results with risk of childhood leukemia ranging from inverse association [28,30,31], no association [27,32,33], to positive association [34]. However, most of these studies focused on symptomatic infection when the asymptomatic infection and the commensal organisms are also likely to be crucial if not more important in the context of the "hygiene hypothesis". An additional consideration is that few studies distinguish early-life infections (which would be immune-modulating) from disease-proximate infections (which would induce risk).

### Allergic diseases and childhood leukemia

Since both allergies and childhood leukemia were thought to have an etiology that is consistent with the "hygiene hypothesis", researchers have also assessed the association between the two diseases. A total of nine case-control analyses on the association between allergy and childhood leukemia have been published [30,35–42]. Seven case-control studies based on self-reported data reported an inverse association between some forms of allergic

diseases and childhood leukemia or acute lymphoblastic leukemia (ALL) [30,35–41]. In contrast, a medical record-based study reported that the risk of ALL was elevated for hives, and asthma [40]. However, another medical record-based case-control study showed that certain allergic disorders (eczema and hay fever) are inversely associated with the risk of ALL and c-ALL [42]. Overall, the majority of the studies to date report an inverse association between having some form of allergies and risk of childhood leukemia or ALL. However, these observations are not what one would predict since evidence has suggested that delayed exposure to infection is associated with an increased risk of both allergy and childhood leukemia, and thus a positive correlation between the two diseases would be expected. Aside from the potential study biases inherent to the case-control study design and self-reported data (e.g. selection of control subjects, recall bias), the unexpected inverse association between allergies and childhood leukemia suggests that the relationship is not a direct causal one, but that the two diseases may share some underlying biological mechanisms.

### Th1, Th2, Th17, and T-regulatory cells

Since the proposal of the "hygiene hypothesis" by Strachan as an explanation for the increased prevalence of allergies in the western population [16], epidemiological and laboratory studies have been performed to provide a biological explanation for the "hygiene hypothesis". The first explanation is called the "missing immune deviation" hypothesis [43]. Newborns are shown to have largely T helper 2 (Th2)-skewed immune profiles [44] and in normal non-atopic individuals, a shift occurs from Th2-dominant to T helper 1 (Th1)-dominant immune profiles with increasing age [45]. It has been suggested that the driving force for this immune shift is the microbial exposures which induce the innate immune cells (e.g. dendritic cells) to produce IL12 and other cytokines important for the development of Th1 responses [43]. The "missing immune deviation" hypothesis explains the increasing prevalence of allergy in the developed countries as a result of reduced microbial burden that leads to reduced Th1 polarization [43]. If the "missing immune deviation" hypothesis is accurate, it is expected that the rise in the prevalence of allergic diseases, which is associated with Th2 responses should be met with a concurrent decrease in the prevalence of Th1-associated autoimmune diseases. However, the opposite has been observed, with the concurrent rise in the prevalence of allergic diseases (e.g. asthma, rhinitis, and atopic dermatitis) and autoimmune diseases (e.g. multiple sclerosis, type I diabetes, and Crohn's disease) [46]. In addition, helminth infection, which induces Th2 responses, is not associated with allergy [47].

The search for a biological explanation for the "hygiene hypothesis" subsequently shifted from the "missing immune deviation" hypothesis to the "reduced immune suppression" hypothesis [43] after Sagaguchi et al. (1995) demonstrated the role of T-regulator cells (Tregs) in autoimmunity [48]. Tregs can be divided into natural-occurring Treg which expresses FOXP3 transcription factor and FOXP3-adaptive Treg (Tr1 and Th3) [49]. Tregs are able to prevent overactive immune reactivity by suppressing both adaptive and innate immune responses, and thus play important roles in maintaining immune tolerance to self-antigens and in controlling anti-microbial, anti-tumor, and anti-graft responses [49]. In the "reduce immune suppression" hypothesis, the reduced microbial burden leads to reduced activities of Tregs and results in overactive Th1 and Th2 activities, which may explain the concurrent rise in the prevalence of both allergic and autoimmune diseases in the developed countries [43]. However, as noted by Romagnani (2004; 2007), new support for the "missing immune deviation" has emerged, suggesting that it may be premature to abandon such hypothesis, and he suggested that the development of allergy may be due to both "missing immune deviation" and "reduced immune suppression" [43,50].

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