

focused on IGF-1 signaling. Mutations that blunt an insulin/IGF-1-like pathway in simple, postmitotic organisms markedly increase the adult life span<sup>5</sup>. Recently, genetic manipulations in mice showed that eliminating the insulin receptor in adipose tissue<sup>6</sup> or reducing IGF-1 receptor levels throughout the animal<sup>7</sup> also increase longevity, albeit modestly. Thus, insulin/IGF-1 signals promote aging in nematodes, fruit flies and mice, at least in protected environments such as laboratories. So does p44 overexpression increase such signals in mice? Indeed it does. p44-transgenic mice had higher circulating IGF-1 levels and higher IGF-1 receptor levels in mitotically active tissues. In transfection studies, p44 overexpression stimulated transcription of the gene encoding the IGF-1 receptor, and enhanced IGF-1 signaling by altering levels of regulatory components that act at multiple points in the pathway. Thus, hyperactivity of p53, caused by overexpression of p44, upregulated the IGF-1 signaling axis.

Could this cause premature aging? After all, IGF-1 promotes growth and has been implicated in driving cancer progression<sup>8</sup>. Why, then, are p44-transgenic mice small and resistant to cancer? Maier *et al.* provide two answers (Fig. 1).

First, one of the genes controlled by p53 encodes p21, a potent cell-cycle inhibitor. Active p53 controls many genes, and the effects of p44 on this regulation are complex—depending on the p44 level and target gene, p44 can augment or blunt p53-dependent regulation. In the case of p21, p44 enhanced its expression in mice and cells<sup>3</sup>. Thus, p44 may promote cell cycle arrest through p21, despite robust growth (IGF-1) signals. Indeed, cells from p44-transgenic mice showed reduced proliferation, rather than smaller size, suggesting that p44 augments p53-regulated growth arrest. This augmentation could also explain the cancer resistance of p44-transgenic mice.

The second answer is less straightforward, but intriguing. Maier *et al.* showed that robust IGF-1 signals engage a fail-safe mechanism that shuts down proliferation. This fail-safe mechanism, implemented in part by sustained ERK activity, causes senescence in mouse and human cells<sup>9</sup>. Cellular senescence is an irreversible arrest of proliferation, accompanied by changes in cell function, that suppresses tumorigenesis in mammals<sup>10</sup>. Indeed, cultures from p44-transgenic mice accumulated senescent cells much more readily than non-

transgenic cultures; this accumulation was blocked by an ERK inhibitor. Thus, the small size and tumor resistance of p44-transgenic mice can also be explained by extensive cellular senescence, driven in part by over-robust IGF-1 signaling.

We are still left, then, with the question of why p44-transgenic mice age prematurely. Because senescent cells are dysfunctional and accumulate with age, they have been proposed to cause or contribute to aging in mitotic tissue<sup>10</sup>. Thus, the senescence response may be antagonistically pleiotropic, protecting complex organisms from cancer early in life but contributing to aging late in life. p44-transgenic mice may therefore resist cancer, but age rapidly, because of accelerated accumulation of senescent cells.

The new findings indicate that hyperactive p53 can drive aging, at least in some tissues, by upregulating IGF-1 signals, and offer intriguing explanations for the small size, cancer resistance and accelerated aging of p44-transgenic mice (Fig. 1). They also raise a host of questions. Does active

p53 normally upregulate IGF-1 signaling, or only when p44 is present? Is this upregulation an unappreciated p53/p44 function that promotes tissue (as opposed to DNA) repair? Does p53 drive aging by stimulating apoptosis<sup>2</sup>, senescence, or both? Whatever the case, p53 clearly orchestrates an exquisite equilibrium between competing and counter-regulatory pathways that balance tissue renewal and tumor suppression. Understanding this balance is crucial if we hope to optimize protection from cancer while minimizing aging.

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## Flu strikes the hygiene hypothesis

Dale T Umetsu

**According to the 'hygiene hypothesis', viral infections prevent the development of asthma and other atopic diseases. Influenza virus appears now to enhance, rather than inhibit, the development of asthma and allergic responses.**

As anyone with asthma knows, respiratory viral infections are hazardous to their health. Such infections, which can rapidly precipitate the development of asthma symptoms, cause nearly 80% of asthma exacerbations in children and in adults<sup>1,2</sup>. Infection with viruses such as respiratory syncytial virus, parainfluenza, influenza and rhinovirus are closely associated with the development of wheezing, pulmonary inflammation and airway obstruction. In the March issue of *Nature Immunology*, Dahl *et al.* use a mouse model of asthma to show how influenza virus exacerbates the inflammatory response in the lung, resulting in asthma<sup>3</sup>.

Although influenza and other respiratory viruses unquestionably cause respiratory exacerbations in patients with asthma, Dahl *et al.* point out that influenza virus induces large quantities of IFN- $\gamma$  and a T-helper type 1-polarized immune response, a form of immunity responsible for cell-mediated and cytotoxic reactions. Because type 1 responses can inhibit T-helper type 2 responses, which are associated with humoral immunity and the development of asthma, influenza infection should inhibit allergic asthma. This would be consistent with the hygiene hypothesis, which states that infections in general have the capacity to protect against, rather than exacerbate, the development of asthma and allergies.

This idea that infections protect against the development of asthma and allergies was first suggested by Strachan, who noted

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that the risk of developing asthma and allergies was inversely related to the number of children in the family<sup>4</sup>. This inverse relationship in large families is thought to be due to the higher incidence of infections that are transmitted in larger families. Similarly, other epidemiological studies have shown that early placement in daycare settings, and presumed exposure to infectious agents, protect against the development of asthma, allergic rhinitis and atopic sensitization<sup>5</sup>, as does exposure to farm animals<sup>6</sup>, tuberculosis<sup>7</sup>, endotoxin<sup>8</sup>, and dogs or cats<sup>9</sup> in early life (Fig. 1).

Improved hygiene in industrialized countries, by removing these 'protective' environmental effects, is proposed to have caused the dramatic increase in the prevalence of asthma and allergy, which has doubled in the past two decades. However, the specific immunological mechanisms and specific infectious agents that are responsible for this inverse relationship between infections and asthma are not at all clear.

Given the high profile of the flu this year—from the recent avian flu debacles in Southeast Asia to the emergence of the vaccine-resistant Fujian strain—there is even more interest in understanding the immunobiology of influenza in the lung and its relationship to asthma.

Investigators have previously shown that inflammation accompanying acute influenza infection greatly exaggerates allergic and respiratory responses<sup>10,11</sup>. Dahl *et al.* show that in a mouse model of asthma, the effects of infection with influenza virus persist in the lungs for weeks after recovery from infection. After viral clearance, the authors found an increase in the number of mature dendritic cells in the lung producing interleukin-12 and expressing high levels of costimulatory molecules (CD40, CD80, CD86 and major histocompatibility class II). In addition, infection with influenza increased airway inflammation, the cornerstone of asthma, although airway hyperreactivity, another important feature of asthma, was unchanged. Moreover, adoptive transfer of the dendritic cells from the lungs of mice that had recovered from influenza infection increased allergen-induced pulmonary inflammation in the recipient mice.

Because transfer of dendritic cells from previously infected mice could recapitulate the effects of influenza on airway disease, we can conclude that influenza alters the biology of the lung to promote, rather than suppress, subsequent allergic airway dis-

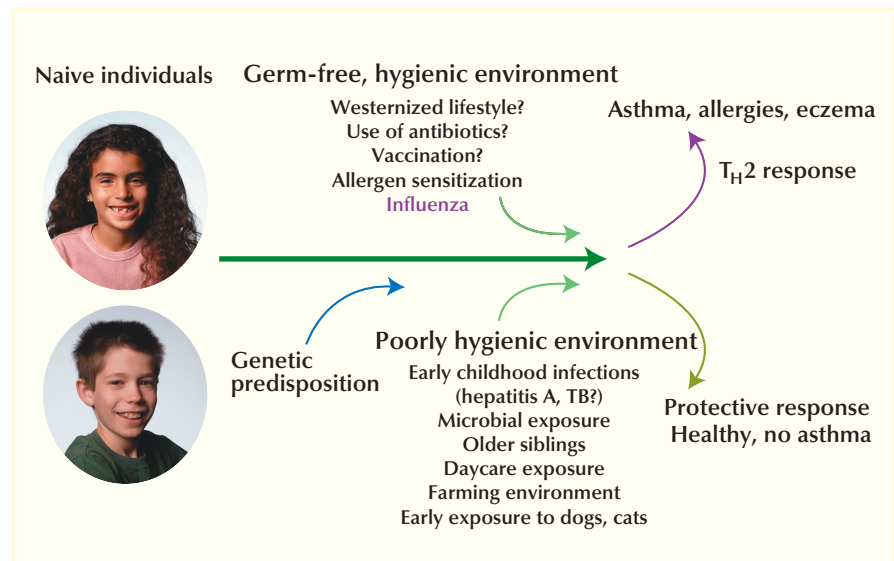


**Figure 1** The environment affects the development of asthma and allergies. According to the hygiene hypothesis, infections with bacteria or viruses contracted from siblings or peers in daycare centers enhance the maturation of the immune system, resulting in protection against asthma and allergy. In the absence of these stimuli, such as in a germ-free, hygienic environment, the immune system follows a T-helper type 2 (T<sub>H</sub>2) pathway, resulting in enhanced development of asthma, allergies and eczema. Infection with influenza virus, as examined by Dahl *et al.*, may in some instances predispose towards allergic asthma.

ease. Influenza infection enhanced type-1 responsiveness in the lung, but this worsened, rather than inhibited, airway inflammation, consistent with other studies showing that type-1 responses in the lung do not counterbalance type-2 responses<sup>12</sup>. These results suggest that other types of responses, such as regulatory (CD25<sup>+</sup>) T-cell responses downmodulate type-2-driven inflammation in asthma.

What do these results say about the hygiene hypothesis and the effects of infection on asthma? First, these results suggest that we should not abandon good hygiene (or the use of vaccines or antibiotics) in patients, because at least some infections such as influenza have clear detrimental effects on health and on asthma development.

Second, we should continue to study influenza infection. Although influenza infection of one strain of adult mice did not reduce the likelihood of developing asthmatic inflammation in the immediate recovery period, it is possible that in young children, over longer periods of time, the cumulative effect of respiratory infections may in some way alter the lung environment and reduce asthma symptoms. Cohort studies indicate that although early respiratory viral infections result in increased wheezing in infancy, colds in infancy are associated with reduced wheezing at ages 6

and 7 (ref. 5), suggesting that protective (or harmful) effects are likely to depend on a complex mixture of exposure time, environmental cofactors and genetics.

Third, it is possible that only a few specific infectious pathogens are responsible for the salutary effects associated with poor hygiene; other infectious pathogens must therefore be examined. For example, infection with hepatitis A virus (HAV), *Toxoplasma gondii* and *Helicobacter pylori* are associated with reduced likelihood of developing asthma and allergies<sup>13</sup>. HAV may be particularly important, as the gene encoding the HAV receptor in humans, TIM-1, has been associated with protection against allergy and asthma in individuals who have been exposed to HAV<sup>14</sup>. Furthermore, bacterial colonization of the gastrointestinal tract with bifidobacteria or lactobacillus strains has been associated with reduced allergies.

It is therefore very possible that only a handful of pathogens, such as HAV or some commensal bacteria, actually limit the development of asthma and allergy, and that only certain 'less hygienic' conditions reduce the development of asthma and allergies. Examination of these infectious agents and the genes that regulate responses to them are likely to provide important insight into the immune mechanisms and regulatory T-cell responses that

protect against the development of asthma and allergies. These studies are also very likely to suggest future therapies for these very common disorders, so that we can continue to recommend good hygiene, rather than eating dirt<sup>15</sup> or moving to a farm.

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## Aurora kinases dawn as cancer drug targets

Edward A Sausville

**A new anticancer compound interferes with aurora kinases, regulators of mitosis. We can now hope for the biology of these kinases to inform clinical trials (pages 262–267).**

There are many ways to stop a cell from dividing. Disordered spindle function, for instance, may be a potent signal for apoptosis. Taxanes and vinca alkaloids arrest cell-cycle progression in mitosis by interacting directly with tubulin and interfering with microtubule spindle function. These two approved anticancer drug classes activate a mitotic-phase checkpoint, which prevents cell-cycle progression.

New drug targets regulating microtubule dynamics have recently emerged (Figs. 1 and 2). Agents directed at these targets may be active against tumors that do not respond well to available antimetabolic agents, or may modulate tumor sensitivity to these agents. They may have a different spectrum of toxicity, particularly related to neuronal function.

VX-680, featured in this issue<sup>1</sup>, is an advanced drug development candidate, discovered by structure-based drug design. The molecule potently inhibits Aurora kinases, recently discovered to regulate key functions in mitosis<sup>2</sup>.

The Aurora kinase family featured here emerged from a *Drosophila* phenotypic screen for defects in mitotic spindle function. Aurora mutants were so named because of the similarity of their disordered mitotic spindles to the *aurora borealis*, or Northern lights. As Aurora was also the goddess of the dawn in antiquity, VX-680 may represent the dawning of a new class of cancer therapeutics.

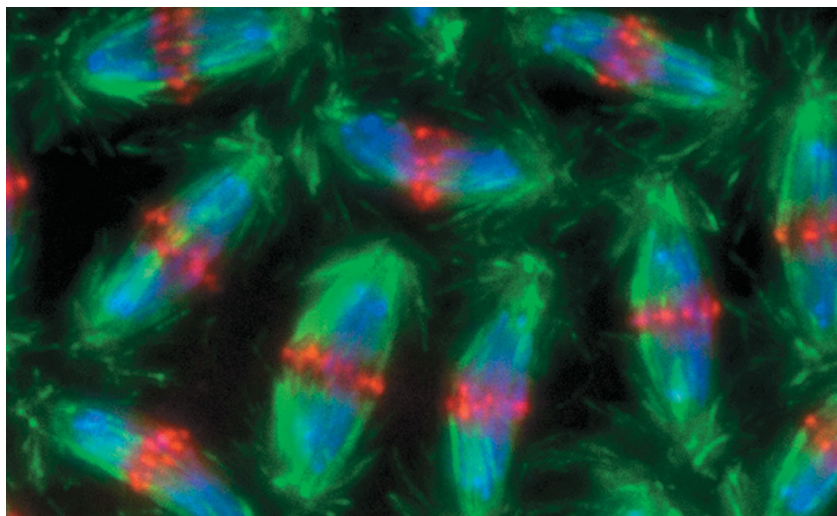


**Figure 1** Chromosomal passengers in anaphase. During mitosis, Aurora-B kinase and its activating factor, inner centromere protein (INCENP; in red), relocate from centromeres to the spindle midzone. The chromosomal passenger proteins Aurora-B, INCENP and survivin are highly conserved from yeast to humans. This image shows the highly synchronous mitoses in an early embryo of *Drosophila melanogaster*. Aurora-B and its binding partners regulate many mitotic activities, including chromosome alignment, mitotic checkpoint function and completion of cytokinesis. Microtubules are shown in green and chromosomes in blue.

In metazoans, Aurora kinases encompass three known family members. Two of them, Aurora-A and Aurora-B, have distinct but important roles in mitosis (Fig. 1 and 2). Aurora-A is normally localized in the pericentrosomal region. The centrosome replicates and divides prior to the onset of mitosis, and the daughter centrosomes serve as the two poles from which microtubules emanate to form the mitotic spindle. Aurora-A recruits several important components on the forming mitotic spindle, such as  $\gamma$ -tubulin, to the

pericentrosomal region.

*AURKA*, the gene encoding Aurora-A, is a *bona fide* oncogene, as forced overexpression of *AURKA* in certain cell types leads to transformation, and its expression seems to be higher in certain cancer cells because of gene amplification. Aurora-B is localized to the interphase chromosomes proximal to the centromere, and as chromosome condensation occurs at the start of mitosis, both Aurora-B and Aurora-A share responsibility for phosphorylating histone H3. Both

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