Can Cancer Trigger Autoimmunity?

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during axonal growth and/or migration (*5*). As neurons of different types and origins adopt different strategies to polarize (*6*), it will be interesting to explore whether apical shedding is a marginal or widespread mechanism in neurogenesis.

During mitosis of apical progenitors in the mouse cortex, a ciliary remnant associates with the centrosome at one pole of the mitotic spindle, resulting in asymmetric inheritance of a ciliary structure (*7*). Thus, the cilium is partly conserved rather than dismantled during cell division. The cell inheriting the ciliary remnant rapidly reconstitutes an apical cilium and is more likely to retain apical progenitor identity. Its sister produces a basolateral cilium, a phenomenon associated with basal progenitor identity. Basal progenitors' restricted capacity to proliferate may result from the reduced exposure of the basolateral cilium to luminal mitogens (*8*). Future research should address whether apical shedding is also present in the developing cortex, where indirect neurogenesis, through basal progenitors, is predominant, and how shedding integrates with asymmetric ciliary recycling and basolateral cilia formation.

The cortex and neural tube appear to have a remarkable plasticity of ciliary structures during neurogenesis. Although mechanistically different, asymmetric recycling of ciliary remnants (*7*), differential positioning of cilia (*8*), and dismantling of the cilium and shedding of the ciliary membrane are many ways for a cell to modulate the timing and dosage of its exposure to environmental signals. These new layers of control in signal reception are independent of the source concentration and may therefore contribute to the diversity of cell fate decisions, allowing progression of neural differentiation and maintenance of a pool of apical progenitors to occur simultaneously in a niche.

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CANCER

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A chronic autoimmune disease sometimes appears coincidently in patients with cancer.

Michele W. L. Teng[1,2] and Mark J. Smyth[1,2]

Autoimmune diseases occur when immune B and T cells fail to distinguish the body's own proteins as self and attack them, ultimately damaging tissues and organs. There are many possible causes of autoimmune diseases, such as chemical exposures, infections, and genetic factors. On page 152 of this issue, Joseph *et al*. (*1*) raise another possibility—nascent growing cancers might express new proteins (neoantigens) whose exposure to the immune system creates the potential for an autoimmune disease to develop.

Systemic sclerosis (scleroderma) is a rare chronic autoimmune rheumatic disease associated with fibrosis of the skin and widespread destruction of blood vessels that affects organs, with life-threatening consequences. Some rheumatic diseases are also paraneoplastic—they are present with cancers—and removal of the tumor or its medical treatment causes regression of the clinical manifestations. Coincidental timing of scleroderma and cancer had been observed in patients with autoantibodies specific for RNA polymerase III subunit (RPC1) (*2*). Joseph *et al*. examined tumor tissue and blood samples from 16 scleroderma patients with various types of cancer. Among the eight patients who had anti-RPC1 autoantibodies and coincident cancer, six had genetic mutations—either somatic mutations or loss of heterozygosity (only one copy of an allele) in *POLR3A* (*polymerase III polypeptide A*, the gene encoding RPC1) (see the figure, below). The other eight patients had autoantibodies to either topoisomerase 1 (anti-TOP1) or centromere protein B (anti-CENPB) and developed delayed cancer.

Interestingly, all the anti-RPC1 antibodies recognized wild-type and mutated RPC1, indicating that the humoral immune response does not directly target the area of the mutation or discriminate between mutant and wild-type versions of RPC1. But some patients with scleroderma who possessed defined *POLR3A* mutations had T cells that reacted to RPC1 protein fragments produced from the mutated gene. The reactivity was specific to the patient and peptide, but the frequencies of these T cells were comparable to those observed in other autoimmune diseases. Given that *POLR3A* mutations are exceedingly rare in cancer (0.7% overall), it is unlikely that the onset

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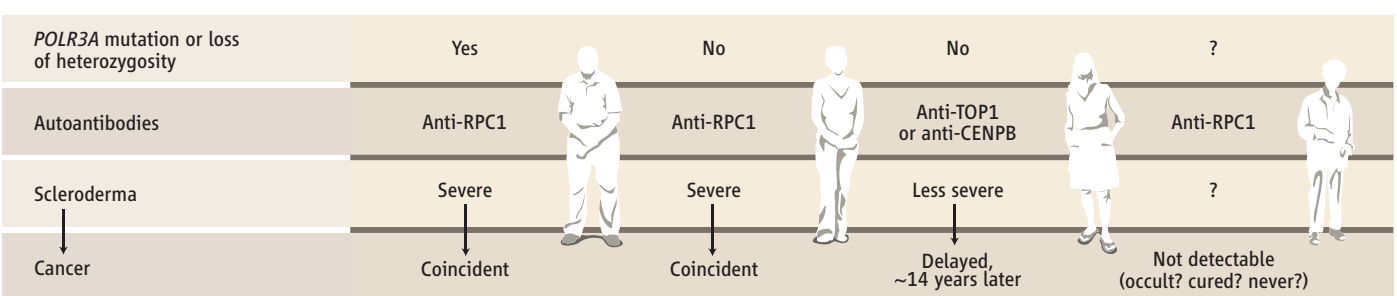

Coincidence. Four subsets of scleroderma patients are shown (as observed by Joseph *et al*. (*1*)) with different autoantibody profiles, mutations, and coincident cancer.

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of scleroderma and the cancer genomes of these patients were unrelated, and that the mutations, and T cell responses directed against them, were coincidental. Rather, *POLR3A* mutation in the occasional cancer triggers the scleroderma.

According to cancer immunoediting (*3*), the host can control tumor growth through innate and adaptive immune mechanisms. Genetic instability in the tumor may create neoantigens that are recognized by the immune system, leading to the selection of tumor cells that can escape immune pressure. Neoantigens have been demonstrated in tumors by means of epitope prediction algorithms (*4*). These principles have been demonstrated in mouse models of carcinogenesis and multistage cancer progression (*3*, *4*), but also recently, the importance of a patient's immune reaction with cancer in dictating disease-free survival (immune contexture) has been established (*5*).

The relatively low fraction of neoplastic cells with genetic alterations in the cancers from some of the scleroderma patients studied by Joseph *et al*. suggests that cancer immunoediting had occurred. Cancer cells targeted by T cells appear to selectively lose the mutant allele, and loss of heterozygosity occurred in most of the tumors that were present synchronously with the scleroderma. In some tumors, the loss of heterozygosity was not yet complete (clonal heterogeneity was observed in which a small percentage of the tumor cells still carried the mutation). Presumably, if those tumors had been sampled a few months later, there might not be any detectable mutant cells because loss of heterozygosity would have been complete. The loss of heterozygosity in the other tumors without detectable mutations is quite possibly a "historical" record of the tumors once carrying mutations. Interestingly, no mutant allele or loss of heterozygosity was detected in some patients with anti-RPC1 autoantibodies, suggesting that other mechanisms can induce their production. The etiology of scleroderma development in these patients may resemble that in patients with anti-TOP1 and anti-CENPB autoantibodies. It is also possible that patients with RPC1-specific autoantibodies and no cancer may once have had nascent cancer or harbor cancer in a state of immune-mediated dormancy. The loss of heterozygosity of *POLR3A* in some patients raises the possibility that immunoediting may involve gene copy-number alterations in the cancer. Alternatively, because RPC1 plays a role in sensing and limiting infection by intracellular bacteria and viruses (*6*), cancer may also mutate or lose *POLR3A* to evade activating innate immunity.

The association between cancer and rheumatic diseases has been intriguing for many years (*7*). Paraneoplastic syndromes may be mediated by autoantibodies due either to tumor antigens that are also expressed by cells targeted by the autoimmune disease or to the release of intracellular antigens from apoptotic tumor cells (*8*). However, these responses are directed to the normal protein, and there is yet no evidence that encoding genes were mutated in the tumors. Joseph *et al*. extend causation to include mutant *POLR3A* in human tumors that elicits an immune response against the mutant RPC1 but cross-reacts with the normal RPC1, resulting in autoimmunity. However, the cancer mutation is likely not enough and additional factors (genetic, environmental, or target tissue–specific) may be required to generate damage to normal tissue.

From an epidemiological viewpoint, the study by Joseph *et al*. is underpowered, but these findings may also prompt research into whether antigens other than RPC1 might trigger autoimmunity (e.g., in myositis and lupus). In larger studies, mining exome sequencing data can help identify a patient's specific tumor antigen profile and potential tumor immunity and autoimmunity. However, the findings by Joseph *et al*. raise interesting issues about tumors with high mutation rates (lung, melanoma) or microsatellite DNA instability (colorectal) and their predisposition to cause autoimmunity. Simple analysis of large tissue collections from cancer patients with accompanying "immunoscores" and patient disease history might reveal correlations with autoimmune syndromes.

Very little autoimmunity has been causally linked to cancer mutations and subsequent immune reactions, but these events have only been examined in cancer patients with clinically detectable disease. Do autoimmune patients in general have an undetectable burden or history of cancer? New immunotherapeutic treatments for cancer that break tolerance will help to clarify the underlying natural human immune reaction to cancer and its side effects on normal tissues.

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PLANETARY SCIENCE

Glimpsing Eruptions on Europa

John R. Spencer

Recent observations with the Hubble Space Telescope reveal what are probably eruptions of water vapor from Jupiter's moon Europa.

Second-closest to Jupiter (after Io) of the four large Galilean satellites, icy Europa is one of the strangest objects in the solar system (*1*). On page 171 of this issue, Roth *et al*. (*2*) present strong evidence for ongoing eruptions of plumes of water vapor from Europa's surface. This is a potentially major discovery, making Europa only the fourth object in the solar system known to exhibit ongoing internally powered geological activity, after Earth, Europa's volcanic neighbor moon Io, and Saturn's icy moon Enceladus.

Europa is slightly smaller than our own Moon, with a radius of 1561 km and a density of 3010 kg m^{-3}, implying an interior mostly composed of silicates plus about 10% water by mass. Gravity observations by the Galileo Jupiter orbiter revealed that Europa is strongly differentiated, with the lower-density water component concentrated near the surface (*3*). The surface is dominated by water ice, along with other hydrated species, probably salts. Europa's surface appearance is truly bizarre, crisscrossed with fractures, sometimes global in extent, that on closer inspection turn out to be double ridges (see the fig-

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