
This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

The following resources related to this article are available online at www.sciencemag.org (this information is current as of June 16, 2011):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/content/332/6032/923.full.html>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/content/332/6032/923.full.html#related>

This article **cites 13 articles**, 2 of which can be accessed free:

<http://www.sciencemag.org/content/332/6032/923.full.html#ref-list-1>

This article appears in the following **subject collections**:

Cell Biology

http://www.sciencemag.org/cgi/collection/cell_biol

bound transition metal d electrons, and single electrons are no longer independent but influence the behavior of all other electrons in the crystal. The large electrical polarizability of oxygen also enhances the response of these materials to electric fields causing ferroelectric (a net electric dipole moment) or multiferroic (both ferroelectric and ferromagnetic) properties (4).

Boris *et al.* used pulsed laser deposition to grow superlattices—precise numbers of oxide layers with atomically sharp interfaces (see the figure). Samples with four-unit-cell thick LaNiO₃ layers grown between LaAlO₃ layers were metallic at temperatures from 8 to 300 K, just like bulk LaNiO₃. Samples with only two layers of LaNiO₃, in which each LaNiO₃ layer is next to a LaAlO₃ layer, showed a metal-to-insulator transition with subsequent magnetic ordering as the temperature was lowered.

Such effects might be mainly the result of strain in the layers, which can be induced by the substrate used for growth. To check whether this was the case, Boris *et al.* grew the same layer structures on strontium titanate (SrTiO₃), which has a larger lattice constant than the superlattice, and on lanthanum strontium aluminate (LaSrAlO₄), in which the lattice constant is smaller. The same behavior was seen in both cases, except for a shift of transition temperature (100 and 150 K, respectively), ruling out strain as the cause.

To demonstrate further that these effects were intrinsic to the superlattice structure, Boris *et al.* applied state-of-the-art surface probes. They used ellipsometry to measure the changes in the sample's electrical conductivity. Ellipsometry is not influenced by extrinsic impurities, particularly interdiffusion of ions between the layers, nor is it influenced by misfit dislocations resulting from inexact matching of the lattice constants at the interface, which can occur in oxide superlattices. They also used low-energy muon spin rotation to identify a change in the magnetic order accompanying the transition from the metallic to the insulating state. Here, spin-polarized muons with well-defined energies are implanted within the oxide heterostructure, where they align their magnetic moments parallel to those of the surrounding electrons. The measured directions of the subsequent positron decay products yield the local magnetic order of the electronic phase. The bilayered LaNiO₃ samples showed a clear magnetic transition, but the superlattices with thicker layers did not.

Deposition techniques such as pulsed laser deposition or molecular beam epitaxy

are now well developed, so nearly defect-free superlattices with atomically sharp interfaces can be routinely grown. Unanticipated phenomena such as the metal-insulator transition described here, or conductivity at interfaces between the insulating oxides such as LaAlO₃ and SrTiO₃ (5) or interfacial superconductivity (6), are now regularly reported. However, there is still much work to be done before oxide materials reach the level of sophistication achieved in semiconductor heterostructures. Improved control and understanding of the role of defects is necessary, as well as systematic incorporation of multiple interfaces with different electronic properties (2).

From a practical point of view, demonstrations of integration with conventional semiconductors would be helpful, as would a detailed understanding of the behavior at interfaces with metallic electrodes (7). On the theoretical front, the aspects that make complex oxides desirable—in particular the strong correlations, the large polarizability, and the

sensitive dependence on crystal chemistry and structure—also make them challenging to describe accurately. Improved techniques must combine many-body physics methods for describing strong correlations with computational materials methods, such as density functional theory, that can account for chemistry and structure. With these developments, which the community is poised to make over the next few years, true predictive capability and layer-by-layer construction of designer oxide superlattices should be achievable.

References

1. D. G. Schlom, L.-Q. Chen, X. Pan, A. Schmehl, M. A. Zurbuchen, *J. Am. Ceram. Soc.* **91**, 2429 (2008).
2. J. Mannhart, D. G. Schlom, *Science* **327**, 1607 (2010).
3. A. V. Boris *et al.*, *Science* **332**, 937 (2011).
4. N. A. Spaldin, S. W. Cheong, R. Ramesh, *Phys. Today* **63**, 38 (2010).
5. A. Ohtomo, H. Y. Hwang, *Nature* **427**, 423 (2004).
6. A. Gozar *et al.*, *Nature* **455**, 782 (2008).
7. M. Stengel, N. A. Spaldin, *Nature* **443**, 679 (2006).

10.1126/science.1206247

CELL BIOLOGY

The TASCC of Secretion

Roberto Zoncu^{1,2,3} and David M. Sabatini^{1,2,3,4}

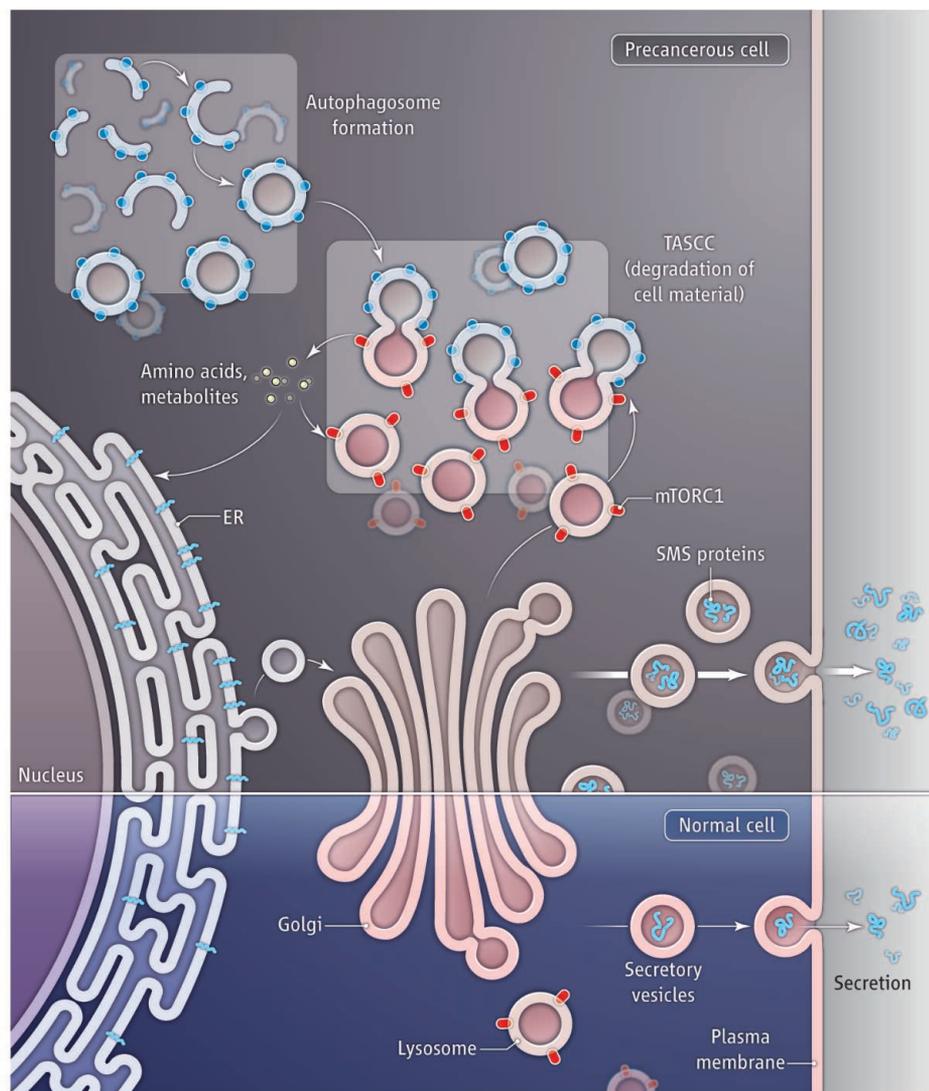
Cells can spatially couple cellular degradation and protein synthesis to boost protein secretion.

The oncogene-induced activation of signaling pathways involving the tumor suppressor proteins p53 and retinoblastoma is likely an important mechanism for preventing the proliferation of potential cancer cells (1, 2). This activation causes cells to exit the cell division cycle and enter a senescent state, which is characterized by major changes in chromatin structure that are thought to render senescence irreversible. Despite the absence of proliferation, senescent cells are not as quiescent as first thought, as they signal to their surrounding environment by activating a protein secretion program (3, 4). On page 966 of this issue, Narita *et al.* (5) show that to enable this secretory state, a senescent cell profoundly reorganizes its endomembrane system.

The secretory program leads to the massive production of factors [collectively called the senescence-messaging secretome (SMS) or senescence-associated secretory phenotype (SASP)] that are released into the surrounding microenvironment (3, 4). The composition of the SMS is heterogeneous. It includes growth factors, inflammatory cytokines, and modulators of the extracellular matrix, and its precise physiological role is highly controversial. For example, inflammation can modify the microenvironment in ways that favor cancer cell invasion and tumor growth (6, 7); however, in the context of oncogene-induced cell senescence, inflammatory cytokines can also exert an autocrine, tumor-suppressive action (8–11).

Narita *et al.* found that expression of the oncogenic protein H-RasV12 in a senescent mammalian cell triggers a reorganization of its endomembrane system, which results in the formation of a membrane compartment that carries out the secretory program. They named this structure the TOR-autophagy spatial coupling compartment (TASCC). As the name suggests, the key components

¹Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA. ²Department of Biology, Massachusetts Institute of Technology (MIT), Cambridge, MA 02139, USA. ³The David H. Koch Institute for Integrative Cancer Research at MIT, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. ⁴Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA. E-mail: sabatini@wi.mit.edu



Reorganized to reinforce. In a normal mammalian cell (**bottom**), autophagy is suppressed by mTORC1. In a cell undergoing senescence (induced by the oncogene H-RasV12) (**top**), autophagosomes form at the cell periphery and as they mature, fuse with lysosomes that contain mTORC1, giving rise to the TASC. Amino acids and other metabolites released from autophagolysosomes activate mTORC1 and boost protein synthesis. Newly synthesized proteins are secreted or rerouted to the TASC for degradation to fuel further rounds of protein synthesis.

of this compartment are autophagosomes and the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) kinase. In the proposed model, autophagosomes, which degrade aged organelles and proteins, generate a high flux of amino acids and other metabolites that provide building blocks for biosynthesis (12). mTORC1 promotes the utilization of these constituents for synthesizing SMS components. The key to this highly efficient process, according to the authors, is the tight spatial coupling of autophagy and mTORC1. In cells undergoing Ras-induced senescence, there is a large accumulation of mTORC1-studded lysosomes together with autophagosomes in a well-defined perinuclear location (see the figure). Blocking the localization of

mTORC1 to the TASC (13) reduced the synthesis and secretion of the SMS cytokines interleukin-6 (IL-6) and IL-8. Moreover, blocking autophagy, and thus cutting off the amino acid supply that activates mTORC1, caused the complete loss of mTORC1 from the TASC.

Although bringing together autophagy and mTORC1 seems like a smart way to increase the secretory output of a cell, it also poses a logical problem: Activated mTORC1 phosphorylates autophagy initiators, including the serine-threonine kinase Unc-51-like kinase 1 (ULK1), thereby suppressing autophagy (12). Indeed, rapamycin, an inhibitor of mTORC1, induces autophagy even when cells are in a nutrient-rich environment. To explain this apparent

paradox, Narita *et al.* analyzed the subcellular distribution of ULK1 and found it to be excluded from the TASC. Moreover, they observed mature autophagosomes in the TASC, whereas early autophagosomes were mostly outside the TASC. Thus, in a senescent cell, autophagosomes form outside the TASC, out of reach from the inhibitory action of mTORC1, but they progressively move inward as they mature. This finding has broad implications, because it suggests that spatial segregation of mTORC1 from autophagy-initiating factors may enable the maintenance of basal autophagy in actively growing cells.

Ultrastructural analyses revealed a close apposition of the TASC with the endoplasmic reticulum (ER), Golgi apparatus, and trans-Golgi network. Moreover, Narita *et al.* found that newly synthesized proteins are enriched in the trans-Golgi network within 30 min of their synthesis, but accumulate in the TASC shortly afterwards. Thus, a continuous flow of newly synthesized proteins traverses the secretory pathway and ends up in the TASC. This extremely rapid protein turnover may be key in fueling the synthesis of SMS components.

A central question is whether senescence increases the activity of the secretory pathway as a whole, or whether it selectively boosts the synthesis and secretion of the SMS components alone. The high rate of protein turnover, together with the elevated autophagic activity, suggests a scenario in which the synthesis of many protein species may be nonselectively increased during Ras-induced senescence. However, most of these proteins would be destined for immediate degradation, whereas only SMS components would be selectively secreted. This seemingly wasteful mechanism may underlie a broader function for the TASC in non-senescent physiological settings. Indeed, Narita *et al.* identified TASC-like structures in leukemia cells undergoing differentiation, as well as in renal glomerular cells in vivo. Thus, it is conceivable that multiple mechanisms could set up the TASC and enhance general secretory activity, but the nature of the proteins being stabilized and secreted may be context-specific.

Narita *et al.* reveal the surprising ability of senescent cells to reorganize the morphology and the function of their endomembrane system. The findings provoke exciting questions about the mechanisms that lead to formation of the TASC, including whether senescence-associated gene expression programs control membrane organization and dynamics, and whether H-RasV12 onco-

gene and/or p53 are directly involved. Answers to these questions may clarify the role of the TASC in maintaining the senescent state and in tumor suppression.

References and Notes

1. S. Courtois-Cox, S. L. Jones, K. Cichowski, *Oncogene* **27**, 2801 (2008).
2. F. d'Adda di Fagagna, *Nat. Rev. Cancer* **8**, 512 (2008).
3. T. Kuilman, D. S. Peeper, *Nat. Rev. Cancer* **9**, 81 (2009).
4. F. Rodier, J. Campisi, *J. Cell Biol.* **192**, 547 (2011).
5. M. Narita *et al.*, *Science* **332**, 966 (2011); 10.1126/science.1205407.
6. J.-P. Coppé *et al.*, *PLoS Biol.* **6**, e301 (2008).
7. D. Hanahan, R. A. Weinberg, *Cell* **144**, 646 (2011).
8. J. C. Acosta *et al.*, *Cell* **133**, 1006 (2008).
9. R. M. Kortlever, P. J. Higgins, R. Bernards, *Nat. Cell Biol.* **8**, 877 (2006).
10. T. Kuilman *et al.*, *Cell* **133**, 1019 (2008).
11. N. Wajapeyee, R. W. Serra, X. Zhu, M. Mahalingam, M. R. Green, *Cell* **132**, 363 (2008).
12. C. He, D. J. Klionsky, *Annu. Rev. Genet.* **43**, 67 (2009).
13. Y. Sancak *et al.*, *Cell* **141**, 290 (2010).

10.1126/science.1207552

ATMOSPHERIC SCIENCE

Subtropical Rainfall and the Antarctic Ozone Hole

Steven B. Feldstein

For more than 100 years, researchers have understood that ozone in the stratosphere, the atmospheric layer between 10 and 50 km above Earth's surface, plays an important role in absorbing ultraviolet radiation and protecting life on Earth (1). In 1985, scientists and the public became alarmed when Farman *et al.* (2) reported that, during the Antarctic spring, stratospheric ozone concentrations over the continent were declining by as much as 50%, indicating the presence of a polar "ozone hole." Implementation of the 1987 Montreal protocol, an international agreement that phased out the use of some chlorofluorocarbons and other compounds that destroy stratospheric ozone, has led to the first stage of recovery (3). Researchers, however, had not widely recognized the ozone hole's impact on the climate of the troposphere (the lowest 10 km of the atmosphere) until recent observational (4) and state-of-the-art climate modeling studies (5–8). These studies showed that ozone depletion has a large influence during the Antarctic summer, when it drives a major air current called the mid-latitude westerly jet to a higher latitude, closer to Antarctica; this reduces sea level pressure over the continent, cooling much of the continental interior, coinciding with a warming of the Antarctic Peninsula. On page 951 of this issue, Kang *et al.* (9) expand our understanding of ozone depletion's impact on climate. Using a series of carefully designed climate model experiments, they show that ozone-induced climate change is not confined just to the vicinity of Antarctica but extends over much of the Southern Hemisphere, even reaching the tropics, where it appears to have

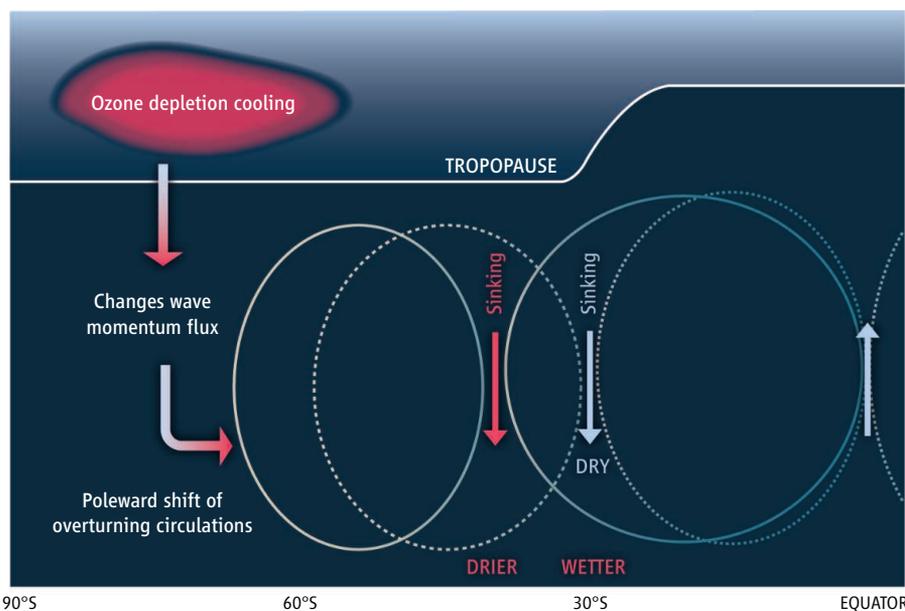
resulted in increased summer precipitation in the subtropics.

To isolate the impact of reduced stratospheric ozone on tropospheric climate, recent studies have compared results from two types of climate model simulations: One specifies pre-ozone-hole concentrations of ozone; the other uses the more recent, ozone-depleted concentrations. Some studies also specify various concentrations of primary greenhouse gases in order to compare their influence on climate with that of depleted ozone. Together, such studies have provided climate modelers with strong support for the claim that stratospheric ozone depletion has been the dominant driver of climate change in the

Simulations show that ozone depletion has had a large impact on Southern Hemisphere climate.

mid- and high-latitude Southern Hemisphere during the summer season. In particular, the pre-ozone-hole and depleted simulations produce differences in wind, temperature, and precipitation patterns that closely resemble changes observed in the atmosphere.

In their models, Kang *et al.* not only accounted for pre-ozone-hole and depleted ozone concentrations but also investigated the sensitivity of the model response to physical "parameterizations" (a key component of climate models that differs between models), and to the coupling of the atmosphere with the oceans and sea ice. All climate models use parameterization to represent important physical processes, such as those associated



Catching a wave. In the Southern Hemisphere, cooling related to stratospheric ozone depletion over Antarctica alters atmospheric wave momentum fluxes, which causes circulation cells (solid and dotted circles) to shift poleward, altering precipitation patterns in the subtropics. Pre-ozone-hole circulation cells are illustrated with dotted lines and blue labels; depleted ozone cells are illustrated with solid lines and red labels.