over the East African continent. In a nearby deep-sea sediment core off the Somalian coast, Holocene aridification over the course of 2000 years was recorded from the radiogenic isotope signature of wind-transported dust (*11*). Tierney and deMenocal instead measured the deuterium-to-hydrogen ratio (D/H) of the leaf waxes; this ratio is directly linked to the isotopic composition of precipitation and hence to total rainfall.

By comparing their Gulf of Aden record with published records, Tierney and deMenocal conclude that the African Humid Period ended abruptly within a few centuries and was synchronous in the western and eastern part of Africa. By considering modern climate observations and model simulations, they propose that East African rainfall responded in a nonlinear way to surface temperatures in the Indian Ocean.

Tierney and deMenocal's Gulf of Aden record provides key information for understanding North African climate during the Holocene. However, much research is still needed to build a comprehensive view of hydroclimatic changes during the African Humid Period. Most published records are based on proxies that are difficult to link unequivocally to rainfall changes. For example, records of wind-transported material reflect both the decrease in vegetation cover and the increase in the dust source area caused by widespread lake desiccation. Documenting these parameters requires information from multiple proxies measured in the same continental or marine archives. The time resolution of records must also be improved by increasing the sampling rate for these proxies. Decadal-to-seasonal profiles measured with geochemical scanners (*12*) allow studying African Humid Period transitions without relying on statistical corrections.

More continuous records are needed from north of the Gulf of Aden, along the Nile Valley and the Red Sea. Obtaining new data from central North Africa is also crucial for backing up observations made in sediments of the small Lake Yoa (*5*, *12*). Of particular importance is the Holocene history of Lake Chad, which was at least 10 times as large during the African Humid Period than it is today (*13*). Pollen data from Lake Chad (*14*) indicate that vegetation changes occurred progressively over about two millennia, but that century-scale variability was superimposed on the mid-Holocene drying trend. Additional proxies remain to be measured and longer continuous cores to be collected and studied from Lake Chad to advance understanding of the African Humid Period.

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CANCER

Potential of the Synthetic Lethality Principle

Elucidating the first principles of synthetic lethality in cancer, including biological context, will assist clinical translation.

Sebastian M. B. Nijman[1] and Stephen H. Friend[2]

Most cancer mutations, including those causing a loss of function, are not directly "druggable" with conventional small-molecule drugs or biologicals, such as antibodies. Thus, despite our growing knowledge of mutations that drive cancer progression, there remains a frustrating gap in translating this information into the development of targeted treatments that kill only cancer cells. An approach that exploits a concept from genetics called "synthetic lethality" could provide a solution. But it has been over 15 years since that framework was proposed (*1*). Does the synthetic lethality principle still have the potential for treating cancer?

Synthetic lethality, first observed in the fruit fly *Drosophila melanogaster* almost a century ago, describes a phenomenon where only the simultaneous perturbation of two genes results in a deadly combination. Thus, cancer aberrations that are not readily targetable [e.g., tumor suppressor proteins such as retinblastoma protein 1 (RB1) and p53 (*TP53*); oncogenes such as *RAS* and c-*MYC*] could be indirectly exploited by inhibiting the product of another gene (*2*–*4*). The broader definition of synthetic lethality has also been referred to as "nononcogene addiction" or "induced essentiality" to distinguish it from its classical meaning in genetics. In the budding yeast *Saccharomyces cerevisiae*, most genes display numerous synthetic lethal interactions (*5*, *6*), which may also apply to many human cancer genes. Furthermore, "passenger" mutations, which do not directly contribute to tumorigenesis, and even rewiring of cellular networks that give rise to a cancerous state, may also be exploited with the synthetic lethal principle. However, to date, only a single synthetic lethal interaction has shown therapeutic promise. Why have synthetic lethal therapies largely failed to deliver?

The proof of principle that the synthetic lethality concept is clinically translatable is the efficacy of drugs that target the single-strand DNA repair enzyme poly(ADP-ribose) polymerase (PARP) in tumors with mutations in the *BRCA1* and *BRCA2* genes (*7*). These genes encode tumor suppressor proteins that help repair damaged DNA. The remarkable ability of tumors to acquire resistance to PARP inhibitors by regaining BRCA function shows that PARP-targeting drugs act through a synthetic lethal mechanism (*8*). This finding triggered an intensive search for synthetic lethal drug targets akin to PARP. In particular, large-scale RNA interference screens (in which RNA molecules block the expression of specific genes) have led to a growing list of potential synthetic lethal

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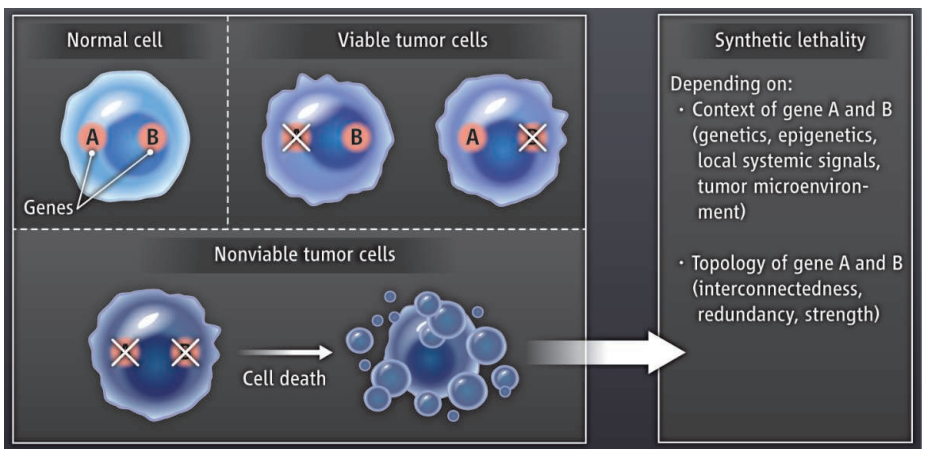
gene targets. It is too soon to know if any of these new drug targets can be translated to the clinic. A major obstacle is that genetic and pharmacological perturbations do not always have the same functional outcome. This means that a genetic synthetic lethal relationship may never be realized pharmacologically. Despite this understanding, there is a growing concern that many synthetic lethal interactions are not easily transferred beyond the models used for screening, challenging synthetic lethality as a broadly applicable therapeutic concept. Indeed, only a few synthetic lethal drug targets are in clinical development, and none are as compelling as the BRCA-PARP paradigm.



Context and topology. Identifying synthetic lethal interactions (when simultaneous mutations in two genes are lethal to the cell) must consider the context of their interactions, such as genetic and epigenetic variability, the microenvironment, and local systemic signals. Topological characteristics (strength, connectivity, degree, and redundancy) of human synthetic lethal interaction networks are also an important consideration, but are largely unknown.

A major obstacle to achieving synthetic lethal therapies is a lack of insight into the first principles that govern the phenomenon in cancer cells. For example, there is little understanding of how variability in genetics, epigenetics, systemic signals, and the microenvironment influences synthetic lethal interactions (see the figure). Too often, a line of investigation focuses on "what works" without considering the context or analyzing unexpected or even contradictory results. Phenotypes are rarely conserved across a panel of biologically diverse replicates (humans), indicating that context matters. This is especially important in cancer, where molecular heterogeneity (contextual variability) is greater than for any other disease. Indeed, delving into biological context can be highly informative and provide therapeutic leads. For instance, colon cancer cells with activating and oncogenic mutations in the gene *BRAF* fail to respond to BRAF inhibitors. However, these cancer cells display a feedback mechanism that induces signaling by the epidermal growth factor receptor, negating the effects of BRAF inhibition. This "bigger picture" view yielded a rationale to combine BRAF inhibitors with epidermal growth factor inhibitors, a solution that blocked growth of seemingly "drug-resistant" cancer cells (*9*, *10*).

Synthetic lethal interactions may be no less context dependent than other cellular phenotypes. The opposite actually may be true. In yeast, single gene perturbations that lead to fitness defects (mutations in essential genes) are evolutionarily more conserved than defects induced by two mutations (*11*). As clonal evolution during tumorigenesis results in a divergence of cell states (through the progressive accumulation of genetic and epigenetic abnormalities in multiple and different genes), context dependencies may be even more pronounced for drugs that exploit synthetic lethality than for those that target "oncogene addiction," in which only one gene that is required for maintaining malignancy is targeted.

The importance of context is also revealed in the comparison of genes that are differentially essential in two yeast strains (*12*). It was predicted that some of these conditional essential genes could be explained by mutations in synthetic lethal interactors in the affected strain. However, crossing the two strains and analyzing the frequency of viable spores showed that most of the conditional essential interactions are due to multiple genes acting in concert. This implies that synthetic interactions may also be susceptible to genetic modifiers and that quantitative differences in gene activity (between cell types, tumors, and individuals) can affect synthetic lethality. Moreover, stochastic variation in gene activity in the worm *Caenorhabditis elegans* can affect the penetrance of synthetic lethal interactions (*13*). This suggests that context will impact synthetic lethality in human cancer cells and argues for a systematic study of this phenomenon to guide more successful clinical translation. Such studies should focus on identifying co-occurring mutations in tumors that can modify the penetrance of synthetic lethal interactions. This can be achieved, for instance, by testing the synthetic lethal interaction in a large panel of well-characterized cancer cell lines or by using engineered isogenic cell lines that model the variability observed in patients in a defined genetic context. Although these cell culture studies would not directly address the role of the tumor microenviroment, any identified genetic modifiers could serve as biomarkers to predict which tumors are most likely to display the synthetic lethal interaction. Ultimately, performing a genome-wide screen for genetic modifiers that enhance or suppress a specific synthetic lethal interaction could reveal those that are least sensitive to contextual variability, and thus would be more likely to be of general use in the clinic. Results of such suppressor-enhancer screens from a variety of candidate synthetic lethal interactions may reveal more fundamental rules that govern context dependency.

There are several additional fundamental aspects of synthetic lethal interactions in human cells that have yet to be systematically explored. Some of these relate to network topology—the parameters that describe the connectivity structure of synthetic lethal interaction. For example, quantitative insights into the strength of synthetic lethality in human cells are lacking; yet this may determine the eventual therapeutic index—the concentration of a drug required for toxic effects divided by the concentration required for therapeutic effects—that can be achieved in patients. Such knowledge will be instructive for selecting the most promising synthetic lethal interactions for drug discovery and development (*4*). Indeed, compared to normal cells, cells lacking *BRCA1/2* are almost three orders of magnitude more sensitive to PARP inhibitors. By contrast, most other described synthetic lethal interactions in human cells are much less striking, and some may not even conform to the strictest definition requiring that each single gene perturbation alone has no effect on cell viability.

Topological information may point to the best cellular processes for identifying syn-

thetic lethal interactions. Which types of genes or cellular processes tend to display the most interactions (interconnectivity) may instruct functional genomics efforts. Screens in model organisms such as yeast and worm indicate that proteins involved in chromatin regulation such as histone deacetylases display the most frequent genetic interactions (*5*, *14*).One explanation is that transcriptional regulation is well positioned for buffering perturbations by tuning the expression of multiple genes simultaneously. However, there are no experiments to corroborate this hypothesis in human cancer cells. Even for DNA synthesis and repair pathways that represent highly conserved functional modules (an obvious place to look for synthetic lethality), an inventory of synthetic lethal interactions in human cells has still not materialized.

Other largely uncharted topological areas concern the number of synthetic lethal connections between genes and their distribution and redundancy. The complexity of a human cell compared to a yeast cell may suggest that human cells display more redundancy, making them more resilient to perturbations and implying that synthetic lethal interactions would be less frequent. Current and next-generation genomics tools will help to answer these questions.

In the near term, the ability to perform personalized screens for synthetic lethal interactions on ex vivo tissue samples may provide clinically useful knowledge until the long-term goal of better understanding the biological rules can be achieved. Until a thorough understanding of synthetic interactions and the ability to assess their promise is in hand, their validation and translation will remain hit-and-miss. Recognizing the challenges facing gene therapy and immune therapy paved the way for moving from concept to clinical reality, and there is hope that learning the principles that govern synthetic lethal interactions in cancer will do the same.

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CHEMISTRY

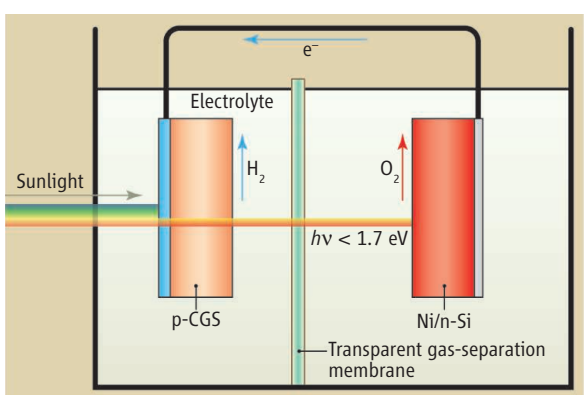
A Nickel Finish Protects Silicon Photoanodes for Water Splitting

Ultrathin nickel coatings allow silicon to act as the oxygen-generating electrode in the direct formation of hydrogen from water with sunlight.

John A. Turner

The large-scale generation of hydrogen from water with sunlight could provide a sustainable source of this industrially important gas, but could also provide fuel for vehicles and a storage medium for solar energy. The direct photoelectrochemical (PEC) splitting of water into hydrogen and oxygen, which combines a photovoltaic cell and an electrolyzer into a single device, remains an important goal (*1*). One problem is that some of the materials that work well for photovoltaics, such as n-type silicon (Si), corrode in electrolyzer solutions. On page 836 of this issue, Kenney *et al*. (*2*) show that a 2-nm-thick nickel (Ni) film on an n-type silicon semiconductor not only provides some stability against corrosion when used for oxygen evolution in a PEC configuration, but also generates a high voltage via a metal-insulator-semiconductor (MIS) configuration.

Hydrogen is used today primarily in the petroleum refining industry and for ammonia synthesis. More than 50 million tons of hydrogen are produced worldwide every year from fossil fuel feedstocks that generate CO_2 emissions. In a carbon-free energy system, however, hydrogen must be produced from water splitting by means of renewable resources such as wind and solar energy. As solar energy is our largest resource, combining photovoltaics with electrolysis would seem to be the clear choice for renewable hydrogen production (*3*), but to date the only commercially available pathway in this scheme is the electrolysis step. Unfortunately, hydrogen from electrolysis with photovoltaic-generated electricity is far too expensive to be commercially viable, so other pathways must be considered.



Doubling up for solar hydrogen production. A design configuration is shown where two separate semiconductors with different band gaps are illuminated in series to form a tandem system for water splitting. Sunlight illuminates the p-type electrode, which absorbs the visible light and transmits the red and near-infrared light that then illuminates the n-type electrode. The work of Kenney *et al*. shows that a thin nickel film can protect n-type silicon from corrosion by the electrolyte.

In a PEC water-splitting system, a semiconductor electrode is immersed in an aqueous solution, and when illuminated it splits water directly at the semiconductor's surface. For the use of n-type silicon, the study of Kenney *et al*. presents several critical results. The 2-nm Ni film combined with the thin native silicon oxide layer (SiO_x) that forms on silicon exposed to air, and the surface of the nickel oxidized in the electrolyte to form nickel oxide (NiO_x). The resulting NiO_x/Ni/SiO_x/Si device generated a voltage of 500 mV when exposed to light, with no need for the thermally grown SiO_x layer that has traditionally been required to achieve that voltage (*4*).

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