

## PHYSICS

# Long-distance operator for energy transfer

Nanophotonics can be used to enhance the electromagnetic coupling between molecules

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**N**onradiative energy transfer is a ubiquitous phenomenon in nature. Photosynthesis begins with light harvesting, where pigment-protein complexes transform sunlight into excitations, usually called excitons, within the molecules. Excitons are formed by an excited electron and the positively charged hole that is left in the ground state. In photosynthesis, the energy of this exciton is finally transferred to the reaction center, where a charge separation process provides chemical energy for plants, algae, and bacteria. Human-made organic photovoltaic cells try to mimic this natural process, and it is the transport of the excitons after light absorption that determines the efficiency of the cell. In organic materials, energy transfer is governed by short-range dipole-dipole interactions through the process of Förster resonance energy transfer (FRET), whose spatial range is limited to distances less than 10 nm. Recent work by Zhong *et al.* (1) shows how this range can be extended to distances larger than 100 nm by taking advantage of a quantum electrodynamics (QED) phenomenon called strong coupling.

The short range of FRET is a consequence of the small interaction between visible light (a photon) and matter (an exciton) in vacuum. However, this coupling can be increased (or decreased) if the photonic environment of the exciton is modified. For example, when a molecule is located inside a cavity able to confine electromagnetic (EM) fields, the light-matter interaction is enhanced. In such systems, two different regimes of light-matter coupling can be distinguished. In the weak-coupling limit, the absorption and emission rates of a photon by the molecule are modified by the presence of a “dressed” vacuum. By using different nanophotonic structures, this weak coupling regime has been exploited to expand the range of FRET between molecules (2, 3). In the strong-coupling regime, the

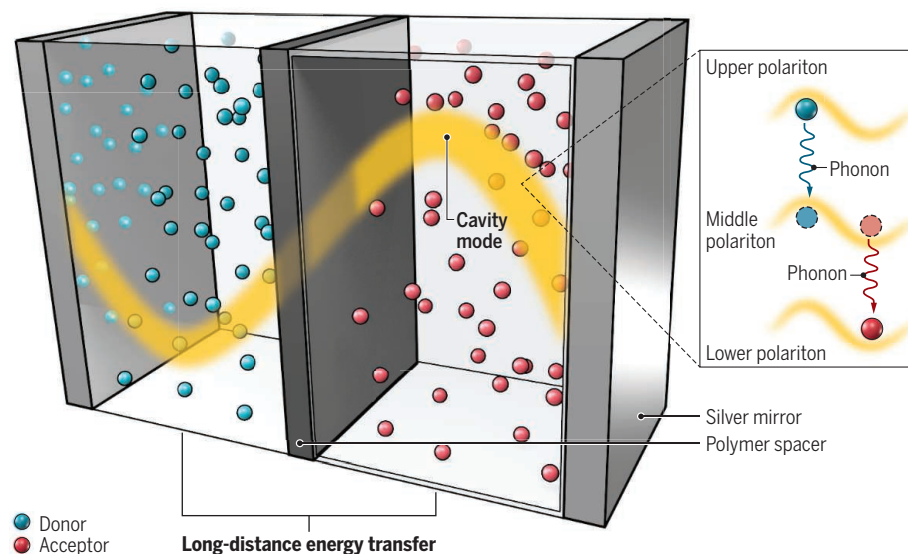
interaction between light and matter is so strong that the photon and exciton components mix to create new hybrid light-matter states called polaritons.

Organic molecules present a favorable case to reach strong coupling (4, 5), as their excitons possess large dipole moments and they can be tightly packed, thereby increasing the coupling strength for collective light-matter interaction. A new area of interdisciplinary research devoted to taking advantage of this QED phenomenon of

conductance of an organic material under strong coupling with surface plasmon EM modes supported by a thick metal film was reported recently (8). Along this line, it has been predicted that exciton transport can also be dramatically enhanced by the same QED effect (9, 10). Furthermore, by properly designing the electric field profile of the confined EM mode, exciton harvesting and funneling can be achieved (11); excitons could then be guided from a collection area to a desired long-distance location.

## Cavity-mediated energy transfer

A cavity formed by two silver mirrors supports an electromagnetic mode (yellow line) whose two intensity maxima coincide with the locations of spatially separated donor (blue) and acceptor (red) molecules. Taking advantage of the collective nature of polaritons, excitons can jump directly from donor to acceptor molecules.



strong coupling to enhance the capabilities of organic materials has emerged. Some experiments have already shown modifications of chemical reaction rates (6), and there have been proposals to completely suppress photochemical reactions (7) by means of strong coupling. One of the biggest assets of QED strong coupling is that polaritons, in contrast to excitons that are localized around a given molecule, extend over the entire structure. In a naïve way, we can view polaritons as “supermolecules” involving all the molecules as well as the confined EM field. This effect has important implications from a materials science perspective. An increase in the electrical

The delocalized character of polaritons has already been exploited for FRET between different molecular species. Polariton-mediated efficient and ultrafast FRET between the excitons of donor and acceptor molecules was reported (12, 13). In these experiments, the two types of dyes were located within a microcavity but were spatially intermixed. By contrast, Zhong *et al.* (1) physically separated the two ensembles of molecular dyes. They placed the J-aggregates of two cyanine dyes (one acting as donors, the other as acceptors) within a Fabry-Perot cavity formed by two silver mirrors and a polymer spacer between the two molecular layers (see the figure). The

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donor and acceptor layers are located at the antinodes of the second EM mode supported by the cavity in order to favor the emergence of strong coupling. This leads to three polariton modes where the excitonic component is either dominated by donors (upper polariton) or acceptors (lower polariton), or formed by a mixture between the two (middle polariton). When donor molecules are excited, energy is first stored in the upper polariton. The exciton energy is then released through local exciton-vibration interactions in the donor molecules to the middle polariton and from there, by the same mechanism in the acceptor molecules, to the lower polariton. In this way, polaritons act as long-distance operators between the two ensembles of molecular dyes. An energy transfer efficiency of 37% is reported for distances between molecular layers larger than 100 nm, although this mechanism would allow FRET over much longer distances because it does not rely on dipole-dipole interactions but only on the spatial extent of the polaritons.

From a quantum perspective, polaritons are a superposition of product states (a ground-state molecule and a photon in the cavity, plus an excited-state molecule with an empty cavity), and are thus closely related to entangled states as studied in quantum information theory. This suggests that local exciton-vibration interactions can have nonlocal effects. From this viewpoint, the long-range energy transfer observed by Zhong *et al.* can be understood as the result of a process in which polaritons provide entanglement between acceptor-donor states and automatically transform local interactions into nonlocal ones. Apart from the immediate prospect of further extending the range of polariton-mediated FRET for practical purposes, it will be interesting to explore whether other concepts of entanglement as a resource can be applied in the case of organic polaritons. ■

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## CANCER BIOLOGY

# New insights into melanoma development

## Telomerase promoter mutations extend cellular life span and increase melanoma susceptibility

By Jerry W. Shay

**M**elanoma is the deadliest form of skin cancer. There will be ~87,000 new cases of invasive melanoma and >9000 deaths in the United States in 2017 (1). Telomerase reverse transcriptase (TERT) is a component of telomerase. This enzyme extends the repeat sequences at the ends of chromosomes (telomeres), which get shorter each time a cell divides, allowing cells to continue to divide. Telomerase is up-regulated in 85 to 90% of all advanced human cancers. However, although they frequently occur, the role of TERT promoter mutations (TPMs) in cancer progression, or even immortalization, is unclear. On page 1416 of this issue, Chiba *et al.* (2) propose a two-step mechanism of melanomagenesis by which TPMs in melanocytes (pigmented cells in the skin that form melanoma) moderately up-regulate telomerase, thereby extending the life span of melanocytes; this increases their chances of acquiring additional mutations and becoming melanoma.

Progression from a melanocyte (that does not express telomerase) to invasive telomerase-expressing melanoma requires the sequential acquisition of mutations and/or epigenetic alterations that include *BRAF* or *NRAS* gain-of-function mutations and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) loss-of-function mutations (3). Additional mutations are required (some of which may result from ultraviolet exposure) as well as further cell divisions (3). In premalignant nevi (moles), melanocyte division results in progressive shortening of telomeres because they do not have a telomere maintenance mechanism (TMM), such as telomerase expression. However, in most benign cutaneous melanocytic nevi, oncogenic activating *BRAF* mutations occur early in the process of melanomagenesis, independently

of telomere length, and lead to a long-term growth arrest, referred to as oncogene-induced senescence (4). Therefore, in spite of oncogenic *BRAF* mutations, the cessation of melanocyte proliferation can last for decades, with cells retaining long telomeres and often high expression of p16<sup>INK4A</sup> (encoded by *CDKN2A*) (5). Thus, oncogene-induced senescence may be an initial tumor suppressor pathway. If *CDKN2A* becomes inactivated, melanocytes start dividing again and develop progressively shorter telomeres. Adult human cells do not have unlimited replicative potential, as most do not express telomerase, and when telomeres become extremely short and “uncapped,” replicative senescence is engaged (which is different from oncogene-induced senescence). Therefore, dividing premalignant melanocytes must activate a TMM to avoid replicative senescence, and this almost universally involves activating or up-regulating telomerase. Approximately 77% of intermediate-stage melanomas, which

have bypassed oncogene-induced senescence and perhaps replicative senescence, harbor TPMs, suggesting that they may be selected for prior to invasive melanoma (3).

Chiba *et al.* found that TPMs did not induce telomerase expression sufficiently in premalignant melanocytes to counteract progressive telomere shortening. Instead, TPMs extended the proliferative capacity past that imposed by the barriers of oncogene-induced senescence and replicative senescence compared to cells without TPMs. This is consistent with the escape-from-crisis model of tumorigenesis, which infers that most precancerous cells must overcome at least two antiproliferative barriers to become immortalized and thus tumorigenic (6). First, melanocytes in nevi bypass oncogene-induced senescence, and then, the Hayflick limit (replicative senescence) is activated owing to shortened telomeres. With the acquisition of tumor suppressor mutations [such as in *TP53* (which encodes p53) or RB transcriptional corepressor 1 (*RBI*)], cells bypass senescence and continue to divide until they have such

“...a TERT promoter mutation permits extended cell divisions...”

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