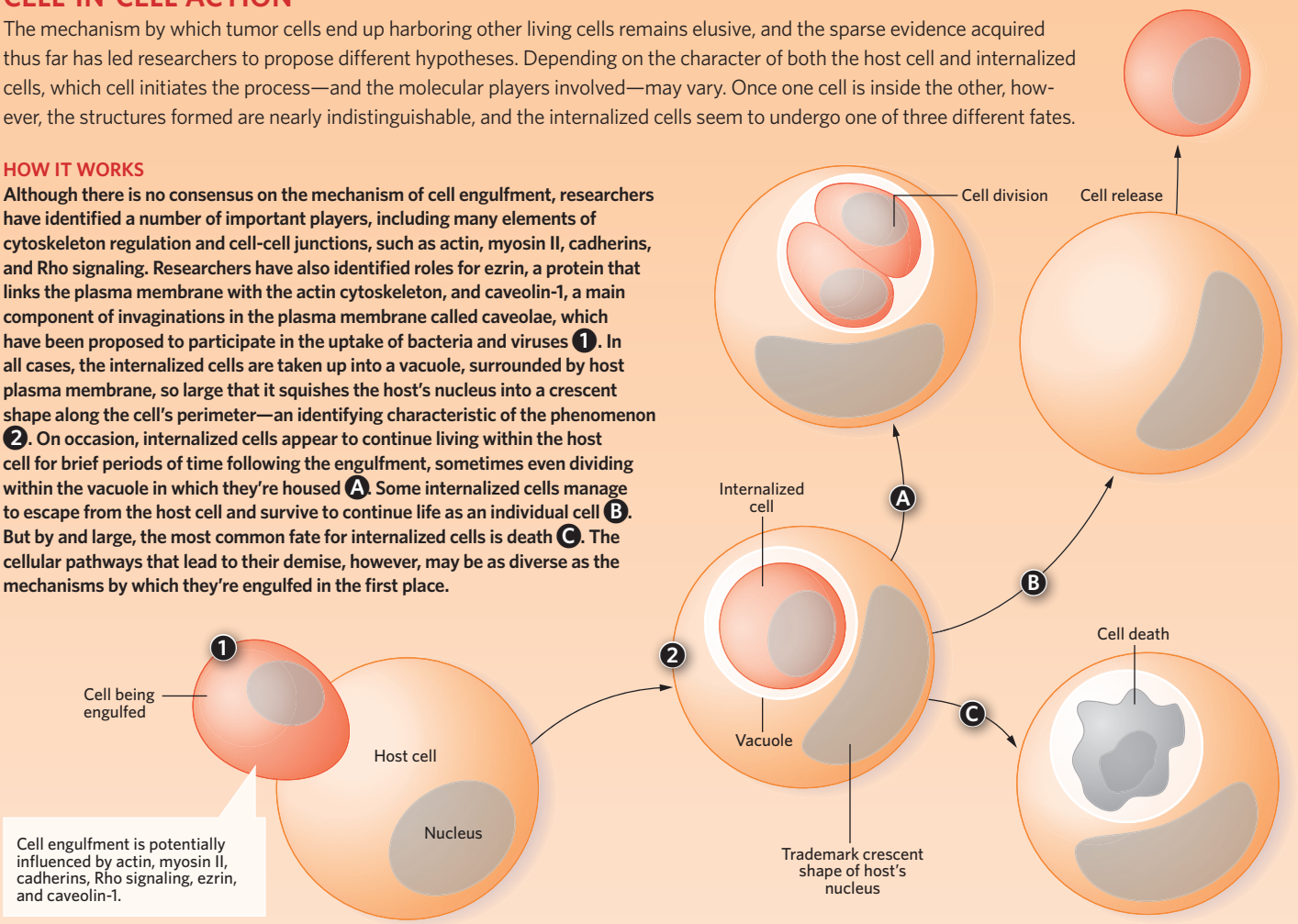
LUCY READING-IKKANDA FOR THE SCIENTIST, AUGUST 2011

CELL-IN-CELL ACTION

The mechanism by which tumor cells end up harboring other living cells remains elusive, and the sparse evidence acquired thus far has led researchers to propose different hypotheses. Depending on the character of both the host cell and internalized cells, which cell initiates the process—and the molecular players involved—may vary. Once one cell is inside the other, however, the structures formed are nearly indistinguishable, and the internalized cells seem to undergo one of three different fates.

HOW IT WORKS

Although there is no consensus on the mechanism of cell engulfment, researchers have identified a number of important players, including many elements of cytoskeleton regulation and cell-cell junctions, such as actin, myosin II, cadherins, and Rho signaling. Researchers have also identified roles for ezrin, a protein that links the plasma membrane with the actin cytoskeleton, and caveolin-1, a main component of invaginations in the plasma membrane called caveolae, which have been proposed to participate in the uptake of bacteria and viruses (1). In all cases, the internalized cells are taken up into a vacuole, surrounded by host plasma membrane, so large that it squishes the host's nucleus into a crescent shape along the cell's perimeter—an identifying characteristic of the phenomenon (2). On occasion, internalized cells appear to continue living within the host cell for brief periods of time following the engulfment, sometimes even dividing within the vacuole in which they're housed (A). Some internalized cells manage to escape from the host cell and survive to continue life as an individual cell (B). But by and large, the most common fate for internalized cells is death (C). The cellular pathways that lead to their demise, however, may be as diverse as the mechanisms by which they're engulfed in the first place.



HOW IT DIFFERS FROM PHAGOCYTOSIS

Most cell-in-cell researchers believe that the engulfment process differs from phagocytosis. In contrast to cells involved in cell cannibalism or entosis, which take up living cells, phagocytes tend to focus on dead or dying cells and other materials floating around the extracellular space. Phagocytosis is driven by changes in the host cell's cytoskeleton, and is usually characterized by the extension of pseudopodia—cellular projections driven by the polymerization of actin microfilaments—which surround the dead material and pull it inside the cell (1). In contrast, researchers studying cell cannibalism or entosis report that the two cells appear to merely come together before the engulfed cell suddenly appears inside the host cell. Once inside a phagocyte, cells are quickly transported by sequential fusion into endolysosomal compartments (2), where they are broken down (3). The degraded materials are then transported into the cytoplasm to be used by the cell for biosynthesis (A), or less commonly, released outside the cell via exocytosis (B). Living cells internalized by tumor cells, on the other hand, remain inside host-membrane-derived vacuolar structures, where they can stay viable for up to a day or more before being degraded or, on occasion, released.