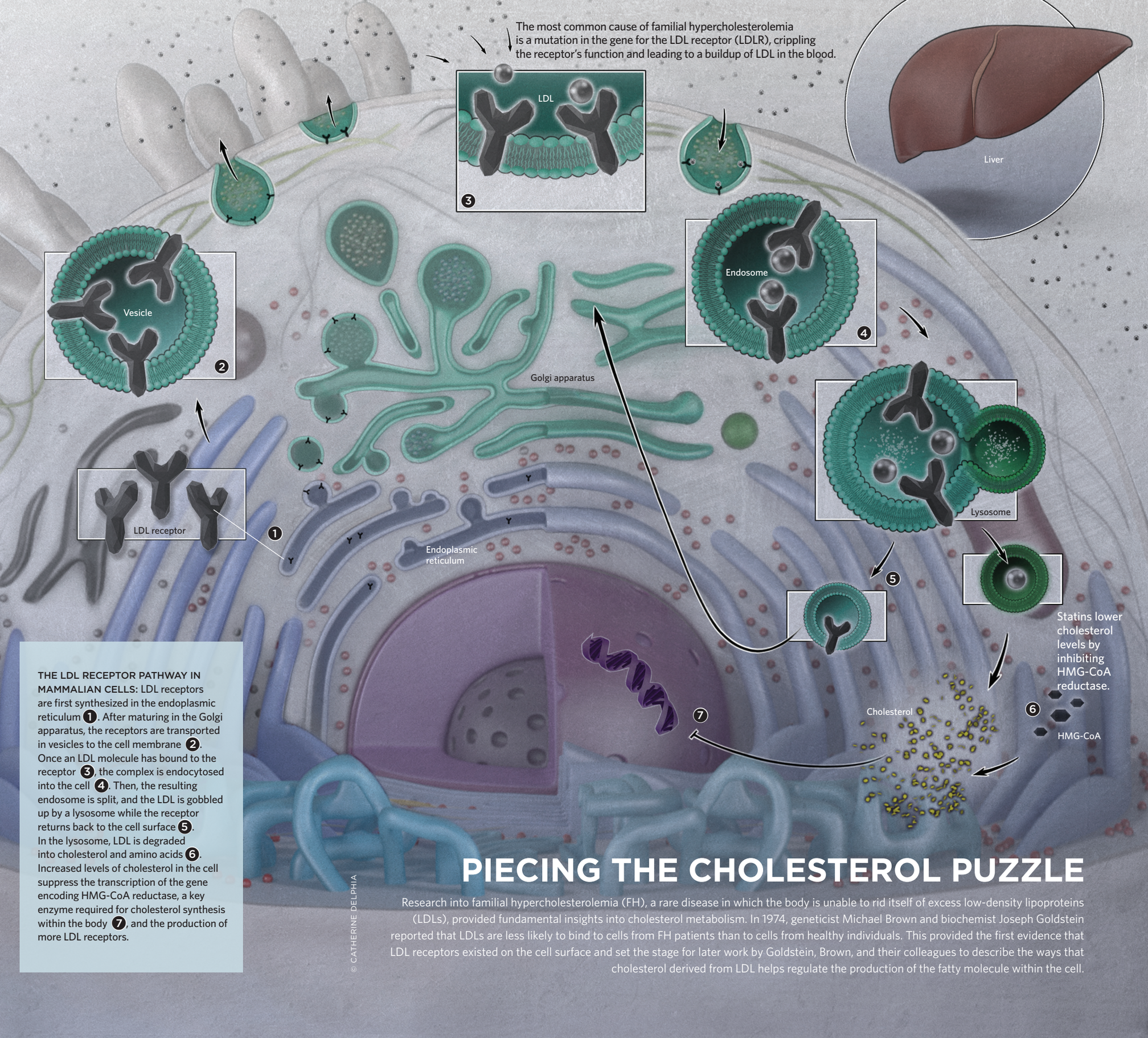

THE LDL RECEPTOR PATHWAY IN MAMMALIAN CELLS: LDL receptors are first synthesized in the endoplasmic reticulum (1). After maturing in the Golgi apparatus, the receptors are transported in vesicles to the cell membrane (2). Once an LDL molecule has bound to the receptor (3), the complex is endocytosed into the cell (4). Then, the resulting endosome is split, and the LDL is gobbled up by a lysosome while the receptor returns back to the cell surface (5). In the lysosome, LDL is degraded into cholesterol and amino acids (6). Increased levels of cholesterol in the cell suppress the transcription of the gene encoding HMG-CoA reductase, a key enzyme required for cholesterol synthesis within the body (7), and the production of more LDL receptors.

PIECING THE CHOLESTEROL PUZZLE

Research into familial hypercholesterolemia (FH), a rare disease in which the body is unable to rid itself of excess low-density lipoproteins (LDLs), provided fundamental insights into cholesterol metabolism. In 1974, geneticist Michael Brown and biochemist Joseph Goldstein reported that LDLs are less likely to bind to cells from FH patients than to cells from healthy individuals. This provided the first evidence that LDL receptors existed on the cell surface and set the stage for later work by Goldstein, Brown, and their colleagues to describe the ways that cholesterol derived from LDL helps regulate the production of the fatty molecule within the cell.