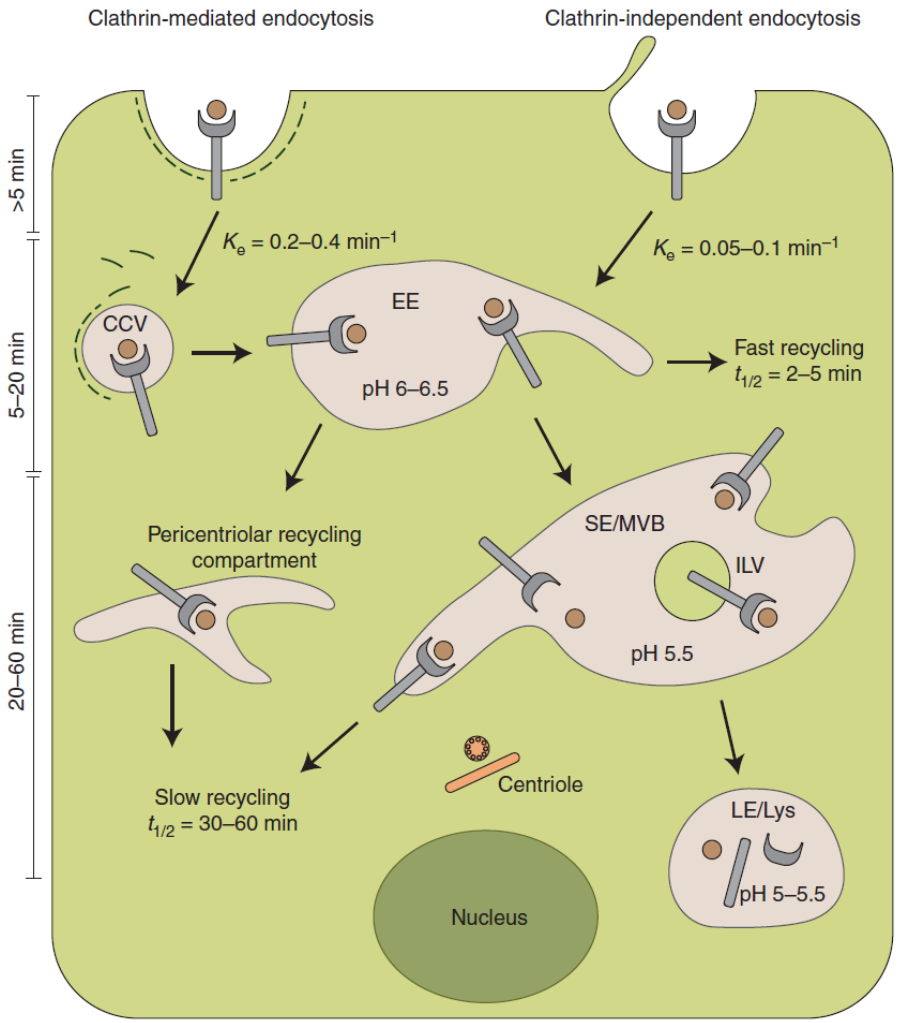

Figure 1. Pathways of RTK endocytosis. RTKs are endocytosed by clathrin-mediated and clathrin-independent mechanisms. Typical rate constants (K_e) for RTK internalization through both pathways are shown. Clathrin-coated vesicles are uncoated shortly after fission from the plasma membrane and fuse with early endosomes (EEs). In the most well-studied EGFR system, EGFR-ligand complexes are detected in these highly dynamic, morphologically heterologous compartments within 2–5 min after EGF stimulation (Haigler et al. 1979; Beguinot et al. 1984; Miller et al. 1986; Hopkins et al. 1990). Ligand-RTK complexes remain intact but certain ligands dissociate from the receptor in the acidic environment of the endosomal lumen. Released ligands remain in the vesicular parts of endosomes (most of the endosomal volume), whereas unoccupied receptors are found mainly in tubular extensions (most of the membrane area). Ligand-occupied and unoccupied RTKs can rapidly recycle from EEs through the process of back fusion of peripheral EEs with the plasma membrane or via tubular carriers derived from these endosomes (retroendocytosis). EEs mature into sorting endosomes (SE) or multivesicular bodies (MVBs) in which RTKs are incorporated into intraluminal vesicles (ILVs) by inward membrane invagination. RTKs can also be delivered to the pericentriolar Rab11-containing recycling compartment. Recycling of unoccupied and ligand-occupied RTKs is slower from the SE/MVBs and recycling compartment. SE/MVBs gradually lose early endosome components, such as Rab5 and EEA.1, and recycling cargo (such as transferrin receptors) while become enriched in resident late endosomal proteins (such as Rab7), thus maturing into late endosomes. Fusion of late endosomes with primary lysosomes carrying proteolytic enzymes results in degradation of receptors and growth factors. A typical time scale of RTK endocytosis, their accumulation in EEs, and SE/MVBs is shown in minutes.