SL08 **Endocytotic Pathways in Drug Delivery**

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With a few exceptions, the uptake of macromolecular cargo into cells occurs by the process of endocytosis. There is currently very good evidence for the existence of multiple, distinct endocytotic pathways, with each being responsible for the cellular uptake of selective subsets of extracellular cargo. The most well characterized endocytotic pathways are the clathrin-dependent and caveolin-dependent pathways, which mediate receptor-dependent endocytosis. On the other hand, clathrin- and caveolin-independent pathways are responsible for either receptor-dependent or fluid-phase endocytosis, although the molecular and mechanistic characterization of these clathrin- and caveolin-independent endocytotic pathways is still preliminary. The particular route of endocytosis will also affect post-endocytotic sorting and processing of endocytosed cargo, which, in turn, may affect the efficacy of drug delivery to target cells and organs. The exploitation of these endocytotic pathways for drug delivery would be greatly facilitated by a better understanding of these pathways at a basic molecular and mechanistic level. An overview of these pathways will be presented. In addition, a number of examples of receptor-dependent pathways that have been targeted for cellular drug delivery will also be presented, including work from our department.

The role of a multi-domain putative scaffold protein, LIM- and SH3-domain containing protein (LASP-1), in a type of clathrin- and caveolin-independent endocytotic pathway, macropinocytosis, will also be presented. LASP-1 is an F-actin-binding protein that is the target of protein kinase A and Abelson tyrosine kinase. LASP-1 is expressed in a select variety of cells in vivo and is also overexpressed in a number of metastatic cancer cells. This overexpression may contribute to a metastatic cellular phenotype. LASP-1 binds to a number of other proteins in addition to F-actin. These binding partners may in turn regulate the ultimate function of LASP-1. Overexpression of LASP-1 stimulates the formation and/or maintenance of filopodia, the formation of actin comet tails, and the formation of large endocytotic structures, which appear to be macropinosomes. The formation of these LASP-1-dependent macropinosomes appears to be stimulated by epidermal growth factor (EGF), and some of these macropinosomes contain endocytosed EGF. LASP-1 may regulate the formation of macropinosomes and may therefore be an important regulator of drug delivery via macropinocytosis.