Nano-scale imaging by secondary ion mass spectrometry (NanoSIMS) is a cutting-edge method to visualize and quantify the assimilation, storage and transfer of metabolites, labeled with stable isotopes, within biological samples at subcellular scales. Pre-imaging of fixed and resin embedded samples with scanning- (SEM) or transmission- (TEM) electron microscopy allows recognition of areas of interest at the ultrastructural level. Images of the isotope distribution obtained with the NanoSIMS instrument on the identical section of the sample can then be correlated with the electron micrographs. The choice of the sample preparation and correlative observation method, SEM or TEM, depends on the spatial resolution required and the nature of the specimen. Pre-imaging in SEM of a sample block face that was previously trimmed with an ultra-microtome is an easy and fast approach for investigation of large tissue or whole unicellular organisms (up to several hundreds of microns). In this way, even partially mineralized samples that are difficult or impossible to section can be analyzed. For higher-resolution and subcellular observations, TEM analysis of ultrathin resin sections (< 100 nm in thickness) have to be performed. Compared to SEM, TEM has a much smaller field of view, however, automatic acquisition of multiple, overlapping images in the TEM allows reconstruction of an entire TEM section at high spatial resolution. Here, we illustrate the power of combining NanoSIMS and electron microscopy in Life Sciences to study trafficking of microbial factors in a beneficial host - bacteria symbiosis and for tracking metabolic fluxes of 13C- and 15N- labeled molecules in marine unicellular organisms or in small invertebrates.

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