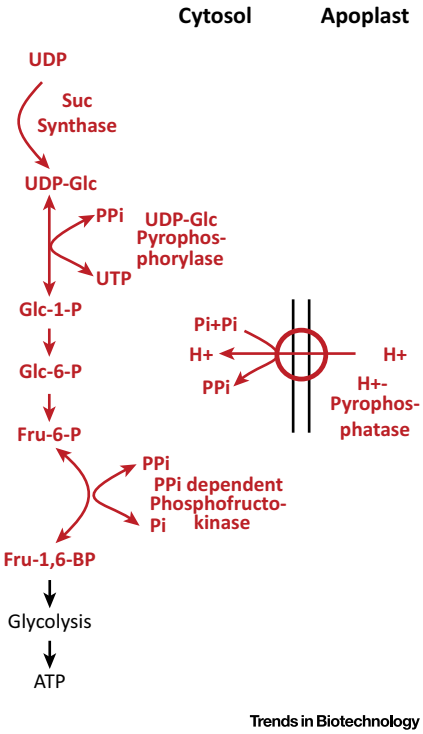

Figure 2. Sucrose Utilization in the Absence of Invertases. Sucrose hydrolysis via the pyrophosphate (PPi)-dependent Sucrose Synthase pathway (modified from [5]).

For example, increased antioxidant enzyme activity has also been observed [8], and further studies are required to determine if this beneficial phenotype is as universal as the improved salt and drought responses, augmented plant biomass, and yield observed in a plethora of other agriculturally important crops.

The ability to dramatically improve both monocot and dicot crops through augmented H^+-PPase expression is now self-evident. However, to fully harness this know-how, and leverage it with other technologies, a mechanistic rationale for these changes in a variety of crops is required. Given the recent advances, it is tempting to now speculate that H^+-PPase upregulation specific to both phloem and heterotrophic tissues could have additive effects that further enhance crop yield.

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Forum

Biomedical Potential of mTOR Modulation by Nanoparticles

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Modulation of the mammalian target of rapamycin (mTOR), the principal regulator of cellular homeostasis, underlies the biological effects of engineered nanoparticles, including regulation of cell death/survival and metabolic responses. Understanding the mechanisms and biological actions of nanoparticle-mediated mTOR modulation may help in developing safe and efficient nanotherapeutics to fight human disease.

Nanoparticles Modulate Mammalian Target of Rapamycin (mTOR) Signaling

Engineered nanoparticles have significant biomedical potential due to their unique physicochemical properties afforded by small size and large surface area. Synthesized by various top-down or bottom-up approaches, they are classified as soft (e.g., lipid- and polymer-based) or hard (e.g., metal, metal oxide, quantum dots, carbon, and ceramic) nanoparticles. Soft nanoparticles are mainly used for drug delivery, while hard nanoparticles can serve as diagnostic agents or therapeutics that directly interfere with the pathological process. In contrast to diagnostic and drug-delivery uses, the direct therapeutic potential of nanoparticles has only rarely been translated into a clinical setting. This mainly stems from a considerable complexity of nanoparticle interaction with

Box 1. Regulation of the mTOR Pathway by Biological Stimuli and Nanoparticles

mTOR serves as the catalytic core of two distinct complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2), which differ in their composition (mainly defined by the adaptors Raptor and Rictor, respectively), downstream targets, and sensitivity to allosteric mTOR inhibitor rapamycin. Binding of growth factors and hormones to receptor tyrosine kinases (RTK) activates mTOR through phosphoinositide 3-kinase (PI3K)-dependent activation of AKT (Figure I), which relieves tuberous sclerosis complex (TSC1/2)-mediated inhibition of the mTOR stimulator Ras homolog enriched in brain (RHEB) (a TSC1/2-independent pathway also exists). RTK-mediated activation of extracellular signal-regulated kinase (ERK) through RAS–RAF–MEK cascade, as well as activation of Ras-related GTPases (RAGs) by amino acids, also stimulate mTORC1 activity (Figure I). Activation of AMP-activated protein kinase (AMPK) by energy deficit inhibits mTORC1 via TSC1/2-dependent and -independent mechanisms, while ROS modulate mTOR activity in an AKT- or AMPK-dependent manner (Figure I). Through phosphorylation of eukaryotic translation initiation factor 4E-binding proteins (4E-BPs) and p70 ribosomal S6 kinases (S6K), and by upregulating the expression of sterol regulatory element-binding proteins (SREBPs), mTORC1 stimulates anabolic processes, such as protein, nucleotide, and lipid synthesis, and regulates energy metabolism to fuel cellular growth, proliferation, and survival (Figure I). Simultaneously, by inhibiting Unc-51-like autophagy-activating kinase 1 (ULK1), mTORC1 suppresses autophagy, a catabolic process that recycles intracellular material, and can either increase or decrease cell survival in a context-dependent manner (Figure I). Much less is known about the regulation and function of rapamycin-insensitive mTORC2, which regulates cytoskeletal organization, energy metabolism, and cell survival via activation of AGC kinases AKT, protein kinase Cα, and serum/glucocorticoid regulated kinase 1 (SGK1) (Figure I). Nanoparticles (NP) inhibit mTORC1 through suppression of AKT and activation of AMPK (Figure I). It is possible that nanoparticle-mediated inhibition of AKT is at least in part secondary to that of mTORC2, or that nanoparticles can directly inhibit mTORC1 (Figure I, broken lines). Nanoparticles can also activate AKT/mTORC1 in particular conditions (Figure I). Both AMPK-mediated suppression and AKT-mediated stimulation of mTORC1 activity by nanoparticles could be achieved through modulation of ROS (Figure I). The proposed interactions are discussed in more detail in the main text.

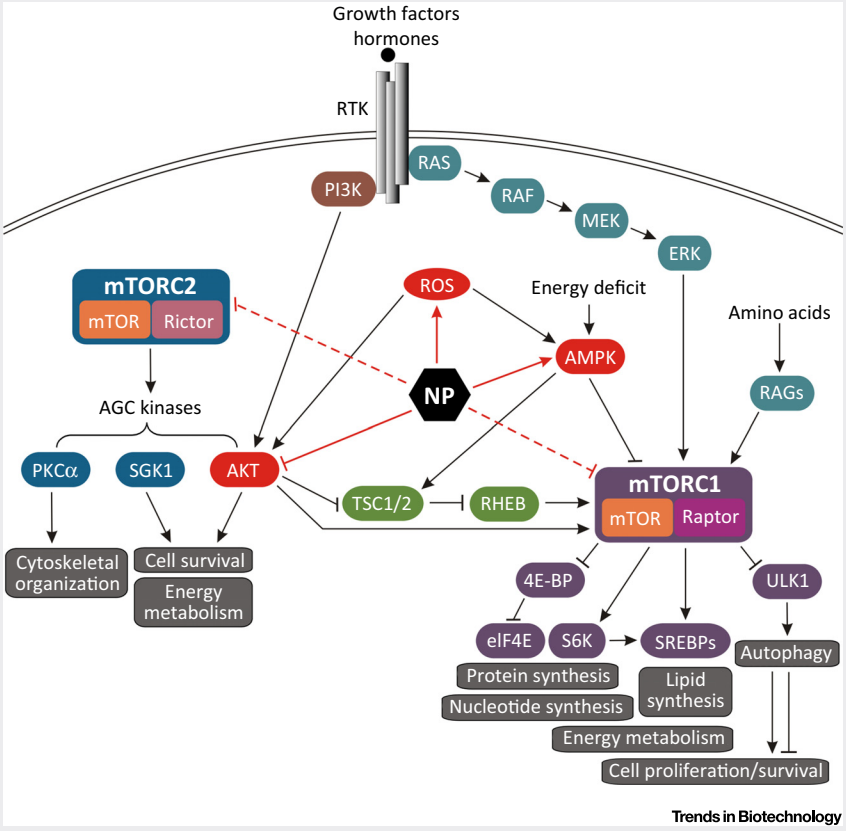

Figure I. Nanoparticle Interaction with Intracellular Signaling Pathways Regulating mTOR Activation and Function.

living cells, resulting in uncertainties concerning the benefits and side-effects. To overcome this, we require a better insight into the interaction of nanoparticles with intracellular signaling pathways regulating cell growth, proliferation, survival, and death, as well as specific cellular functions. Recent research demonstrated that various nanoparticles modulate the activation of the serine/threonine kinase mTOR [1–12], an evolutionarily conserved master regulator of cell/organismal homeostasis that integrates diverse environmental cues (nutritional and hormone/growth factor-mediated) to control cell physiology [13]. Dysregulation of mTOR signaling underpins aging and plethora of diseases, and mTOR modulators (e.g., rapamycin, active-site mTOR inhibitors, and biguanides) are candidates for the therapy of cancer, metabolic, inflammatory, cardiovascular, and neurological disorders [13]. Herein we highlight recent findings that nanoparticles exert their biological effects at least in part via mTOR modulation (Box 1).

mTOR Inhibition by Nanoparticles

Most of the investigated nanoparticles inhibited mTOR activation in various types of both cancer and normal cells (Table 1). The treatment with nanoparticles reduced the phosphorylation of mTOR [1–10] and the mTORC1 substrate S6K [1–6,9,10], thus indicating a decrease in mTORC1 catalytic activity. In accordance with the crucial role of mTORC1 in cell homeostasis and autophagy inhibition, its suppression by nanoparticles caused cell dysfunction and death, accompanied by an increased autophagic response [1–9]. Interestingly, while autophagy supports cell survival by removing damaged macromolecules and organelles, as well as by recycling macromolecules during energy deficit, autophagy induced by mTOR-inhibiting nanoparticles apparently contributed to cell death [1,3–6,9]. This is consistent with the findings that induction of autophagy by mTOR-inhibiting drugs frequently results in cell cycle arrest and cell death [13]. Although inactivated during autophagy initiation, mTORC1 is