This commentary discusses general concepts introduced in the article ‘Bulk autophagy induction and life extension is achieved when iron is the only limited nutrient in Saccharomyces cerevisiae’ by Montella-Manuel et al. (Biochem J (2021) 478: 811–837). Montella-Manuel et al. show that like central carbon metabolism, iron metabolism is also closely implicated in autophagy-mediated life extension via the TORC2 activator Ypk1p and the iron regulator Aft1p. While not being an iron-sulfur cluster protein, Aft1p interacts with such proteins and thus senses the redox status of the cell, which, similar to amino acids and AMP, reports its energetic status. Furthermore, glucose and iron deficiencies are interrelated as the diauxic shift in glucose depleted cells requires iron uptake for activating respiration in the absence of fermentation.

Longevity and its regulation have been intensively studied in the last three decades [1]. The assembly of different works on cell biology, nutrition and metabolism led to hallmark articles characterizing aging and health. In 2013 Lopez-Otin et al. [2] described nine molecular, intracellular, and intercellular characteristics as hallmarks of aging, responsible for the age-dependent deterioration in health. In 2016, the same group showed that all these hallmarks of aging are actually caused by metabolic perturbations [3], which constitute a general hallmark of health when involved in the interactions among the different components (molecules, tissues, cells, circuitries etc.) forming an organism [4]. However, there is a general consensus that longevity is directly correlated with functional autophagy (e.g. [5,6]) and caloric restriction (e.g. [7,8]). Both are regulated by the molecular target of rapamycin (mTOR) pathway, which serves as a hub integrating growth, stress resistance, anabolic/catabolic balance and nutrient availability [9]. Thus mTOR inhibition, similar to dietary restriction [10], can extend lifespan.

The article by Montella-Manuel and colleagues lies in illustrating the integration of iron in cellular energy transformation pathways and ensuing effects on cell fate. The main significance of this work by Montella-Manuel and colleagues lies in illustrating the integration of iron and central carbon metabolism as key regulators of autophagy, which consequently control lifespan. Moreover, the authors show that the mTOR-mediated iron regulation of autophagy is dependent on yeast proteins, which are key sensors of cell energy status, Ypk1p and Aft1p. Ypk1p closely interacts with the TORC2 autophagy activating complex and is a necessary mediator of its activity [11]. The Ypk1-TORC2 positively regulates autophagy via specific effects on mitochondrial respiratory parameters [12,13], electron transport chain complexes [14], the mitochondrial biogenesis factor peroxisome proliferator-activated receptor γ (PPARγ), and the catabolic master regulator protein kinase A, which regulates mitochondrial protein import through Tom22 [15]. Even more interesting is the involvement of the rheostat of the iron regulon, Aft1p, in mediating up-modulation of autophagy and lifespan. Aft1p is an iron sensor, which activates the iron regulon (a set of genes conjunctly increasing iron uptake upon activation and iron export and sequestration upon
inactivation) when iron-sulfur cluster (ISC) synthesis decreases [16]. This suggests that, while not being an ISC protein by itself, as the mammalian iron-responsive protein IRP1, which binds and activates the iron regulon as an ISC-devoid apo-protein [17], Aft1p senses iron through non-intrinsic ISC proteins, mainly Glutaredoxin 3 or 4 (Grx3p/4p) [18]. Upon binding of the Grx3p/4p ISC, which signals an iron replete status, Aft1p is dissociated from the iron regulon and thus inactivates iron uptake. Further control on iron regulon activation by Aft1p is provided by its translocation from the nucleus, mediated by Msn5 [19], which is also regulated by Aft1p phosphorylation by the MAP kinases Hog1p [19] and Slt2 [20].

Another meaningful result uncovered by Montella-Manuel and colleagues is revealed when iron metabolism is viewed in the context of the diauxic shift. Under this glucose-limited condition, the yeast cell is forced to activate mitochondrial respiration using respiratory carbon sources such as glycerol or ethanol. Contrarily, under glucose replete conditions the relative contribution of glycolysis, or, in yeast, glucose fermentation to ethanol and CO2, as a source of energy increases. The balance between these two energy transformation pathways is well investigated. The previously coined 'Warburg paradox', where the energetically less efficient glycolysis is preferred over mitochondrial respiration even under aerobic conditions enabling that respiration, has been extensively discussed, especially in the context of cancer metabolism. In general, while less ATP per glucose is produced in glycolysis as compared with respiration, ATP turnover is faster in glycolysis and therefore it might better maintain the rapid energy demand of a proliferating cell, its requirement for an efficient macromolecule synthesis, and its evasion of ROS produced in mitochondrial respiration. Indeed, plasticity between glycolysis and respiration can provide an important competitive advantage to intractable tumors such as [21], enabling them to proliferate in a fluctuating environment.

The Montella-Manuel article introduces additional players to the glycolysis-respiration duality: iron availability and its inter-dependent autophagy. The diauxic shift, and, comparably, hypoglycemic microenvironments in metazoans, force cells to revert to respiratory energy production. This shift is linked with higher iron demand since Krebs cycle enzymes and respiratory complexes contain ISC and heme prosthetic groups essential for their activity. Therefore, if the diauxic shift, or possibly hypoglycemic insult in metazoans, takes place in an iron deprived microenvironment, iron uptake will be upmodulated by Aft1p to ensure iron supply to its dependent respiratory complexes. Two key kinases are able to co-ordinate iron and glucose cellular availability — protein kinase A (PKA), inhibited in low glucose conditions due to scarcity of its cAMP activator [22], and the AMP Kinase (AMPK) Snf1p, which is an autophagy activating catabolic master regulator [19]. However, Snf1p is a general sensor of energetic deficiency and therefore activates catabolism using various substrates. Consequently, under glucose deficiency it is expected to not only activate iron uptake by the Aft1p-regulated iron regulon, but also to up-modulate glucose uptake [23], and, as shown by Montella-Manuel and colleagues, also iron deficiency-dependent autophagy. It is thus important to acknowledge that energy switches such as Snf1 are rheostatic rather than binary. In our example, iron deprivation might lead to autophagy, compensatory iron replenishment, but also glucose uptake — all of which may increase catabolism and correct the energetic deficiency caused by iron deprivation. The increased glucose uptake might down-modulate iron uptake through
glucose-dependent PKA activation and Snf1 inhibition, thus shifting energy transformation to fermentative instead of respiratory, with reduced iron demands. It is important to note, in this context, the work of Schothorst et al. [24], which shows that upon re-addition of iron and zinc after their depletion, the fermentation promoting PKA pathway is restimulated and causes a shift from storage and stress tolerance metabolism (i.e. accumulation of trehalose and glycogen) to an energy producing metabolism, which mobilizes these stores. Importantly, the quiescent state characterized by trehalose accumulation induces autophagy [25,26], which is required to maintain cell viability under nutritionally deprived conditions [27], such as those represented by iron depletion [28]. Functional autophagy is thus a prerequisite for maintaining quiescence and lifespan extension, which promote carbohydrate storage as potential energy (e.g. trehalose and glycogen). At the same time, autophagy is also a catabolic and degradative pathway of excess and potentially hazardous cytoplasmic substrates, which is also capable of moderately mobilizing stored carbohydrates upon ATP demand (glycophagy [29]). Figure 1 summarizes the role of autophagy in integrating central carbon and iron metabolism into a cellular mode which enables long term senescence and lifespan extension.

The involvement of autophagy in maintaining the quiescent state raises an important issue concerning the role of senescence in yeast and sporulating organisms, as compared with metazoans. The quiescent state in yeast and other sporulating organisms is aimed at maintaining cell homeostasis and survival under stress until conditions become favorable. Indeed a cross-talk between autophagy and sporulation in yeast has been documented [30]. In metazoans, on the other hand, cellular senescence, defined as permanent arrest of the cell cycle, usually protects against propagation of a damaged and potentially hazardous cell population, whose growth arrest enables its clearance and tissue regeneration. Cellular senescence thus correlates with organismal aging [31–33] mainly because high levels of senescent cells indicate that they evaded immunological surveillance and that the regenerative capacity is deficient. Namely, cellular senescence essentially reports immunological and regenerative deficiencies. On the other hand, in cancer, senescence, and, in particular, oncogene-induced senescence, demonstrated in some cases to be supported by autophagy [34], is generally considered tumor suppressive. Therefore, the presence of senescent cells within tumors (e.g. in premalignant pancreatic intraepithelial neoplasia (PanIN) lesions) is generally not considered immunosurveillance evasion because these senescent tumor islets are growth arrested and do not proliferate. A known exception, however, is the tumorigenic paracrine effect of PanIN, in which those cells are not a part of the tumor [35].

Lastly, we would like to close this commentary by demonstrating the similarity between iron, or, more precisely, iron in ISC, and known energy sensors. Autophagy is generally activated by starvation, which means that the cell senses an energetic insufficiency it needs to correct by activating a catabolic pathway. The molecules directly sensed are usually amino acids, whose deficiency can be detected by unconjugated tRNA [36], or AMP, whose levels are inversely correlated with energy status and which is sensed by the mTOR inhibitor AMPK. Iron depletion, on the other end, might seemingly not represent cell energy levels and yet it also activates autophagy. If iron is sensed via ISCs, as done by Aft1, which interacts with the ISC proteins Grx3p/4p, it can actually report the energy status of the cells by the redox potential. Each ISC protein probably has a different redox potential [37] and therefore together ISC proteins report the redox potential of the cell. As reducing equivalents (NADH, NADPH and glutathione) are convertible to ATP, the reducing capacity of the cells is a direct measure of its available energy. Thus, sensing iron levels (via ISC) by the Aft1-Snf1 system, as reported by Montella-Manuel and colleagues, and the activation of autophagy in a manner inversely proportional to iron levels is equivalent to the activation of autophagy according to cellular energy demand — in the same way it is done for the canonical energy sensors amino acids and AMP.

Competing Interests
The author declares that there are no competing interests associated with this manuscript.

Abbreviations
ISC, iron-sulfur cluster; PKA, protein kinase A; PanIN, pancreatic intraepithelial neoplasia; mTOR, molecular target of rapamycin.

References
