Regulation of nutrient utilization in filamentous fungi

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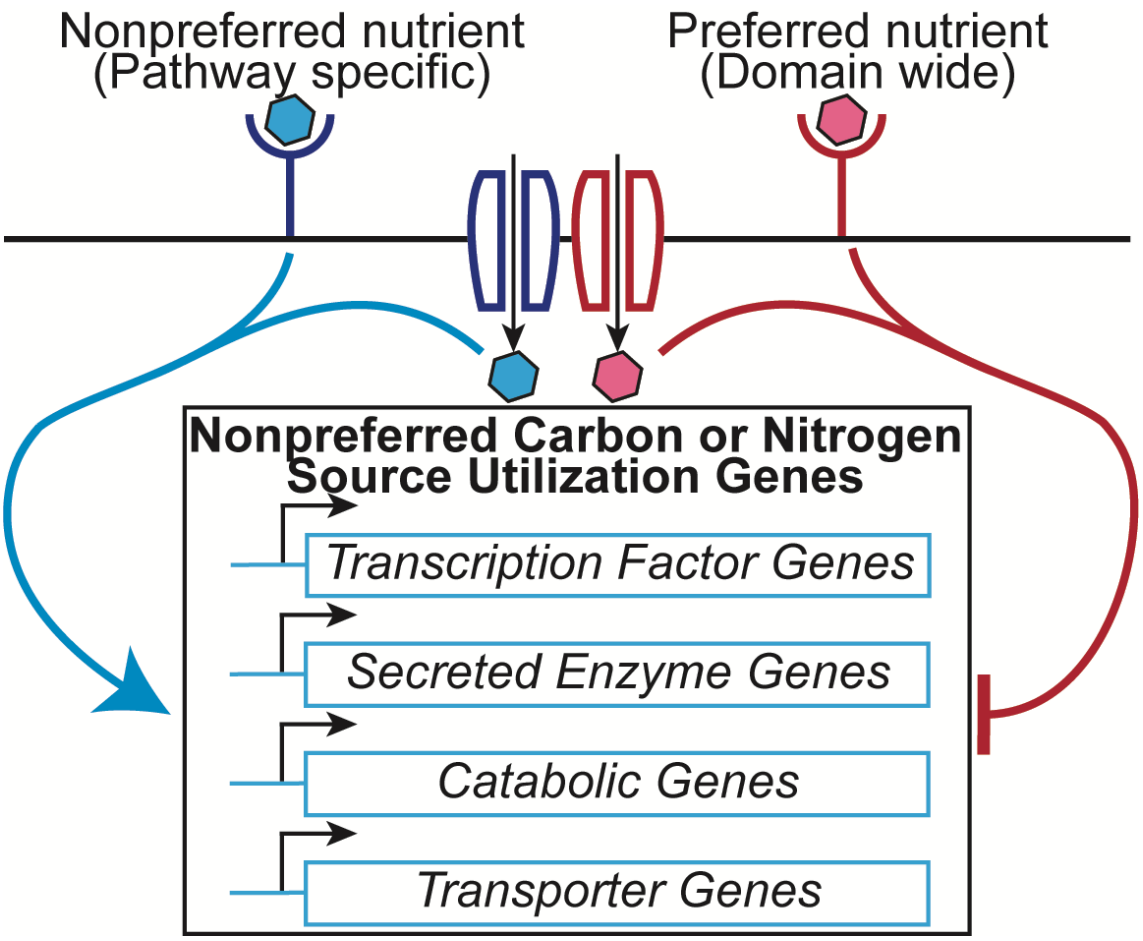

Abstract

Organisms must accurately sense and respond to nutrients to survive. In filamentous fungi, accurate nutrient sensing is important in the establishment of fungal colonies and in continued, rapid growth for the exploitation of environmental resources. To ensure efficient nutrient utilization, fungi have evolved a combination of activating and repressing genetic networks to tightly regulate metabolic pathways and distinguish between preferred nutrients, which require minimal energy and resources to utilize, and nonpreferred nutrients, which have more energy intensive catabolic requirements. Genes necessary for utilization of nonpreferred carbon sources are activated by transcription factors that respond to the presence of the specific nutrient and repressed by transcription factors that respond to the presence of preferred carbohydrates. Utilization of nonpreferred nitrogen sources generally requires two transcription

factors. Pathway-specific transcription factors respond to the presence of a specific nonpreferred nitrogen source, while another transcription factor activates genes in the absence of preferred nitrogen sources. In this review, we discuss the roles of transcription factors and upstream regulatory genes that respond to preferred and nonpreferred carbon and nitrogen sources and their roles in regulating carbon and nitrogen catabolism.

Key Points

- Interplay of activating and repressing transcriptional networks regulates catabolism
- Nutrient-specific activating transcriptional pathways provide metabolic specificity
- Repressing regulatory systems differentiate nutrients in mixed nutrient environments

Keywords

Metabolic regulation, nutrient sensing, carbon catabolite repression, nitrogen catabolite repression, transcriptional regulation, filamentous fungi

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Introduction

Filamentous fungi occupy a vast diversity of environmental niches and lifestyles ranging from soil and marine-dwelling saprophytes to plant symbionts to pathogens of plants and animals. To facilitate their diverse lifestyles, fine-tuned metabolic regulatory systems have evolved that allow fungi to efficiently sense and utilize nutrients available in their environment. In particular, the ability to readily utilize insoluble nutrient sources distinguishes filamentous fungi from many other microorganisms. The size and insoluble nature of these nutrients necessitates extracellular processing. Filamentous fungi secrete substantial quantities of glycosyl hydrolases, proteases, and other degradative enzymes in order to access these nutrients with otherwise low bioavailability (Benocci et al. 2017; Gurovic et al. 2023; Hage and Rosso 2021; Huberman et al. 2016; Sakekar et al. 2021). While the capacity to breakdown and utilize complex and insoluble substrates is paramount to the ecological roles of many filamentous fungi, these traits are also highly desirable industrially where filamentous fungi are utilized as microbial factories to produce enzymes, secondary metabolites, and fermentation products. The breakdown of insoluble nutrients is also important in breaching plant and, potentially, animal defenses during pathogenesis (Doehlemann et al. 2017; Rafiei et al. 2021; Ries et al. 2018). The study of nutrient sensing and utilization in filamentous fungi clarifies the role of these organisms within their ecological niches, improves our understanding of fungal diseases, and informs genetic engineering for industrial purposes.

Not all nutrients have the same enzymatic requirements for utilization. The diversity of nutrients utilized by filamentous fungi, coupled with the differing energy and resource costs needed for their breakdown, has led to the evolution of fine-tuned and hierarchical catabolic regulatory systems. To activate genes necessary for utilization of a specific nutrient, the nutrient itself, a breakdown product of the nutrient, or a modified version of the nutrient can act as a signaling molecule to indicate the presence of the nutrient (Najjarzadeh et al. 2021; Van Dijck et al. 2017; Wu et al. 2020; Znameroski et al. 2012). Subsequently, this signal turns on specialized

activating transcription factors that ensure the transporters, secreted enzymes, and catabolic enzymes necessary for utilization are expressed (Fig. 1 and Table 1). Meanwhile, other regulatory systems distinguish between the available nutrients and either repress or fail to activate the expression of genes associated with utilization of less preferred nutrients when a more preferred nutrient is available (Fig. 2).

While many reviews focus on the regulation and utilization of a subset of nutrients (e.g. lignocellulose [rev. in (Benocci et al. 2017)]), or nutrients containing a particular element (i.e., sulfur [rev. in (Amich 2022)], iron [rev. in (Misslinger et al. 2021)], or phosphate [rev. in (Bhalla et al. 2022)], etc.), recent and historical work suggests that regulation of the genes involved in different nutrient classes is intertwined (Arst and Cove 1973; Cohen 1973; Dementhon et al. 2006; Huberman et al. 2021a; Huberman et al. 2021b; Katz et al. 2006; Kelly and Hynes 1977; Macios et al. 2012; Snyman et al. 2019; Wu et al. 2020; Xiong et al. 2017). In this review, we provide an overview of the interplay of the activating and repressing regulatory systems involved in carbon and nitrogen catabolism in filamentous fungi. We briefly discuss a number of the genetic pathways that respond to specific carbon and nitrogen sources to activate expression of genes necessary for utilization of specific nutrients (Fig. 1 and Table 1). We then focus in more detail on the carbon and nitrogen catabolite repression pathways, which repress or fail to activate genes necessary to utilize nonpreferred nutrients when preferred nutrients are available (Fig. 2). As the history of the discovery and early characterization of many of these pathways has been covered in detail in a number of other reviews [reviewed in (Benocci et al. 2017; Hoffmeister 2016; Huberman et al. 2016; Marzluf 1997; Ries et al. 2018; Tudzynski 2014)], this review gives a brief background of the discovery of the genes that regulate nutrient utilization as context for our focus on more recent studies that use modern genomic, genetic, cell biological, and biochemical tools to investigate the role these regulatory networks play in nutrient utilization and the questions for further study that are still outstanding.

Activation of Nutrient Utilization Pathways

Activation of genes required for nutrient utilization can occur in response to specific nutrients or in response to starvation for a nutrient element. Filamentous fungi generally activate genes necessary for utilization of specific carbon sources in response to that carbon source or degradation products of that carbon source (Wu et al. 2020). Activation of nitrogen utilization genes can occur in response to nitrogen starvation and/or the presence of a specific nitrogen source (Huberman et al. 2021a). Here we discuss transcription factors that activate expression of nutrient utilization genes in response to specific carbon and nitrogen sources (Fig. 1 and Table 1).

ACTIVATION OF CARBON UTILIZATION PATHWAYS

Filamentous fungi can utilize a wide variety of carbohydrates from simple sugars to the complex carbohydrates present in the plant cell wall. Many of these carbohydrates require specialized enzymes and transporters for utilization. The genes encoding these enzymes and transporters are activated by transcription factors in response to the presence of specific nutrients. Many of these transcription factors are broadly conserved among ascomycete filamentous fungi with some divergence in the nutrient specificity and breadth of the regulon (Dalal and Johnson 2017; Todd et al. 2014).

Many filamentous fungi exist as saprotrophs, where they break down dead plant material into its component parts. The plant cell wall is composed of four main carbohydrate polymers: cellulose, hemicellulose, pectin, and lignin. Cellulose is the most abundant plant cell wall polysaccharide and is composed of long chains of β-1,4-linked glucose molecules organized into microfibrils that provide structural support (Rongpipi et al. 2018). These cellulose microfibrils are held together by a combination of hemicellulose, pectin, and lignin, which are all more amorphous in nature (Zhang et al. 2021a). Hemicellulose crosslinks cellulose microfibrils and is mainly composed of xylans, arabinans, mannans, mixed linkage β-glucans, and

xyloglucans (Zhang et al. 2021a; Zhang et al. 2021b). Pectin forms a matrix for cellulose microfibrils and is rich in galacturonic acid (Shin et al. 2021). Lignin is composed of phenolic compounds and has covalent linkages with hemicellulose (Ralph et al. 2019; Terrett and Dupree 2019). Filamentous fungi are capable of degrading and utilizing all of these complex carbohydrates. However, more is known about the regulation of cellulose, hemicellulose, and pectin utilization than that of lignin. Filamentous fungi also utilize other plant-, microbe-, and animal-derived carbon sources.

Cellulose utilization

Most of the transcription factors required for activation of carbohydrate utilization fall into the zinc binuclear cluster class of transcription factors (Benocci et al. 2017). The zinc binuclear cluster transcription factor CLR-2/ClrB, is required for cellulose utilization in a number of filamentous fungi, including *Neurospora* and aspergilli (Coradetti et al. 2012). CLR-2 was originally identified in the Sordariomycete *Neurospora crassa*, where it regulates expression of cellulases, sugar transporters, and a small number of hemicellulases (Coradetti et al. 2012; Wu et al. 2020). Expression of *clr-2* in *N. crassa* is sufficient to activate its target genes, implying that posttranslational activation is unnecessary (Coradetti et al. 2013). In contrast, the transcriptional activator of *clr-2,* CLR-1, is another zinc binuclear cluster transcription factor that is regulated mainly by posttranslational interactions with CLR-3 (Coradetti et al. 2012; Huberman et al. 2017). CLR-3 inhibits CLR-1 activity in the absence of an inducer and contains a domain of unknown function that may be capable of binding sugar molecules (Ghosh et al. 2014; Huberman et al. 2017). CLR-1 is responsible for activating expression of *clr-2* and a small number of cellulase and transporter genes, while CLR-2 activates the majority of genes necessary for cellulose utilization (Coradetti et al. 2012; Craig et al. 2015; Wu et al. 2020).

Homologs of CLR-1 and CLR-2 exist in the genomes of many ascomycete filamentous fungi (Coradetti et al. 2012). While the role of these genes in cellulase production is generally conserved, the transcription factor regulons and regulatory mechanisms that control these

transcription factors differ somewhat between species. Like in *N. crassa*, CLR-2/ClrB is essential for full cellulase production in *Aspergillus nidulans* (Coradetti et al. 2012), *Aspergillus niger* (Raulo et al. 2016), *Aspergillus oryzae* (Ogawa et al. 2013), *Thermothelomyces thermophilus* (formerly *Myceliophthora thermophila*) (Zhang et al. 2022), and *Penicillium oxalicum* (Li et al. 2015). However, in several of these fungi, the expression of *clrB* is not sufficient to generate inducer-independent expression of cellulases, suggesting ClrB may be regulated posttranslationally (Coradetti et al. 2013; Gao et al. 2019). Additionally, while the activator of *clr-2* expression in response to cellulose in *N. crassa* is CLR-1, the same is not true for all ascomycete filamentous fungi (Coradetti et al. 2012). In *P. oxalicum* the transcription factor CxrA appears to play an important role in *clrB* activation (Liao et al. 2019; Yan et al. 2017).

A suite of additional transcription factors is also involved in cellulase production in various filamentous fungi, although their roles are less well conserved. In *Trichoderma reesei*, *xyr1* (described below) and four additional transcription factors regulate cellulase production. Two of these transcription factor genes were identified in a yeast one-hybrid screen for transcription factors that promote expression of a selectable marker under the promoter of the *cbh1* cellulase gene, leading these transcription factors to be termed *ace* for activator of cellulase expression (Saloheimo et al. 2000). Ace2 does activate expression of cellulase genes (Aro et al. 2001), however it was later determined that Ace1 is actually a cellulase gene repressor (Aro et al. 2003). Subsequent investigations identified two additional transcription factor genes involved in cellulase gene activation: *ace3* (Hakkinen et al. 2014) and *ace4* (Chen et al. 2021).

Although many transcription factors that regulate carbon utilization play a role specifically relating to utilization of that nutrient, there are a number of transcription factors that regulate cellular processes beyond what is strictly necessary for utilization of that specific carbon source. ClrC from *P. oxalicum* regulates cellulase gene expression along with

conidiation and the stress response (Lei et al. 2016). The *N. crassa* CLR-4 transcription factor plays a role both in modulating cellulase expression and in the cyclic AMP pathway (Liu et al. 2019). The evolutionary coupling of these catabolic and cellular processes in different fungi could potentially provide insights into their respective lifestyles and ecological roles.

Hemicellulose utilization

In *T. reesei*, expression of cellulases is fully coupled with hemicellulase expression and is regulated by the zinc binuclear cluster transcription factor *xlnR/xlr-1/xyr1* (Mach-Aigner et al. 2008; Rauscher et al. 2006; Stricker et al. 2006). This transcription factor is highly conserved among ascomycete filamentous fungi. In all but a few organisms, in which its regulon is more limited, *xlnR/xlr-1/xyr1* regulates xylose metabolism and xylanolytic enzyme production (Benocci et al. 2017). Regulation of additional enzymes differs among species. In *T. reesei*, *P. oxalicum*, and a few aspergilli, XlnR/Xyr1 regulates cellulase expression as well as xylanase expression (Li et al. 2015; Mach-Aigner et al. 2008; Rauscher et al. 2006; Stricker et al. 2006; van Peij et al. 1998a; van Peij et al. 1998b). However, in other species, such as *N. crassa*, the XLR-1 regulon is mainly limited to genes necessary to degrade and utilize hemicellulose (Sun et al. 2012; Wu et al. 2020). In *T. reesei*, expression of *xyr1* is sufficient to activate hemicellulase expression even in the absence of an inducer (Lv et al. 2015). However, a conserved point mutation in *xyr1/xlr-1* improves hemicellulase expression in the absence of an inducer in both *T. reesei* and *N. crassa*, suggesting that posttranslational modifications or conformational changes that occur upon interaction with an inducer of this transcription factor are important for function (Craig et al. 2015; Derntl et al. 2013). In *T. reesei*, Xyr1 activates gene expression by recruiting a subunit of the mediator complex, Gal11 (Med15), which in turn recruits RNA polymerase II (Zheng et al. 2020). Xyr1 also interacts with the conserved Cyc8/Tup1 corepressors to regulate (hemi)cellulase gene expression, perhaps through chromatin remodeling (Wang et al. 2021).

Hemicellulose also includes arabinan. While *xlnR/xlr-1/xyr1* plays a role in the regulation of arabinanolytic activity, in a number of fungi a separate transcription factor is the major

regulator of most genes encoding arabinanolytic enzymes and arabinose catabolic enzymes (Battaglia et al. 2011; Benocci et al. 2018; Ishikawa et al. 2018; Klaubauf et al. 2016; Meng et al. 2022; Wu et al. 2020). Transcription factors associated with arabinan utilization are present in several ascomycete filamentous fungi, however the arabinanolytic regulators are not well conserved relative to other transcription factors associated with plant cell wall degradation. The Sordariomycete transcription factor ARA-1/Ara1 regulates arabinan utilization in *N. crassa*, *T. reesei*, and *Magnaporthe oryzae* (Benocci et al. 2018; Klaubauf et al. 2016; Wu et al. 2020). Deletion of *ara-1* in *N. crassa* results in substantially reduced growth on arabinan, arabinose, and galactose, but no growth phenotype on xylan or xylose (Wu et al. 2020). Gene regulation by ARA-1 further supports its role in arabinan utilization (Wu et al. 2020). In the Eurotiomycetes, an unrelated transcription factor, AraR, regulates arabinan utilization. AraR is a paralog of XlnR in aspergilli that activates genes necessary for arabinan utilization in the presence of arabinose and arabinan (Battaglia et al. 2011; Ishikawa et al. 2018; Meng et al. 2022). Intriguingly, in *A. niger* a single point mutation is sufficient to yield inducer-independent expression of arabinanolytic enzymes (Reijngoud et al. 2019).

Mannans are another important component of hemicellulose. Despite this, the regulation of mannan utilization is more closely linked with cellulose than hemicellulose utilization in ascomycete filamentous fungi with significant crosstalk between cellulose and mannan utilization and competition at the level of carbohydrate uptake (Hassan et al. 2019). The major cellulase regulator CLR-2/ClrB also regulates production of mannanases (Craig et al. 2015; Ogawa et al. 2012; Ogawa et al. 2013; Samal et al. 2017; Wu et al. 2020). Indeed in *A. oryzae* the CLR-2/ClrB homolog was initially identified for its role in mannan utilization and named ManR (Ogawa et al. 2012). Curiously, *N. crassa* is capable of both mannan and glucomannan utilization but appears only to be able to sense glucomannan. However, constitutive expression of *clr-2* in *N. crassa* is sufficient to enable the utilization of mannan as a sole carbon source (Samal et al. 2017).

Pectin utilization

Pectin is primarily composed of galacturonic acid monomers and is structurally a much more heterogeneous substrate than either cellulose or hemicellulose. Perhaps as a consequence of this, no single transcription factor controls expression of all pectin utilization genes. In *N. crassa*, pectin degradation is regulated by two transcription factors: PDR-1 and PDR-2 (Thieme et al. 2017; Wu et al. 2020). PDR-1 is required for utilization of rhamnose, with a moderate role in galacturonic acid utilization (Thieme et al. 2017), while PDR-2 is required for galacturonic acid utilization (Wu et al. 2020). Although both transcription factors regulate pectin degradation, PDR-1 is responsible for degradation of homogalacturonan and rhamnogalacturonan I, while PDR-2 regulates pectate lyase gene expression (Thieme et al. 2017; Wu et al. 2020). Deletion of both transcription factor genes still allows for some growth on pectin substrates (Wu et al. 2020), perhaps because degradation of the pectin components arabinan and arabinose is regulated by a separate transcription factor (ARA-1), or because other unknown transcription factors are involved in regulating pectin utilization.

Orthologs of these two transcription factors play a role in pectin degradation in aspergilli. The PDR-1 ortholog RhaR regulates rhamnose utilization and secreted enzymes necessary for rhamnogalacturonan I degradation (Gruben et al. 2014; Pardo and Orejas 2014). RhaR is induced to activate expression of genes necessary to utilize pectin, not by rhamnose, but by a downstream metabolic intermediate, L-2-keto-3-deoxyrhamnoate (Chroumpi et al. 2020; Khosravi et al. 2017). The PDR-2 ortholog GaaR activates genes necessary for galacturonic acid utilization in both aspergilli and *Botrytis cinerea* (Alazi et al. 2016; Zhang et al. 2016). In *A. niger*, GaaR activity is repressed by the cytosolic protein GaaX (Niu et al. 2017). Inducer-independent expression of pectinolytic genes is possible through deletion of *gaaX* (Niu et al. 2017), a point mutation in *gaaR* (Alazi et al. 2019), and overexpression of *gaaR* (Alazi et al. 2018). The specific chemical inducer of galacturonic acid utilization genes and a number of

pectinases in *A. niger* is the pathway intermediate 2-keto-3-deoxy-L-galactonate (Alazi et al. 2017).

Utilization of other plant cell wall-derived sugars

Plant cell wall components are made up of soluble sugar molecules that require specialized catabolic enzymes for utilization. These catabolic pathways can be regulated by the transcription factor that is also responsible for activating expression of genes encoding the secreted enzymes that degrade the complex carbohydrate in which the sugar is found, specialized transcription factors that specifically activate the genes in the sugar catabolic pathways, or a combination of the two (Benocci et al. 2017; Wu et al. 2020). Xylose, arabinose, and galactose are found in hemicellulose and/or pectin (Shin et al. 2021; Zhang et al. 2021a; Zhang et al. 2021b). Utilization of these sugars by aspergilli involves an overlapping set of enzymes, including the genes involved in pentose catabolism, which are regulated by a combination of XlnR, AraR, and the transcription factor(s) that regulate galactose utilization (Christensen et al. 2011; Chroumpi et al. 2022; Gruben et al. 2012; Kowalczyk et al. 2015). The transcription factor GalX regulates galactose utilization in most aspergilli (Christensen et al. 2011; Gruben et al. 2012). In contrast, *A. nidulans* has two galactose utilization regulators: GalX and GalR. GalX is the major regulator of galactose utilization, regulating the expression of both enzymes necessary for galactose utilization and the transcription factor GalR, which has a more minor role in the regulation of galactose catabolic enzyme genes (Christensen et al. 2011; Meng et al. 2022).

A. nidulans utilizes galactose and arabinose simultaneously in media containing both sugars (Németh et al. 2019). In aspergilli GalX and AraR are the primarily regulators of galactose and arabinose utilization, respectively; however, there is crosstalk in the regulation of genes required for their utilization (Meng et al. 2022). AraR activates the expression of galactose catabolic enzymes in response to arabinose, allowing for utilization of galactose in the presence of arabinose even when cells are lacking *galR* and *galX* (Meng et al. 2022; Németh et

al. 2019). In a similar fashion GalR and/or GalX can compensate for the loss of *araR* and activate arabinose utilization genes in response to galactose (Meng et al. 2022). In the Sordariomycetes *N. crassa* and *T. reesei* ARA-1/Ara1 regulates utilization of both arabinose and galactose (Benocci et al. 2018; Wu et al. 2020).

The pentose catabolic pathway is necessary for utilization of both arabinose and the hemicellulose sugar xylose (Battaglia et al. 2014; De Groot et al. 2007). In *A. niger*, xylose and arabinose utilization are regulated by both AraR and XlnR. Deletion of both transcription factor genes is necessary to abolish xylose utilization in *A. niger* as both transcription factors regulate genes in the pentose catabolic pathway (Battaglia et al. 2011; Chroumpi et al. 2022). A similar phenomenon occurs in *T. reesei* where Xyr1 and Ara1 coregulate arabinose utilization, and deletion of both transcription factors is necessary to fully abolish growth on xylose (Benocci et al. 2018). This coregulation by AraR or Ara1 and XlnR/Xyr1 is in contrast to the regulation of xylose and arabinose utilization in *N. crassa*, where XLR-1 and ARA-1 are responsible for regulation of xylose and arabinose utilization, respectively, and these transcription factors do not show functional redundancy (Sun et al. 2012; Wu et al. 2020). As mentioned above, utilization of the major components of pectin, rhamnose and galacturonic acid, is regulated by PDR-1/RhaR and PDR-2/GaaR, respectively, although some crosstalk exists between the two regulons (Alazi et al. 2016; Gruben et al. 2014; Niu et al. 2017; Pardo and Orejas 2014; Thieme et al. 2017; Wu et al. 2020; Zhang et al. 2016).

Cellulose is made up of glucose, which, as a preferred carbon source, does not require specialized regulatory pathways to utilize. However, cellobiose, a dimer of β-1,4-linked glucose molecules, is a breakdown product of cellulose. Utilization of cellobiose is regulated by CLR-1/ClrA and CLR-2/ClrB in *N. crassa* and *A. nidulans* (Coradetti et al. 2012). In *N. crassa*, CLR-1 is the major regulator of cellobiose utilization, while CLR-2 appears to have no role in regulating utilization of cellobiose. In contrast, both ClrA and ClrB play a role in cellobiose utilization in *A.*

nidulans. ClrB is required for cellobiose utilization, while the role of ClrA in cellobiose utilization is more minor (Coradetti et al. 2012).

Utilization of plant energy storage molecules

Beyond the plant cell wall, plants also contain substantial quantities of other polymerized carbon sources. These include the energy storage molecules starch and inulin. Inulin consists of diverse species of β-1,2-linked fructose molecules (An et al. 2022), and its utilization requires the expression of inulolytic enzymes and sugar transporters. In aspergilli these genes are regulated by the transcription factor InuR, which also plays a role in sucrose utilization (Yuan et al. 2008).

Starch consists of amylose, linear chains of α-1-4-linked glucose molecules, and amylopectin, α-1-4-linked glucose polymers branched at α-1-6 glycosidic bonds. Starch is readily used as a carbon source by filamentous fungi, and this utilization is regulated by AmyR in aspergilli (Gomi et al. 2000; Tani et al. 2001) and penicillia (Liu et al. 2013) and COL-26/BglR/ART1 in *N. crassa*, *T. reesei*, and *Fusarium* (Nitta et al. 2012; Oh et al. 2016; Xiong et al. 2017). Unlike many of the other transcription factors directly regulating utilization of plant carbohydrates, the transcription factors regulating starch utilization have a number of homologs, and phylogenetic analysis reveals that AmyR from the Eurotiomycetes is not in the same clade as COL-26/BglR/ART1 from the Sordariomycetes (Xiong et al. 2017).

The expansion of AmyR and COL-26/BglR/ART1 homologs may have resulted in specialization of regulators in some of the aspergilli. Maltose is a soluble disaccharide building block of starch. In *A. nidulans*, starch and maltose utilization are both regulated by AmyR (Tani et al. 2001). However, while starch utilization is regulated by AmyR in *A. oryzae*, a small gene cluster of maltose utilization genes is regulated by the AmyR homolog MalR, which phylogenetically groups in a clade separate from both AmyR and COL-26 (Hasegawa et al. 2010). AmyR is translocated from the cytoplasm to the nucleus and activates expression of

target genes in response to isomaltose in both *A. nidulans* and *A. oryzae* (Makita et al. 2009; Suzuki et al. 2015). However, in *A. oryzae* MalR is constitutively found in the nucleus, and the maltose gene cluster is induced in response to maltose (Suzuki et al. 2015). Along with its role in starch utilization, COL-26 also plays a role in glucose sensing in *N. crassa* (Xiong et al. 2014), perhaps through regulation of glucose transporters (Li et al. 2021c).

There may be some crosstalk between AmyR and InuR regulation of sucrose and inulin in *A. niger*. While InuR plays the primary role in regulating sucrose and inulin utilization, AmyR has a small effect on the expression of genes necessary for utilization of these substrates in solid media, although minimal effect was seen in liquid media (Kun et al. 2023). A previous study of differences in the utilization of a whole plant biomass substrate in solid as opposed to liquid media observed some differences in the regulation of genes involved in plant biomass degradation (Garrigues et al. 2021). This effect is likely due to a wide variety of variables that differ between solid and liquid media, including fungal cellular development, aeration, osmolarity, and substrate availability. The extent of the role of AmyR and its homologs in the regulation of sucrose and inulin utilization and the difference in the utilization of these substrates in solid as opposed to liquid media still requires additional investigation.

Cutin utilization

One of the barriers plant pathogenic fungi must overcome to infect plants is the water-repellent plant cuticle, made up of the waxy polymers of hydroxy fatty acids cutin and cutan. Pathogenic fungi secrete cutinases to break down this polymer into fatty acid monomers, and cutinase expression is regulated by the transcription factors CTF1α/Ctf1 and CTF1β/Ctf2 in *Fusarium* species (Bravo-Ruiz et al. 2013; Li and Kolattukudy 1997; Li et al. 2002; Rocha et al. 2008). CTF1α and CTF1β and their orthologs FarA/Far1 and FarB/Far2, respectively, also regulate utilization of both short and long chain fatty acids. However, the role of the CTF1α/FarA/Far1 and CTF1β/FarB/Far2 transcription factors in short chain versus long chain

fatty acid utilization differs somewhat between species (bin Yusof et al. 2014; Bravo-Ruiz et al. 2013; Hynes et al. 2006; Li et al. 2002; Luo et al. 2016; Rocha et al. 2008; Roche et al. 2013; Sugui et al. 2008). Some fungal species also have a third homolog, FarC, whose function is unclear (Luo et al. 2016). While the roles of Ctf1/FarA/Far1 and Ctf2/FarB/Far2 in regulating lipid utilization are broadly conserved, the impact of these transcription factors on virulence varies among the plant pathogens *Fusarium oxysporum*, *Aspergillus flavus*, and *M. oryzae* (bin Yusof et al. 2014; Bravo-Ruiz et al. 2013; Li et al. 2002; Luo et al. 2016; Rocha et al. 2008). FarA and FarB may also play a role in mammalian pathogenesis, as the expression of these transcription factors is induced in response to neutrophils (Sugui et al. 2008).

Lignin utilization

FarA is also required for the utilization of the lignin component ferulic acid in *A. niger* (Arentshorst et al. 2022). Ferulic acid is a hydroxycinnamic acid that is metabolized by fungi through the CoA-dependent β-oxidative pathway, which is involved in fatty acid metabolism (Lubbers et al. 2021). Utilization of ferulic acid also requires the transcription factor FarD, which has some sequence similarity to FarA and FarB. However, unlike FarA and FarB, whose structures are typical for zinc binuclear cluster transcription factors, FarD contains a fungal specific transcription factor domain but lacks the zinc binuclear cluster domain that normally accompanies it (Arentshorst et al. 2022). Regulation of cinnamic acid utilization, another hydroxycinnamic acid lignin component, involves a different transcription factor in *A. niger*, SdrA (Lubbers et al. 2019a). SdrA regulates genes in a gene cluster responsible for the non-oxidative decarboxylation of cinnamic acid and sorbic acid (Lubbers et al. 2019a). Previous work showed that SdrA is also involved in regulating utilization of sorbic acid (Plumridge et al. 2010). Deletion of SdrA still allows for limited growth on both cinnamic acid and sorbic acid and some expression of several of the genes necessary for cinnamic and sorbic acid catabolism, so it is possible another transcription factor is also involved in the utilization of these organic acids (Lubbers et al. 2019a).

Utilization of plant-derived organic acids

Filamentous fungi are capable of utilizing a number of additional plant-derived organic acids as carbon sources. Quinic acid is an organic acid found in plant leaves and fruits (Clifford et al. 2017). The genes for quinic acid utilization are found in a gene cluster in Ascomycete fungi. While the genes in this cluster are well conserved, the order of the genes within the cluster differs from species to species (Asch et al. 2021). The quinic acid utilization gene cluster includes genes that encode quinic acid utilization enzymes and a quinic acid permease along with two regulatory genes: an activator, *qa-1F/qutA* that encodes a zinc binuclear cluster transcription factor, and a repressor, *qa-1S/qutR* (Case et al. 1992; Case et al. 1977; Case et al. 1978; Geever et al. 1989; Grant et al. 1988; Huiet 1984; Lamb et al. 1990; Whittington et al. 1987). QA-1F/QutA activates all of the genes in the quinic acid utilization gene cluster, and the activity of QA-1F/QutA is repressed by QA-1S/QutR in the absence of an inducer (Case et al. 1992). More recent genomic studies indicate that a number of additional genes outside of the quinic acid utilization gene cluster are also activated either directly or indirectly by QA-1F in response to quinic acid. One of these genes is the transcription factor gene *far-2* (discussed above for its role in regulating fatty acid metabolism (Roche et al. 2013)), which may play a role in activating genes in response to quinic acid (Tang et al. 2011). Due to the tight regulation and careful characterization of the quinic acid utilization regulatory system, *N. crassa qa-1F* and *qa-1S* are used as a powerful tool for precise control of gene expression in plants and animals (Persad et al. 2020; Potter and Luo 2011; Reis et al. 2018).

Tannins, including tannic acid, are polyphenolic aromatic compounds found in bark and other plant tissues (Tong et al. 2021). Fungi secrete tannases to degrade tannic acid and release gallic acid, which can be utilized as a carbon source (Lubbers et al. 2019b; Shao et al. 2020). In *A. niger*, expression of tannase and gallic acid utilization genes is repressed by TanX, which is a paralog of both the quinic acid utilization repressor QA-1S/QutR and the galacturonic acid utilization repressor GaaX (Arentshorst et al. 2021). Similar to the *qa-1S/qutR* and *qa-*

1F/qutA repressor-activator module, *tanX* is adjacent to the zinc binuclear cluster transcription factor gene *tanR* in the *A. niger* genome. TanR activates expression of tannase and gallic acid utilization genes, and the activity of TanR is repressed by TanX in the absence of an inducer. A fourth paralog of *qa-1S/qutR*, *tanX*, and *gaaX* exists in the *A. niger* genome whose role is yet to be elucidated (Arentshorst et al. 2021).

Utilization of fermentation-derived carbon sources

Filamentous fungi can also utilize nutrients produced by other microorganisms, including the common fermentation products ethanol and acetate. Ethanol utilization requires a specialized transporter and alcohol and aldehyde dehydrogenases, which are localized in a gene cluster regulated by the AlcR transcription factor (Fillinger and Felenbok 1996; Lockington et al. 1985). A number of carbon metabolites act as inducers for AlcR, including alcohols and threonine, which are converted to acetaldehyde, a toxic metabolite thought to be the true inducer of AlcR (Flipphi et al. 2002).

Acetate utilization by filamentous fungi is regulated by FacB/ACU-15. Catabolism of acetate requires the glyoxylate shunt, and specifically isocitrate lyase, whose expression is regulated by the FacB/ACU-15 transcription factor (Bibbins et al. 2002; Todd et al. 1997). FacB appears to be important for fungal virulence, as *Aspergillus fumigatus* strains lacking *facB* have reduced morbidity in murine and insect infection models (Ries et al. 2021). However, isocitrate lyase was demonstrated to be dispensable for virulence in *A. fumigatus* (Schöbel et al. 2007), and transcriptomic data suggests FacB plays a broader regulatory role than simply acetate utilization (Ries et al. 2021). This raises the possibility that the reduced virulence of strains lacking *facB* may not strictly be due to an inability to utilize acetate.

Scout enzyme activation

Because plant cell wall components are large polymers, the genes necessary to utilize these carbohydrates are induced by soluble plant cell wall breakdown products (Wu et al. 2020; Znameroski et al. 2012). To release these soluble breakdown products, when no carbon source

is readily available, filamentous fungi are predicted to secrete low levels of plant cell wall degrading “scout” enzymes, so named because they are used by the fungus to “scout” the surrounding environment for available plant cell wall polymers. These scout enzymes are regulated, at least in part, by the transcription factor VIB-1 (Wu et al. 2020). VIB-1 is a member of the p53 superfamily and plays roles in several cellular processes, including utilization of polymeric carbon sources (Ivanova et al. 2017; Wu et al. 2020; Xiong et al. 2014), heterokaryon incompatibility, and self/nonself recognition in filamentous fungi (Dementhon et al. 2006; Xiang and Glass 2002). Expression of a number of genes encoding plant cell wall degrading enzymes, as well as *clr-2* and *pdr*-2, are directly activated by VIB-1 (Wu et al. 2020). Additionally, we discuss a role for VIB-1 and its homolog XprG in protease regulation below.

ACTIVATION OF NITROGEN UTILIZATION PATHWAYS

During saprophytic and plant pathogenic growth, carbon is abundant, but nitrogen is limiting (Donofrio et al. 2006; Hao et al. 2021; Talbot et al. 1997). Filamentous fungi are capable of scavenging nitrogen from a variety of organic and inorganic sources. These include the preferred nitrogen sources glutamine, ammonium, and, for some fungi, glutamate, which can be imported and utilized with a limited repertoire of transporters and catabolic enzymes (Margelis et al. 2001). Nonpreferred nitrogen sources, including nitrate, nitrite, most amino acids, purines, amides, urea, and proteins, require production of a much more specialized and substantial array of transporters, catabolic enzymes, and, in the case of polymeric nitrogen sources, secreted enzymes (Huberman et al. 2021a; Marzluf 1997). Utilization of these nonpreferred nitrogen sources is regulated by a combination of pathway-specific transcription factors that activate genes in response to a particular nitrogen source and the more generalized transcription factor NIT-2/AreA, which activates genes in the absence of a preferred nitrogen source. We will discuss several known pathway-specific transcription factors (Fig. 1 and Table 1).

Nitrate utilization

The most well-studied pathway-specific transcription factor is NIT-4/NirA, which controls nitrate utilization (Burger et al. 1991; Yuan et al. 1991). This transcription factor is regulated, at least in part, through nuclear localization in the presence of nitrate. In *A. nidulans*, NirA nuclear localization is mediated by the nuclear exportin KapK (also known as CrmA). In the absence of nitrate, a conserved methionine in the nuclear export signal is oxidized by a flavin-containing monooxygenase, FmoB, exposing the nuclear export signal (Gallmetzer et al. 2015). In the presence of nitrate, the methionine is reduced, and the interaction of KapK with NirA is disrupted, leading to nuclear localization (Bernreiter et al. 2007; Gallmetzer et al. 2015). A similar nitrate-dependent nuclear localization of NirA occurs in *Fusarium fujikuroi* (Pfannmüller et al. 2017a). In *N. crassa*, NIT-4 binds the promoters and regulates expression of eight genes associated with nitrate utilization (Chiang and Marzluf 1995; Fu et al. 1995; Huberman et al. 2021a). Interestingly, activation of seven of these eight genes by NIT-4 occurs not only in response to nitrate but also in the absence of a nitrogen source, suggesting that NIT-4 may play a role in the activation of genes necessary for utilization of nonpreferred nitrogen sources when fungi are starved for nitrogen (Huberman et al. 2021a).

Amino acid utilization

Filamentous fungi can also utilize most amino acids as a nitrogen source. Several transcription factors are responsible for activating expression of amino acid utilization. However, only a limited number of transcription factors necessary for amino acid utilization have been identified thus far in filamentous fungi. In *A. nidulans*, the ArcA transcription factor induces expression of arginine catabolism genes in the presence of arginine (Bartnik and Weglenski 1974; Empel et al. 2001). Transcript levels of *arcA* appear to be independent of the presence of arginine and a single point mutation (L60I) is sufficient to yield constitutive arginase expression and activity (Empel et al. 2001). In addition to ArcA, the pleiotropic regulators KaeA and RrmA regulate expression of arginine catabolic genes at the level of transcription and RNA stability, respectively (Dzikowska et al. 2015; Krol et al. 2013; Olszewska et al. 2007).

PrnA is a transcription factor that regulates, and is a member of, a proline utilization gene cluster in *A. nidulans* (Hull et al. 1989; Jones et al. 1981; Sharma and Arst 1985). Unlike NirA, which is regulated through nuclear localization, PrnA exists in the nucleus even in the absence of an inducer (Pokorska et al. 2000). However, PrnA can only bind its targets when proline is present (Gómez et al. 2002). Nucleosome rearrangement also contributes to the regulation of proline utilization genes, which is dependent on PrnA and other factors (García et al. 2004). Tyrosine utilization is regulated by HmgR in *A. fumigatus* (Keller et al. 2011; Schmaler-Ripcke et al. 2009). The tyrosine utilization gene cluster, which includes HmgR, is conserved in aspergilli (Greene et al. 2014). HmgR is also conserved throughout penicillia and in *Talaromyces marneffei* (formerly *Penicillium marneffei*), although it is not always found in the tyrosine utilization gene cluster (Boyce et al. 2015; Greene et al. 2014).

In *N. crassa*, the regulatory roles of PrnA and HmgR are combined in a single transcription factor, AMN-1, which regulates proline, aromatic amino acid, and branched-chain amino acid utilization. AMN-1 has some sequence similarity to HmgR, although HmgR is not the closest homolog to AMN-1 in the aspergilli and *T. marneffei* (Huberman et al. 2021a). A clear homolog for PrnA does not exist in *N. crassa*. Neither the proline nor aromatic amino acid catabolic genes are contained in a gene cluster in *N. crassa*. However, AMN-1 binds the promoters and regulates most of the *N. crassa* homologs of the genes in the proline and tyrosine utilization gene clusters from aspergilli. AMN-1 activates genes necessary for amino acid catabolism not only in response to proline, aromatic amino acids, and branched-chain amino acids but also mannose (Huberman et al. 2021a). Intriguingly, the tyrosine utilization gene cluster in *T. marneffei* also contains a putative mannosidase (Boyce et al. 2015), suggesting the connection between mannose and amino acid catabolism may be conserved. This may indicate that cells use mannose as a signal for the presence of amino acids in the environment, perhaps because proteins secreted from eukaryotic cells are glycosylated with

mannose residues. However, further work will be necessary to investigate the connection between mannose and amino acid utilization.

Purine utilization

Purines are a nitrogen source for filamentous fungi whose utilization is regulated by the zinc binuclear cluster transcription factor PCO-1/UaY (Liu and Marzluf 2004; Suárez et al. 1995; Suárez et al. 1991). Both *pco-1* in *N. crassa* and *uaY* in *A. nidulans* are expressed constitutively (Liu and Marzluf 2004; Suárez et al. 1991). UaY activity is induced by uric acid and dihydroorotic acid (Scazzocchio and Darlington 1968; Suárez et al. 1995), and, like many other zinc binuclear cluster transcription factors, UaY functions as a homodimer (Cecchetto et al. 2012). Prior to induction, UaY can be found in both the cytoplasm and the nucleus. When *A. nidulans* cells are exposed to an inducer, UaY rapidly localizes entirely to the nucleus, which is necessary but not sufficient for UaY-mediated gene induction (Galanopoulou et al. 2014). Binding of UaY to DNA is at least partially dependent on the presence of an inducer (Oestreicher et al. 1997). Nicotinate (vitamin B3) is a nitrogen source for aspergilli that has some metabolic crosstalk with purine utilization (Bokor et al. 2022). The transcription factor HxnR regulates the three nicotinate utilization gene clusters in *A. nidulans*. This regulatory pathway is conserved in aspergilli, although the clustering of the genes varies between species (Ámon et al. 2017; Bokor et al. 2021).

Protein utilization

Proteins can serve as a nitrogen, carbon, and/or sulfur source. Thus, genes encoding proteases are activated in response to a number of stimuli, including nitrogen, carbon, or sulfur limitation, pH, and temperature (Dementhon et al. 2006; Hanson and Marzluf 1975; Jarai and Buxton 1994; Katz et al. 2006; Kitano et al. 2002; Snyman et al. 2019). Proteases are important during saprophytic growth, where they break down proteins from dead plant and animal matter, and during plant and human pathogenesis. In a subset of the aspergilli and penicillia, including *A. niger, A. fumigatus*, and *A. oryzae* but not *A. nidulans*, regulation of proteases and peptide

transporters is accomplished by the transcription factor PrtT/PrtR (Ballester et al. 2019; Chen et al. 2014; Mizutani et al. 2008; Punt et al. 2008; Sharon et al. 2009; Tanaka et al. 2021). The *prtT/prtR* and *amyR* genes are very close to each other in the genome, and AmyR and PrtT/PrtR appear to have opposing roles in the regulation of some amylases and proteases (Chen et al. 2014). Indeed, AmyR appears to repress the expression of *prtT* and some protease genes in *A. niger*, suggesting an interesting crosstalk between utilization of proteins and starch (Huang et al. 2020). Along with the connection between protease and amylase production in *A. niger*, PrtT also plays a role in regulating iron uptake and ergosterol biosynthesis in *A. fumigatus* (Hagag et al. 2012). Although proteases are thought to play a role in fungal virulence, deletion of *prtT* does not affect virulence in *Penicillium digitatum* or *A. fumigatus* (Ballester et al. 2019; Sharon et al. 2009).

Another transcription factor with a role in regulating protease gene expression is VIB-1/XprG (Dementhon et al. 2006; Katz et al. 2006), which we discussed above for its role in activating expression of plant cell wall degrading “scout” enzymes. VIB-1 and XprG have a pleiotropic effect in *N. crassa* and *A. nidulans*, respectively, controlling a multitude of functions involved in fungal development, including cell fusion and sexual development (Dementhon et al. 2006; Katz et al. 2013). Through the role of these orthologs in protease and plant cell wall degrading enzyme gene expression, VIB-1 and XprG are required for the fungal response to starvation (Katz et al. 2015; Katz et al. 2006; Wu et al. 2020). Surprisingly, despite the wide-ranging role of XprG, neither deletion of *xprG,* nor deletion of both *xprG* and *prtT,* in *A. fumigatus* causes reduced virulence in immunocompromised mice (Shemesh et al. 2017).

Carbon and Nitrogen Catabolite Repression

Environmental niches occupied by filamentous fungi are nutritionally complex and rarely composed of a singular carbon and/or nitrogen source. As such, transcriptional regulatory mechanisms have evolved to prioritize utilization of easily catabolized, high-value nutrients over

559 those that require more energy to catabolize (Fig. 2). Here we describe the known genetic
560 mechanisms by which nutrients are prioritized.
561
562 *CARBON CATABOLITE REPRESSION*
563 When repressing, or preferred, carbon sources are available, fungi repress transcription
564 of genes associated with uptake and catabolism of less preferred carbon sources. This
565 mechanism of nutrient differentiation is referred to as carbon catabolite repression. Most
566 catabolic pathways require both the presence of an activating signal and the absence of a
567 repressing signal for robust transcription of genes associated with the transport and catabolism
568 of less preferred carbon sources. In filamentous fungi, glucose, fructose, and, to a lesser extent,
569 other mono- and di- saccharides induce carbon catabolite repression. These sugars are thus
570 preferentially consumed in a mixed carbon environment over harder-to-catabolize sources, such
571 as cellulose, or lower-value carbon sources, such as ethanol (Fig. 2).
572 *CRE-1/CreA/Cre1 is a major transcription factor mediating carbon catabolite repression*
573 The C2H2 zinc-finger transcription factor CRE-1/CreA/Cre1 is a major regulatory
574 element mediating carbon catabolite repression in all filamentous fungal species in which
575 carbon catabolite repression has been studied (Adnan et al. 2017; Arst and Cove 1973; Benocci
576 et al. 2017; Dowzer and Kelly 1991; Hong et al. 2021; Huberman et al. 2016; Ries et al. 2018;
577 Strauss et al. 1995; Sun and Glass 2011). Disruption of *cre-1/creA/cre1* results in a loss of
578 glucose-mediated repression of alternative carbon source utilization. The primary consensus
579 binding motif of CreA/CRE-1 is SYGGRG and TSYGGGG in *A. nidulans* and *N. crassa,*
580 respectively (Chen et al. 2022; Kulmburg et al. 1993; Strauss et al. 1995; Wu et al. 2020).
581 Examination of RNA sequencing (RNAseq) data, electrophoretic mobility shift assays,
582 chromatin-immunoprecipitation sequencing (ChIPseq), and DNA affinity purification sequencing
583 (DAPseq) experiments revealed that CreA/CRE-1 utilizes a hierarchical mechanism to regulate
584 carbon catabolite repression (Antonieto et al. 2014; Beattie et al. 2017; Chen et al. 2022; García

et al. 2004; Kulmburg et al. 1993; Wu et al. 2020). CreA/CRE-1 represses only a portion of the enzymes in any given catabolic pathway and rather leverages repression of transporters and activating transcription factors to prevent intracellular signaling and subsequent activation of downstream catabolic genes (Chen et al. 2022; Wu et al. 2020). Curiously, some evidence has suggested that CRE-1 in *N. crassa* can also act as an activator of gene expression under carbon starvation conditions (Huberman et al. 2017)

Early carbon catabolite repression studies investigating CreA in *A. nidulans*, combined with mechanistic studies on the *S. cerevisiae* functional homolog of CreA, Mig1, led to a canonical model of carbon catabolite repression regulation (Arst and Cove 1973; Bailey and Arst 1975; De Vit et al. 1997; Shroff et al. 1997; Treitel et al. 1998; Vautard-Mey and Fèvre 2000). In this model, CreA is localized to the nucleus when preferred carbon sources are available and actively represses transcription of genes associated with nonpreferred carbon source utilization. When preferred carbon sources are unavailable, CreA is thought to be phosphorylated by the AMP-activated kinase SnfA and sequestered in the cytoplasm, relieving transcriptional repression. Supporting the canonical model of regulation, altered localization of CreA as a function of carbon source has been observed in several studies, with the degree of nuclear localization correlating with the strength of repression (Brown et al. 2013; Cupertino et al. 2015; de Assis et al. 2021; de Assis et al. 2018b; Hong et al. 2021; Ries et al. 2016; Vautard-Mey and Fèvre 2000). Additionally, phosphoproteomics, molecular genetics, and assays of phosphorylation via western blotting have demonstrated that CreA activity is regulated by phosphorylation (Alam et al. 2017; de Assis et al. 2021).

In contrast to the canonical model, more recent data on carbon catabolite repression in filamentous fungi leveraging ChIPseq, DAPseq, RNAseq, and molecular techniques suggest that CreA has a significantly expanded functional role relative to Mig1 in *S. cerevisiae* and is regulated in manners beyond what is described in the canonical model (Beattie et al. 2017; Chen et al. 2022; Hong et al. 2021; Wu et al. 2020). Expression of *creA* at the transcript level

611 varies by carbon source, is highly dynamic over short time intervals, and appears to be
612 autoregulated by CreA itself (Chen et al. 2022; Strauss et al. 1999). Despite this transcriptional
613 regulation, there is a lack of correlation between transcript, protein, and activity levels,
614 suggesting a substantial role for posttranscriptional and posttranslational regulation (Roy et al.
615 2008; Strauss et al. 1999). Overexpression of a C-terminal GFP-tagged CreA protein causes
616 constitutive nuclear localization but normal repression/derepression function, indicating that
617 nuclear localization is not sufficient to induce repression (Roy et al. 2008). While the canonical
618 model involves phosphorylation-mediated regulation, more recent studies have shown that
619 rather than a binary model of CreA phosphorylation, a number of phosphorylation states have
620 been observed in phosphoproteomic studies comparing repressing and non-repressing
621 conditions (Alam et al. 2017; de Assis et al. 2021; Ribeiro et al. 2019). Further, no single
622 mutation of a phosphorylation site fully accounts for regulation of CreA function. Single amino
623 acid phospho-null and phospho-mimetic mutants have demonstrated that the regulatory role of
624 CreA/Cre1/CRE-1 phosphorylation differs depending on the specific phosphorylation site
625 (Cziferszky et al. 2002; de Assis et al. 2021; Han et al. 2020; Ribeiro et al. 2019; Vautard-Mey
626 and Fèvre 2000). Supporting these differing roles for phosphorylation sites, CreA protein
627 domains have varying regulatory roles (Ries et al. 2016; Roy et al. 2008; Shroff et al. 1997).
628 However, in several studies investigating the roles of various CreA/Cre1 domains and
629 phosphorylation sites, a *creA*/*cre1* null strain was not included in functional assays, complicating
630 interpretation of the degree of impact of each mutation.
631 Further expanding our understanding of gene regulation by CreA, a recent study utilizing
632 ChIPseq and RNAseq to thoroughly examine the regulatory role of CreA in *A. nidulans* showed
633 CreA is constitutively localized to the nucleus (Chen et al. 2022). CreA occupied most promoter
634 binding sites under both repressing and derepressing conditions, with the intensity of binding
635 largely correlated with total CreA protein abundance. These data beg the question of whether
636 prior studies observed a true nuclear to cytoplasmic shift or simply a decrease in total CreA

levels below the limitations of the microscopy setups used. Alternatively, it is possible the ChIPseq promoter binding signal was due to CreA nuclear localization and promoter occupancy in a small subpopulation of nuclei, as frequently microscopy experiments report at least a small population of nuclei containing CreA in many conditions. This conflict calls for further study to differentiate to what degree localization, protein levels, population heterogeneity, or some combination of all three are involved in CreA-mediated regulation. Additionally, if CreA is constitutively nuclear in some or all nuclei regardless of condition, this further brings into question the regulatory role of specific phosphorylation states, condition dependent CreA protein binding partners, and what, if any, other mechanisms contribute to CreA function.

Other Regulators of Carbon Catabolite Repression

Beyond *creA/cre1/cre-1*, several kinases and genes associated with ubiquitination have been implicated in regulating carbon catabolite repression. While an in-depth examination into the role of the AMP-activated kinase SnfA/Snf1/SNF-1 in carbon catabolite repression is still needed, studies in several plant pathogenic species have demonstrated a role for Snf1 in carbon catabolite repression-related phenotypes. These include production of plant cell wall degrading enzymes, polysaccharide utilization, and growth on non-repressing carbon sources, as well as roles in plant virulence (Tonukari et al. 2000; Yi et al. 2008; Yu et al. 2014). In *A. nidulans*, loss of *snfA* increases the proportion of CreA-containing nuclei and glucose-mediated repression (Brown et al. 2013; de Assis et al. 2020).

Several components of the cyclic AMP/protein kinase A and hyperosmotic response mitogen-activated protein (MAP) kinase pathways have also been implicated in carbon catabolite repression and regulation of carbon metabolism broadly (Brown et al. 2013; de Assis et al. 2015; de Assis et al. 2020; Huberman et al. 2017; Kunitake et al. 2019; Kunitake et al. 2022; Ribeiro et al. 2019; Schalamun et al. 2023; Wang et al. 2013; Ziv et al. 2008). In aspergilli, the catalytic subunit of the protein kinase A complex, PkaC1, physically interacts with SakA, the central kinase of the hyperosmotic response pathway to impact carbon metabolism

(de Assis et al. 2018a; de Assis et al. 2020; Ribeiro et al. 2019). Repression of genes encoding plant cell wall degrading enzymes is modulated by osmolarity in *N. crassa* in a hyperosmolarity response pathway-dependent manner (Huberman et al. 2017). However, any potential interaction of these pathways with CreA appears to be indirect. It remains unclear what downstream transcription factors are responsible for the role of these pathways in carbon catabolite repression and carbon metabolism.

In addition to kinases, several genes associated with ubiquitination also appear to have a role in either carbon catabolite repression or the related concept of carbon catabolite inactivation in which catabolism of preferred and nonpreferred carbon sources is regulated at the posttranslational level. The F-box family of proteins target proteins for poly-ubiquitination and subsequent proteasome degradation (Nguyen and Businо 2020). Several F-box proteins impact carbon catabolite repression/carbon catabolite inactivation regulation and carbon source prioritization in *A. nidulans* and *N. crassa* (de Assis et al. 2018b; Gabriel et al. 2021).

Further implicating ubiquitination in carbon catabolism regulation are the CreB-D proteins in *A. nidulans*. The deubiquitinating enzyme CreB and the WD40-repeat protein CreC interact to form a deubiquitinating complex (Lockington and Kelly 2002; Ries et al. 2016). Loss of either *creB* or *creC* in *A. nidulans* results in decreased glucose-mediated repression (Hynes and Kelly 1977; Lockington and Kelly 2001; Todd et al. 2000). Additionally, loss of function mutations in the ubiquitinating enzyme gene *creD* repress the *creB* and *creC* loss of function phenotypes (Boase and Kelly 2004; Kelly and Hynes 1977). Despite a clear regulatory role for ubiquitination, it was determined that the CreB/C complex does not physically interact with CreA (Alam et al. 2017). Furthermore, when CreA was tested for ubiquitination by mass spectrometry by two independent groups, neither group found evidence of CreA ubiquitination (Alam et al. 2017; de Assis et al. 2021). The lack of CreA ubiquitination signatures calls for examinations into whether carbon catabolite inactivation is occurring in filamentous fungi, what mechanisms and proteins may be subject to ubiquitination and subsequent protein degradation, and if these

mechanisms are conserved across species. Conservation of the specific ubiquitination regulatory mechanisms may not be strong. Some F-box proteins identified in *N. crassa* and *A. nidulans* do not have clear homologs in the other species (de Assis et al. 2018b; Gabriel et al. 2021). Additionally, *N. crassa* mutants lacking the *creB* and *creD* homologs do not have a clear carbon catabolite repression defect (Xiong et al. 2014).

NITROGEN CATABOLITE REPRESSION

Unlike carbon catabolite repression, in which the major known regulator is a transcriptional repressor, the major known regulator of nitrogen catabolite repression (also called nitrogen metabolite repression) is the GATA transcriptional activator NIT-2/AreA (NRE in *Penicillium chrysogenum* and NUT1 in *M. oryzae*) (Caddick et al. 1986; Froeliger and Carpenter 1996; Fu and Marzluf 1990; Haas et al. 1995; Tudzynski et al. 1999). When nonpreferred nitrogen sources are present in the absence of the preferred nitrogen sources ammonium, glutamine, or glutamate, NIT-2/AreA activates expression of genes necessary for utilization of nonpreferred nitrogen sources. Thus, utilization of nonpreferred nitrogen sources requires activation of genes not only by the pathway-specific transcription factors discussed above, but also the transcriptional activator NIT-2/AreA (Fig. 2).

NMR/NmrA-mediated regulation of nitrogen catabolite repression

Regulation of NIT-2/AreA occurs in a number of ways, which differ somewhat from species to species. The most conserved mechanism of NIT-2/AreA regulation is through interaction with the repressor NMR (sometimes called NMR-1)/NmrA (Andrianopoulos et al. 1998; Young et al. 1990). NMR/NmrA lacks a DNA binding domain and regulates gene expression through direct interactions with NIT-2/AreA (Lamb et al. 2004; Xiao et al. 1995). In the presence of preferred nitrogen sources, NMR/NmrA binds to the C-terminal tail and zinc finger DNA binding domain of NIT-2/AreA, blocking the ability of AreA to bind DNA and activate target genes (Kotaka et al. 2008; Pan et al. 1997; Xiao et al. 1995). Although this mechanism of

NIT-2/AreA regulation is well conserved, the extent to which NMR/NmrA represses NIT-2/AreA differs between species. Nmr plays only a slight role in repressing the activity of AreA in *F. fujikuroi*, even though it interacts with AreA and can complement *N. crassa* and *A. nidulans nmr/nmrA* mutants (Mihlan et al. 2003; Schönig et al. 2008).

There are a number of speculations for how the NMR/NmrA-mediated repression of NIT2/AreA is regulated mechanistically and the identity of the metabolic signal to which NMR/NmrA responds. NmrA is absent in cells experiencing nitrogen starvation, and NmrA proteins levels are regulated by nitrogen source, with high levels of NmrA in cells exposed to the preferred nitrogen source ammonium and low levels of NmrA in cells exposed to nitrate (Zhao et al. 2010). The expression of *nmrA* is directly activated by the bZIP transcription factor MeaB in response to preferred nitrogen sources (Wong et al. 2007). Along with this transcriptional regulation, the NmrA protein product is also regulated by protease degradation during nitrogen starvation (Zhao et al. 2010). PnmB is one of the proteases responsible for degradation of NmrA during nitrogen starvation. PnmB-mediated degradation of NmrA increases the speed of AreA derepression, and the expression of *pnmB* is activated by AreA during nitrogen starvation, creating a positive feedback loop (Li et al. 2021a). Interestingly, there is no *N. crassa* homolog of PnmB, suggesting that this method of NMR/NmrA regulation may be specific to a subset of filamentous fungi.

Initially, it was hypothesized that NMR/NmrA might bind glutamine, the primary nitrogen source for filamentous fungi. However, careful biochemical analysis showed that NMR/NmrA does not bind glutamine, glutamate, or ammonium, but rather the dinucleotide cofactors NAD+ and NADP+ (Lamb et al. 2003). Despite this observation, minimal data currently exists showing that this binding has biological significance in the regulation of nitrogen catabolite repression. Binding of NmrA to AreA is possible regardless of whether NmrA is bound to NAD+/NADP+, and the structure of the NmrA-AreA complex is unaffected by NmrA binding to NAD+/NADP+ (Kotaka et al. 2008). If NAD+/NADP+ binding of NMR/NmrA does have biological significance in

nitrogen catabolite repression, it is possible that it functions to limit expression of nitrogen catabolic enzymes that require NADH/NADPH cofactors when the concentrations of these metabolites are low (Wilson et al. 2010).

Other mechanisms of NIT-2/AreA regulation

Despite sufficient conservation of the NIT-2 and AreA proteins that *nit-2* can complement *areA* mutants (Davis and Hynes 1987), regulation of NIT-2/AreA by mechanisms other than NMR/NmrA binding appears significantly less conserved. In *A. nidulans*, the *areA* transcript is regulated posttranscriptionally (Morozov et al. 2001). In the presence of ammonium and glutamine, the poly-A tail of the *areA* transcript is shortened, leading to *areA* mRNA degradation (Morozov et al. 2000). The mRNA degradation is dependent on a sequence in the 3' region of the *areA* mRNA, which is recognized by the mRNA stability regulatory protein RrmA. This sequence is sufficient to cause mRNA degradation in an RrmA dependent manner in response to preferred nitrogen sources (Krol et al. 2013; Platt et al. 1996). Interestingly, unlike *areA, nit-2* mRNA stability does not appear to be regulated in response to nitrogen conditions (Tao and Marzluf 1999), and transcriptomics across a broad range of nitrogen sources indicated limited *nit-2* transcriptional regulation (Huberman et al. 2021a). However, NIT-2 protein levels are elevated in response to nonpreferred nitrogen sources (Tao and Marzluf 1999).

NIT-2/AreA-mediated gene activation is also regulated by localization. During nitrogen starvation, NIT-2/AreA localizes to the nucleus (Bernardes et al. 2017; Todd et al. 2005). *A. nidulans* AreA has six nuclear localization signals that direct AreA to the nucleus – five classical nuclear localization signals and one bipartite nuclear localization signal (Hunter et al. 2014). These nuclear localization signals show redundancy with respect to AreA nuclear accumulation, but the bipartite nuclear localization signal is required for AreA function (Hunter et al. 2014). *Fusarium graminearum* AreA has only three nuclear localization signals, which includes a bipartite nuclear localization signal that is required for AreA nuclear localization (Hou et al. 2015). AreA import into the nucleus in response to nitrogen starvation is relatively slow, taking

several hours, while export from the nucleus in response to the presence of nitrogen happens over a matter of minutes and is mediated by the nuclear exportin KapK (CrmA) (Todd et al. 2005). Import of NIT-2 into the nucleus may be mediated by the highly conserved importin-α (Bernardes et al. 2017). Surprisingly, despite a role for AreA-mediated activation during exposure to nonpreferred nitrogen sources, AreA does not appear to be localized to the nucleus at detectable levels during exposure to the nonpreferred nitrogen sources proline, alanine, or uric acid in *A. nidulans* (Todd et al. 2005). However, AreA is necessary for utilization of proline when preferred carbon sources are present (Arst and Cove 1973), and RNAseq on proline showed NIT-2-mediated transcriptional regulation of target genes in *N. crassa* (Huberman et al. 2021a). Although it is potentially possible these NIT-2-mediated changes in gene expression occur through indirect means, promoter binding data by NIT-2 suggests this regulation occurs through binding of promoters in the *N. crassa* nucleus during exposure to proline (Huberman et al. 2021a). The mechanisms and species-level variation of NIT-2/AreA nuclear localization and posttranscriptional/posttranslational modification require further study.

Interplay of NIT-2/AreA with pathway-specific transcription factors

Much of the early work describing the interplay between NIT-2/AreA-mediated gene activation with pathway-specific transcription factors focused on the activation of genes responsible for nitrate utilization. Both NIT-2/AreA and the pathway-specific transcription factor NIT-4/NirA bind the promoter of the nitrate reductase gene *nit-3*/*niaD* (Chiang and Marzluf 1995; Narendja et al. 2002). This may be due, at least in part, to the role of AreA in opening the chromatin in the *niaD* promoter (Muro-Pastor et al. 1999). There are also data suggesting that NIT-2 and NIT-4 may physically interact (Feng and Marzluf 1998), although there is conflicting evidence surrounding this observation (Xiao et al. 1995).

A recent systems biology study investigating genome-wide NIT-2 regulation and promoter binding demonstrated that binding of both NIT-2 and a pathway-specific transcription factor to the same promoter may be mainly limited to a small number of nitrate-responsive

genes (Huberman et al. 2021a). NIT-2 and the amino acid utilization regulating transcription factor AMN-1 bind almost entirely separate promoters, with only a single gene directly coregulated by these two transcription factors (Huberman et al. 2021a). The genes directly regulated by NIT-2/AreA are enriched for transporters in a manner similar to that of the targets of the carbon catabolite regulator CRE-1/CreA, suggesting that a major mechanism of both nitrogen and carbon catabolite repression is limiting import of nonpreferred nutrients that may act as signaling molecules (Chen et al. 2022; Huberman et al. 2021a; Schönig et al. 2008; Wu et al. 2020). While genes encoding nitrogen transporters are mainly regulated by NIT-2/AreA, genes encoding catabolic enzymes tend to be directly regulated by pathway-specific transcription factors. This regulatory pattern likely accounts for why both NIT-2/AreA and pathway-specific transcription factors are necessary for utilization of nonpreferred nitrogen sources (Huberman et al. 2021a).

Other regulators of nitrogen catabolite repression

A few additional transcription factors have also been implicated in the regulation of nitrogen catabolite repression. The zinc binuclear cluster transcription factor TamA plays a minor role in nitrogen catabolite repression as an AreA co-activator and directly activates the NADP-glutamate dehydrogenase in a nitrogen source-dependent fashion (Davis et al. 1996; Downes et al. 2014). Another GATA transcription factor, AreB, plays a minor role in repressing utilization of nonpreferred nitrogen sources in the presence of preferred nitrogen sources (Wong et al. 2009), and in *F. fujikuroi* AreB directly interacts with AreA during nitrogen starvation (Michielse et al. 2014). However, the role of AreB and its *N. crassa* homolog ASD-4 is pleiotropic. In *A. nidulans*, AreB has roles in asexual development and conidial germination and regulates transcription factors with roles in both carbon and nitrogen metabolism (Chudzicka-Ormaniec et al. 2019; Wong et al. 2009). *N. crassa* ASD-4 regulates sexual development, including ascus and ascospore development but does not appear to play a role in nitrogen regulation (Feng et al. 2000). *F. fujikuroi* AreB regulates significant numbers of genes

regardless of nitrogen sufficiency including substantial numbers of transcription factors (Pfannmüller et al. 2017b). The *M. oryzae* AreB/ASD-4 homolog Asd4 is bound by all three *M. oryzae* NMR homologs and plays a role in regulating appressorium formation and genes involved in nitrogen assimilation (Marroquin-Guzman and Wilson 2015; Wilson et al. 2010). In the entomopathogenic fungus, *Metarhizium acridum*, the AreB homolog plays a role in appressorium formation and virulence and a minor role in utilization of both the preferred nitrogen sources glutamine and glutamate and the nonpreferred nitrogen sources nitrate and proline (Li et al. 2021b).

Conclusions

Regulation of carbon and nitrogen metabolism in filamentous fungi involves a hierarchical combination of broad-acting repression systems and more specific activating transcription factors. While substantial advances in our understanding of these regulatory systems have been achieved, much remains to be known and several conflicts exist within the published literature. The diversity of environmental niches occupied by filamentous fungi logically implies that the intricacies of nutrient sensing and regulation likely vary across phylogenetic distances and lifestyles. However, the bulk of our understanding of these topics at the genetic and molecular levels derives from a small number of Ascomycete species. Thus, thorough examinations across more phylogenetically diverse fungi could yield novel insights into the physiological, evolutionary, and ecological roles of nutrient sensing and utilization, as well as potentially clarify some of the literary conflicts.

Putative links between the regulation of carbon and nitrogen utilization have long been noted. A major regulator of carbon catabolite repression, *creA*, was originally identified in a suppressor screen for an inability to utilize proline or acetamide as a nitrogen source by an *A. nidulans* strain lacking a functional *areA* gene (Arst and Cove 1973). Despite these and subsequent observations, very little is known regarding the regulatory links between various

845 nutrients. Recent data surveying transcriptional profiles across diverse nutrient sources suggest
846 cross-regulation of nutrient utilization likely goes beyond carbon and nitrogen to include other
847 nutrient regulatory systems, including sulfur, phosphorous, and micronutrients (Huberman et al.
848 2021a; Huberman et al. 2021b; Wu et al. 2020). Future insights into the diversity of nutrient
849 regulatory systems and cross-regulation of nutrients may have substantial applications ranging
850 from improved and expanded industrial use of fungi to the development of novel pathogen
851 prevention and treatment strategies for clinical and agricultural use.
852

Figure legends

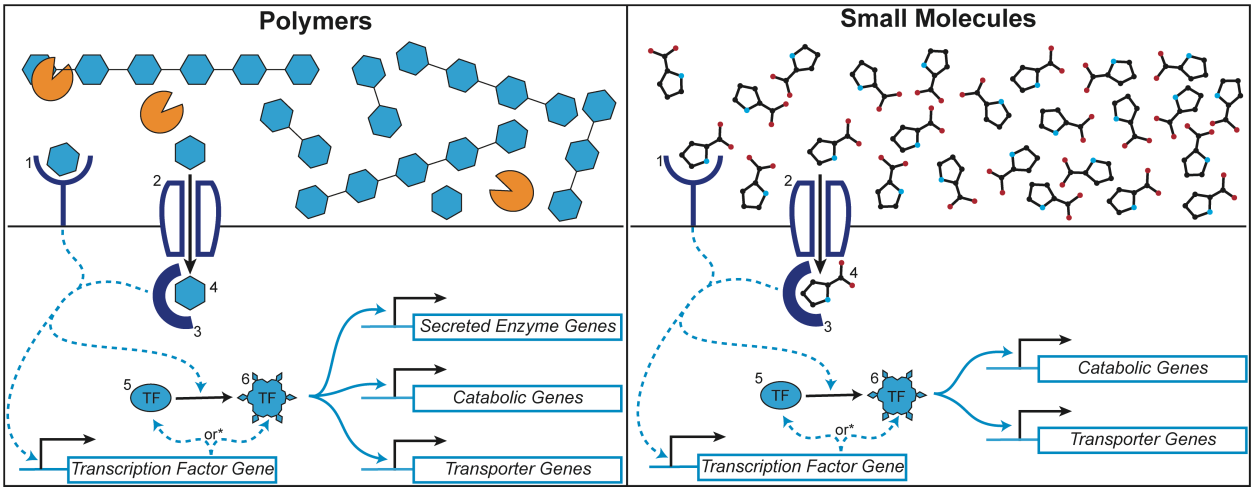

Fig. 1 Activating transcription factors respond to specific nutrient sources. The signal for the presence of a nonpreferred nutrient is either the nutrient itself (small molecules), a soluble breakdown product of the nutrient (polymers), or a modified version of the nutrient or soluble breakdown product. These signals are sensed using extracellular or intracellular receptors, which directly or indirectly activate transcription factors (TF) through upregulation of their transcription, posttranslational modifications, conformational changes upon binding an inducer, and/or protein-protein interactions. Activated transcription factors go on to activate the expression of genes necessary to utilize the specific nutrient source including secreted enzyme genes, catabolic genes, and transporter genes. Dotted lines indicate mechanisms which vary from pathway to pathway and/or for which data is inferred genetically but for which biochemical data is not necessarily available (or not available for all pathways). Solid lines indicate mechanisms with direct support from published literature. 1. Extracellular receptor; 2. Transporter; 3. Intracellular receptor; 4. The monomer and molecule represent the inducer which can be a monomer, oligomer, or metabolic derivative or downstream catabolic product of the nutrient; 5. Transcription factor in an inactive form; 6. Transcription factor in an active form; *Transcription factors can be regulated entirely by expression levels and translated in an active

form directly or regulated by a combination of expression and/or posttranslational modifications/conformational changes.

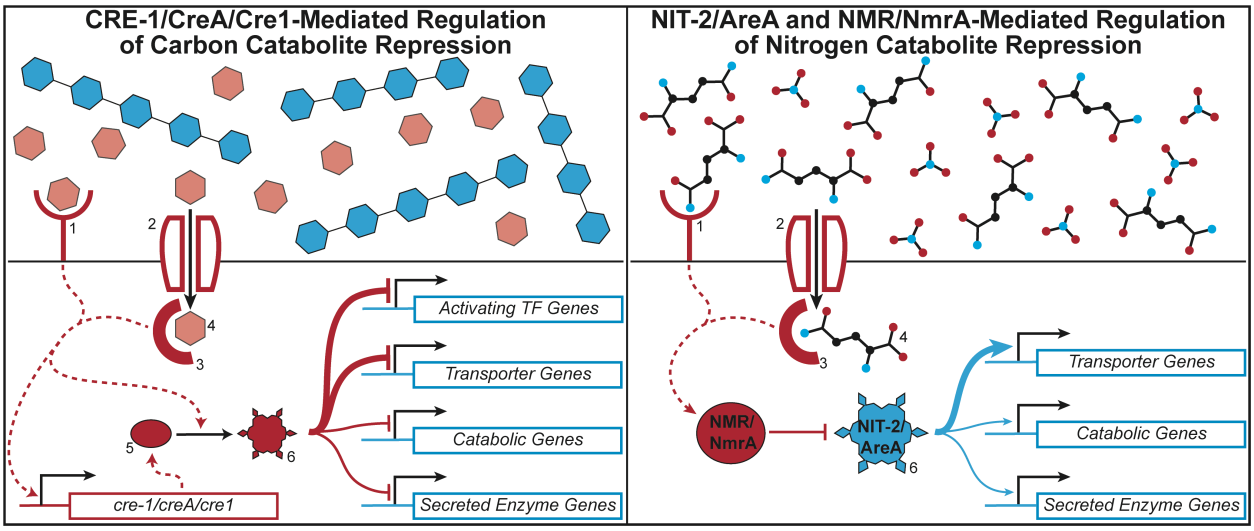

Fig. 2 Carbon and nitrogen catabolite repression systems repress or fail to activate, respectively, the expression of genes necessary for utilization of nonpreferred nutrient sources when preferred nutrient sources are available. CRE-1/CreA/Cre1, a major regulator of carbon catabolite repression, is activated through posttranslational modification and, to a lesser extent, transcriptional activation in response to the presence of glucose and other preferred carbon sources. Activated CRE-1/CreA/Cre1 represses expression of genes necessary to utilize nonpreferred carbon sources with a focus on transcriptional repression of activating transcription factor (TF) genes and transporter genes. NIT-2/AreA is a major regulator of nitrogen catabolite repression. NIT-2/AreA activates expression of genes necessary for utilization of nonpreferred nitrogen sources, particularly transporter genes, in the absence of preferred nitrogen sources. When preferred nitrogen sources are present, NIT-2/AreA activity is inhibited by NMR/NmrA, and NIT-2/AreA-activated genes are not expressed. Both carbon and nitrogen catabolite repression focus on regulation of genes involved in propagating signals that indicate the presence of a nonpreferred nutrient source, including transporter and transcription factor genes. Dotted lines indicate mechanisms for which data is inferred genetically but for which biochemical data is not necessarily available and multiple mechanisms may be possible. Solid lines indicate pathways with direct support from published literature. Thicker solid lines

892 from activated CRE-1/CreA/CRE1 and NIT-2/AreA indicate a larger percentage of that class of
893 genes is directly regulated by that transcription factor. Activators are indicated in blue, and
894 repressors are indicated in red. 1. Extracellular receptor; 2. Transporter; 3. Intracellular receptor;
895 4. Preferred nutrient source or metabolic derivative or downstream catabolic product of the
896 preferred nutrient source; 5. Transcription factor in an inactive form; 6. Transcription factor in an
897 active form.
898

Table 1. Activating transcription factors of nutrient utilization pathways discussed in this review. Single horizontal lines group orthologs. Double horizontal lines group transcription factors that activate genes necessary to utilize a particular nutrient.

Nutrient	Transcription factor	Species	Citation
Cellulose	CLR-1	*N. crassa*	(Coradetti et al. 2012)
	ClrA	Aspergilli	(Coradetti et al. 2012)
	CLR-2	*N. crassa*	(Coradetti et al. 2012)
	ClrB	Aspergilli	(Coradetti et al. 2012)
		P. oxalicum	(Li et al. 2015)
		T. thermophilus	(Zhang et al. 2022)
	ManR	*A. oryzae*	(Ogawa et al. 2013)
	CxrA	*P. oxalicum*	(Yan et al. 2017)
	Ace3	*T. reesei*	(Hakkinen et al. 2014)
	Xyr1	*T. reesei*	(Stricker et al. 2006)
	XlnR	*P. oxalicum*	(Li et al. 2015)
		some Aspergilli	(van Peij et al. 1998a)
Xylan	XLR-1	*N. crassa*	(Sun et al. 2012)
	XlnR	Aspergilli	(van Peij et al. 1998a)
		P. oxalicum	(Li et al. 2015)
	Xyr1	*T. reesei*	(Stricker et al. 2006)
		T. thermophilus	(Wang et al. 2015)
Arabinan	ARA-1	*N. crassa*	(Wu et al. 2020)
	Ara1	*T. reesei*	(Benocci et al. 2018)
		M. oryzae	(Klaubauf et al. 2016)
	AraR	Aspergilli	(Battaglia et al. 2011)
Mannan	CLR-2	*N. crassa*	(Samal et al. 2017)
	ManR	*A. oryzae*	(Ogawa et al. 2012)
Pectin	PDR-1	*N. crassa*	(Thieme et al. 2017)
	RhaR	Aspergilli	(Gruben et al. 2014; Pardo and Orejas 2014)
	PDR-2	*N. crassa*	(Wu et al. 2020)
	GaaR	Aspergilli	(Alazi et al. 2016)
		B. cinerea	(Zhang et al. 2016)
Inulin	InuR	Aspergilli	(Yuan et al. 2008)
Starch	COL-26	*N. crassa*	(Xiong et al. 2017)
	BglR	*T. reesei*	(Nitta et al. 2012)

	ART1	*Fusarium* sp.	(Oh et al. 2016)
	AmyR	Aspergilli	(Gomi et al. 2000)
		Penicillia	(Liu et al. 2013)
Cutin/Fatty acids	CTF1α	*Fusarium solani*	(Li and Kolattukudy 1997)
	Ctf1	*F. oxysporum*	(Rocha et al. 2008)
	FAR-1	*N. crassa*	(Roche et al. 2013)
	Far1	*M. oryzae*	(bin Yusof et al. 2014)
	FarA	Aspergilli	(Hynes et al. 2006)
	CTF1β	*F. solani*	(Li et al. 2002)
	Ctf2	*F. oxysporum*	(Bravo-Ruiz et al. 2013)
	FAR-2	*N. crassa*	(Roche et al. 2013)
	Far2	*M. oryzae*	(bin Yusof et al. 2014)
	FarB	Aspergilli	(Hynes et al. 2006)
Tannin	TanR	*A. niger*	(Arentshorst et al. 2021)
Galactose	GalR	Aspergilli	(Christensen et al. 2011)
	GalX	*A. nidulans*	(Christensen et al. 2011)
	ARA-1	*N. crassa*	(Wu et al. 2020)
	Ara1	*T. reesei*	(Benocci et al. 2018)
Maltose	MalR	*A. oryzae*	(Hasegawa et al. 2010)
Sucrose	InuR	Aspergilli	(Yuan et al. 2008)
Ferulic acid	FarA	*A. niger*	(Arentshorst et al. 2022)
	FarD	*A. niger*	(Arentshorst et al. 2022)
Cinnamic acid	SdrA	*A. niger*	(Lubbers et al. 2019a)
Sorbic acid	SdrA	Aspergilli	(Plumridge et al. 2010)
Quinic acid	QA-1F	*N. crassa*	(Huiet 1984)
	QutA	Aspergilli	(Grant et al. 1988)
Ethanol	AlcR	Aspergilli	(Lockington et al. 1985)
Acetate	ACU-15	*N. crassa*	(Bibbins et al. 2002)
	FacB	Aspergilli	(Todd et al. 1997)
Proteins	PrtT	some Aspergilli	(Punt et al. 2008)
		Penicillia	(Chen et al. 2014)
	PrtR	*A. oryzae*	(Mizutani et al. 2008)
	VIB-1	*N. crassa*	(Dementhon et al. 2006)
	XprG	Aspergilli	(Katz et al. 2006)
Nitrate	NIT-4	*N. crassa*	(Yuan et al. 1991)
	NirA	Aspergilli	(Burger et al. 1991)
Proline	AMN-1	*N. crassa*	(Huberman et al. 2021a)

	PrnA	Aspergilli	(Hull et al. 1989)
Tyrosine	AMN-1	*N. crassa*	(Huberman et al. 2021a)
	HmgR	Aspergilli Penicillia *T. marneffei*	(Keller et al. 2011) (Greene et al. 2014) (Boyce et al. 2015)
Branched chain amino acids	AMN-1	*N. crassa*	(Huberman et al. 2021a)
Arginine	ArcA	*A. nidulans*	(Empel et al. 2001)
Purines	PCO-1 UaY	*N. crassa* Aspergilli	(Liu and Marzluf 2004) (Suárez et al. 1995)
Nicotinate	HxnR	Aspergilli	(Ámon et al. 2017)

Availability of data and materials

Not applicable.

Statements and Declarations

Ethics approval: This article does not contain studies with human or animal participants performed by the authors.

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