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NICHE-SPECIFIC GENE EXPRESSION DURING *C. albicans* INFECTION

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SUMMARY

Infection by the opportunistic pathogen *Candida albicans* may occur in virtually any organ of the human host. Studies of *C. albicans* gene expression during experimental infection reveal that different stress responses are mounted during different types of infection, presumably because different environments present different challenges. In addition, at least two mechanisms allow expression of common genes or activities in multiple sites within the host: differential expression of isozymes in a multigene family and regulation of a common set of genes by multiple transcription factors. Thus, analysis of *C. albicans* gene expression illuminates details of host-pathogen interactions and the differences between sites within the host.

The opportunistic fungal pathogen *Candida albicans* is a notably versatile pathogen, capable of causing infection of numerous sites within the human body. For example, while oral thrush is prominent in AIDS patients, hematogenously disseminated disease with deep organ invasion is observed in neutropenic patients [1,2]. *C. albicans* is also a human commensal, colonizing the gastrointestinal tract, genitourinary tract and skin [3]. In order to survive in such diverse environments within the host, *C. albicans* cells probably express genes needed to overcome the challenges unique to certain sites and activities that are needed for infection of any site. The results reviewed here show that stress responses mounted by the organism in different sites of infection are distinct. In contrast, expression of an aspartic protease seems to be important for infection of multiple host sites. One mechanism that allows expression of a protease in multiple sites of infection involves a family of differentially regulated isozymes. For expression of another co-regulated set of genes during infection of multiple host sites, *C. albicans* may use a different mechanism, relying on a collection of transcriptional regulatory factors that converge to control expression of a common set of genes.

Approaches used to study *C. albicans* gene expression during growth within the host

Pioneered by Morschhauser and co-workers [4], one of the first approaches used to analyze *C. albicans* gene expression during host growth involved cloning the gene encoding a site-specific recombinase under control of a promoter of interest. Promoter activation is detected by recombinase-dependent excision of a reporter gene. This powerful approach, based on similar systems used in bacteria [5], allows sensitive detection of gene upregulation.

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The significant contributions of Brown and coworkers [6] utilized fusions between promoters of interest and the gene encoding green fluorescent protein (GFP). Using such fusions, gene expression is monitored at the single cell level [7], allowing detection of gene expression occurring only in a subpopulation of cells. Thus, *C. albicans* cells recovered from infected mouse kidneys following intravenous inoculation were analyzed [6] [8] and “niche-specific” gene expression, i.e. gene expression that occurs in a subpopulation of cells occupying a particular niche, was demonstrated for several genes.

In their seminal work, Hube and coworkers performed microarray analysis of gene expression in *C. albicans* cells invading the mouse liver following intraperitoneal inoculation [9], *C. albicans* cells recovered from human oral thrush lesions [10] and *C. albicans* cells invading artificial reconstituted human epithelium (RHE) [10]. These studies allowed a comprehensive analysis of gene expression during infection. Microarray studies of *C. albicans* contacting host macrophages or neutrophils have also been performed [11-15]. Despite the challenges and limitations of these kinds of studies, which were recently reviewed in depth [16], these studies illuminate the nature of the host environment, and the responses of the organism to the host.

At the level of cellular physiology, it is usually the protein products of gene transcription that determine the effects of gene expression and thus, in most cases, changes in transcript levels are most relevant if they are accompanied by related changes in protein levels. Proteomic analysis of *C. albicans* cells interacting with macrophages shows that, for many genes, there is excellent agreement between transcript levels and protein product levels [12]. However, discrepancies exist and therefore, results of transcript profiling must be interpreted with caution.

Common genetic responses to the host environment

The above studies show that when *C. albicans* infects a host or contacts host immune cells in culture, there are common fungal genetic responses. A well studied example is upregulation of the gene encoding isocitrate lyase, an enzyme of the glyoxylate cycle, which was first demonstrated by Lorenz and Fink [13] and subsequently observed in numerous other studies [6,9,10,14,15]. These results show that in many host niches, metabolic adaptation for growth with low levels of glucose occurs.

Another set of commonly up-regulated genes is the hypha-coregulated genes [17], which include genes such as *HWPI* (encoding an adhesin [18]), *ECE1* (encoding a protein of poorly defined function [19,20]), *SAP5* (encoding a protease [21]) and *ALS3* (encoding an adhesin [22]). These genes, and others, are highly expressed in laboratory-grown hyphae [19,23-25]. In many infection studies, *C. albicans* cells are predominantly in the hyphal form [9,13,26], and expression of the hypha-coregulated genes is seen in these situation [9-11,13,26-31]. Unexpectedly, expression of these genes is also seen in yeast cells during commensal colonization of the murine intestinal tract by *C. albicans* [32], showing that in the host, expression of these genes is not strictly tied to cellular morphology. Presumably, genes such as the hypha-coregulated genes, that are expressed by *C. albicans* in many host niches, promote adaptation of *C. albicans* to growth and survival within a host.

Niche specific genetic responses to the host

In contrast to these general responses of *C. albicans* to the host, there are responses that are seen only in some types of infection, ie. niche-specific patterns of gene expression, which are probably important for responses to specific features of certain niches.

Niche specific gene expression in the host was first detected through studies of the *SAP* gene family, encoding a series of aspartic proteases. Consistent with the microarray data described

above, e.g. [9,10], the *SAP5* gene is expressed in multiple sites [28,29]. In contrast, *SAP2* upregulation is seen in cells infecting the kidney [4,29] but not in cells infecting the esophagus or vagina [4,28,29]. *SAP6*, by contrast, is upregulated in cells that are invading RHE and in cells recovered from human oral lesions [33], but not in cells infecting the liver [29]. This *SAP* gene was not highly expressed in cells colonizing the mouse vagina [28], while *SAP4* was expressed in this niche [28], but not in esophagus, kidney or liver [29]. Thus, in the host, *SAP4*, *SAP5* and *SAP6* show distinctive patterns of expression. Differential expression of *LIP* genes, encoding a family of secreted lipases, has also been demonstrated in host samples [34,35] and in laboratory growth [36]. Thus, one way that *C. albicans* ensures that a *SAP* gene will be expressed when needed for infection in different host niches is through differential expression of a large family of Sap isozymes.

Niche-specific gene expression: metabolic genes

More recently, microarray and GFP fusion studies have expanded our understanding of niche specific gene expression (Table 1). When growing in the liver, *C. albicans* cells express genes associated with sugar utilization and respiration, e.g. *PFK2* encoding phosphofructokinase and *KGD1* and 2, encoding 2-oxoglutarate dehydrogenase involved in the TCA cycle [9]. *C. albicans* cells express *PFK2* and *PYK1* (encoding pyruvate kinase) and require glycolysis to grow within the kidney [6]. It is thought that glucose from the blood stream is an important carbon and energy source for fungal cells growing in this tissue site [6].

Interestingly, by transcript profiling, expression of gluconeogenesis genes and glyoxylate cycle genes is observed in the same population of fungal cells that express glycolytic genes. The authors suggested that the cells are heterogeneous and that some of the cells may be in an environment that does not supply high levels of sugar. Supporting this idea, Barelle et al showed that a GFP reporter gene expressed from the promoter of the gluconeogenesis gene *PCK1* (encoding phosphoenolpyruvate carboxykinase) was expressed by only about one third of the cells [6], providing direct experimental evidence for the idea of heterogeneity of cells in tissue.

In contrast, *C. albicans* cells cultured with macrophages or neutrophils do not upregulate glycolytic genes [13,15] and at the protein level, the enzymes of glycolysis are in fact reduced in abundance [12]. In these coculture experiments, it is likely that there are fewer niches and the infection is more synchronous, resulting in a more uniform population of fungal cells. Therefore, subpopulations of cells in different metabolic states are not observed in these studies.

In some niches (*C. albicans* invading RHE, recovered from human oral lesions, or cultured with macrophages or neutrophils), nitrogen appears to be limiting and genes involved in amino acid biosynthesis or amino acid uptake are upregulated [10,13–15]. In contrast, in the liver, these genes are not upregulated, indicating that nitrogen sources are available [9]. Thus the availability of glucose and nitrogen sources varies depending upon the particular host niche, necessitating niche specific expression of genes involved in carbon and nitrogen utilization.

Niche-specific gene expression: responses to oxidative and nitrosative Stress

One response of the host to microbial invaders is the production of antimicrobial compounds such as reactive oxygen species (ROS) and reactive nitrogen species (e.g. NO). A comparison of genes expressed after exposure of *C. albicans* cells to oxidative stress in the laboratory, during co-culture with neutrophils or macrophages or during growth in distinct sites within the host has revealed host niches where *C. albicans* responds to oxidative stress.

In laboratory studies, *C. albicans* responds to oxidative stress by upregulating oxidative stress response genes such as *SOD* genes (encoding superoxide dismutase) and *CTA1* (encoding catalase); the products of these genes convert ROS into harmless molecules [8,37]. Glutathione reductase (*TTR1*) and other enzymes of the glutathione and thioredoxin systems are also upregulated following exposure to oxidative stress [8,37]. Neutrophils produce ROS as part of their antimicrobial function and *C. albicans* cells cocultured with neutrophils upregulate the oxidative stress response genes [8,14,15]. In contrast, cells phagocytosed by macrophages generally do not upregulate these genes [8,15] although some upregulation was detected in one study [13]. Thus, *C. albicans* cells within macrophages are protected from oxidative stress while fungi within neutrophils are exposed to this stress.

During tissue invasion (liver, kidney, RHE), the oxidative stress response genes are not upregulated [8–10]. Therefore, in tissue, oxidative stress is not a pronounced feature of the environment.

Host cells also produce reactive nitrogen species such as nitric oxide (NO) and *C. albicans* cells defend themselves against these compounds in part by producing detoxifying activities such as flavohemoglobins (encoded by the *YHB* genes). In laboratory culture, cells incubated with an NO generating compound express *YHB1* but not *YHB4* or *YHB5* [38,39]. *YHB5* is upregulated in post exponential growth phase [32].

YHB genes are expressed by *C. albicans* cells recovered from human oral infection, invading RHE [10], or colonizing the intestinal tract of mice [32]. In contrast, cells invading the liver do not upregulate genes involved in nitrosative stress resistance [9]. Therefore, nitrosative stress appears to be a significant component of the environment on epithelial surfaces but not in deep tissue.

In summary, several examples of niche specific gene expression show that the environments in different locations within the host are different. Even within one tissue, there appear to be different microenvironments and, therefore, infecting *C. albicans* cells are heterogeneous. Thus, in order to survive within its host effectively, *C. albicans* must respond to many different environments.

Niche-specific transcriptional regulatory factors?

Niche-specific transcriptional regulation of genes might predict the existence of niche-specific transcriptional regulatory proteins. While numerous transcription factors are needed for full virulence of *C. albicans*, their roles in gene expression in different host niches are not known. For example, the well studied transcription factor Efg1p, is required for expression of *SAP5*, *ECE1*, *RBT1*, *RBT4* and other hypha-coregulated genes during growth of cells in laboratory conditions [24,25,40–42]. However, Efg1p is not required for expression of *ECE1*, *RBT1* or *RBT4* during commensal colonization of the murine intestinal tract [32]. There is also substantial Efg1p-independent expression of *SAP5* at late stages of liver infection [43]. Similarly, the transcription factor Tec1p is required for expression of *SAP5* during growth in the laboratory but not during growth in the murine liver or kidney [44,45].

Laboratory studies show that multiple transcription factors regulate overlapping sets of genes during growth under different conditions. In particular, several transcription factors regulate the expression of the hypha-coregulated genes (Table 2). As shown by Liu and coworkers, expression of these genes is dependent on Efg1p when cells are grown in serum-containing medium at 37°C, on Cph2p when cells are grown in “Lee’s medium,” a minimal medium with a specific composition of amino acids, or on Cph1p in succinate-amino acids medium [40]. These genes are also repressed by factors such as Nrg1p and Tup1p [46,47] or Sfl1p [48]. It is likely that in different host niches, in response to different conditions, different transcription

factors or combinations of transcription factors are important for controlling the expression of the hypha co-regulated genes. Thus, the ability of *C. albicans* to express common sets of genes in diverse niches probably reflects the activity of multiple transcription factors. Unraveling the regulatory circuits that control gene expression within the host remains a challenge for future studies.

Conclusions and future directions

As an opportunistic pathogen that colonizes numerous sites within the human host, *C. albicans* must express genes that promote colonization or virulence in multiple environments. Some of the genes are produced in some host niches but not others and presumably allow the fungi to adapt themselves to the environmental features of a particular niche. Some of the genes that promote colonization or virulence may be expressed in a truly constitutive manner. However, for other genes that are needed for colonization or infection at multiple sites, there are at least two mechanisms that allow them to be expressed in multiple niches: the use of differentially expressed multigene families and the use of multiple transcription factors with overlapping genetic targets. These mechanisms for controlling and optimizing gene expression in diverse niches allow *C. albicans* to be a highly successful colonizer and pathogen of the human host.

The findings that *C. albicans* cells elaborate characteristic genetic responses to particular host environments provide tools for understanding the nature of each host niche. In addition, the information is useful for validation of model infection systems. For example, the response of *C. albicans* during infection of a model organism such as *Drosophila* may resemble a fungal response to a particular mammalian niche. This observation would allow the model system to be used as a surrogate for human infection. These studies of gene expression within a host thus pave the way for future detailed analyses of host-pathogen interactions.

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Table 1
Niche-Specific genetic responses of *C. albicans* to the host.

Niche	Glycolysis, TCA	Amino acid transport	Response to oxidative stress	Response to nitrosative stress	References
Invading liver	++ ^a	---	---	---	[9]
Invading kidney	++	c	--	c	[6,8]
Invading RHE	--	++	--	YHB1,5 ++	[10]
Human oral lesions	c	++	++	YHB1,5 ++	[10]
Cultured with macrophages	-- ^b	++	++	YHB1 ++	[12,13]
Cultured with neutrophils and other granulocytes	--	++	++	YHB1 ++	[14,15]
Colonizing mouse intestine	c	c	++	YHB5 ++	[32]

^a up-regulated
^b not up-regulated
^c unknown

Table 2

Regulators of hypha co-regulated genes.

Regulator	Conditions	Reference
Cph1p	Succinate-amino acids medium	[40]
Cph2p	Lee's medium	[40]
Efg1p	Serum-containing medium	[24,25,40–42]
Rim101p	pH 8	[49]
Bcr1p	Spider medium	[20]
Flo8p	Serum-containing medium	[50]
Fkh2p	Serum-containing medium	[51]
Tec1p	Serum-containing medium	[40]
Repressor		
Nrg1p	Repression in rich medium	[46,47]
Tup1p	Repression in rich medium	[25,46,47]
Sfl1p	Repression in minimal medium	[48]