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Modeling Dissemination of Pathogenic Fungi within a Host: A Cartoon for the Interactions of Two Complex Systems

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Abstract

The understanding of host-pathogen interactions is a field of outmost importance for human health and prototype for biological research. However, it is not yet systematically tackled by approaches dealing both with the complexity of the pathogen and the host in isolation and with the multitude of their mutual interactions. The ultimate goal of classic microbiology is to capture all the principles underlying every genomes' and proteomes' member functions as well as its complex interactions, responses to different physical and chemical stimuli, drugs and multiple combinations of any of them. The field of systems biology aims at system-level understanding of biological systems and as such is strongly dependent on experimental data. The systeome models capturing genome and proteome interactions as well as spatial and dynamic information will be extremely useful for medical applications and provide a great potential for pharmaceutical companies for novel drug discoveries and for generating predictions of theirs applications. With constantly evolving experimental techniques as well as a growing computer infrastructure it seems feasible in the future to generate systeome models, to run numerical simulations on them and to derive medically relevant predictions. A priori it is conceivable to use systeome models to monitor a disease progress. In case the disease is driven by a pathogen disseminating within a host, systeome models will be used to control the infection, block it and even reverse it leading to elimination of the invading microbe from the host. We give here a cartoon for the invasion of the host by a commensal opportunistic pathogen *Candida albicans* as an example for such a systeome project. This way we discuss the perspectives of host-pathogen interaction studies and the challenges of related modeling projects.

Keywords: *Candida albicans*; Dissemination; Systeome; Host-pathogen interactions; Computational modeling

Introduction

Systems biology and the study of the systeome - an assembly of system profiles for all genetic variations and environmental stimuli responses [1] - allow new approaches and new perspectives on the analysis of infectious and immune response stimulating diseases. The view on the whole cell and its interaction in the healthy and in the attacked organism allows to analyze not just components but networks and to understand regulation processes on both host and pathogen sides in their mutual conditionality. This requires that the processes are increasingly well understood in both systems separately. Systeome projects are thus extremely important. As suggested in [1] the focus is on establishing systeome models for model organisms such as human, mouse, *Caenorhabditis elegans*, *Drosophila melanogaster* and baker's yeast *Saccharomyces cerevisiae*. Important attempts have also been made since for an organism with a very small genome, *Mycoplasma pneumoniae* [2-4]. However, to understand infection, only their combined investigation allows us to tackle questions such as

- Which path does a pathogen take through different organs, cells or milieus of the host?
- Which signaling systems of the pathogen are activated when and to what extent?
- How works the cross-talk among the pathogen biochemical networks (signaling, metabolism, cell cycle)?
- Does the pathogen modify host networks to use their capacity for its own purposes, to undermine defense processes, and to make physical conditions (pH, osmolarity, temperature) less hostile? If so how does it do it?
- What are specific and unspecific reactions of the host to pathogen invasion?
- Under which conditions are host defense mechanisms successful, when do they collapse? What is the contribution of fever or apoptosis?
- What is the spatial orientation of host and pathogen and how do they mutually inuence the positions and spatial extension of invaders and immune cells or intracellular cues?
- Are there memory effects in the host or pathogen and what are its determinants?

To find answers to such questions, we need on one hand data from high throughput techniques targeted to either the host or the pathogen. In the ideal case, these data are obtained for individual cells on different stages of the infectious interaction and are amenable to extensive bioinformatics analysis highlighting general pattern of changes and the nature of interaction of molecules and regulatory units. On the other hand, we have mathematical models that can be developed to understand the ongoing processes in their entirety and in detail. Although especially for host-pathogen interactions, there is

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still a lack of comprehensive and satisfactory modeling approaches, despite some promising exceptions [5]. Model building can support experimental design, since it focuses on the necessary and relevant new information to substantiate or falsify the model. For host-pathogen interactions experiments will specifically be devoted to time-resolved measurements under defined conditions and to the verification of component interactions in a given context, e.g. at different stages of infection. Models must be iteratively optimized and can then be used to understand mutual dependencies or feedbacks, and other network-based or dynamic features. Eventually, we strive for a better understanding of the dynamics of the mutual interaction on the level of the pathogen (e.g. adaptation to the new milieu, metabolic adaptation, morphogenesis, cell invasion, replication) and the reaction of the host (fever, activation of immune response, apoptosis, and many more). This way it may become possible to answer above posed questions, which is impossible by separate analysis of different omic data. Using the model-based strategy, inferences and potential drug targets can be detected, also drug effciency or drug resistance can be calculated. Altogether, the superposition of two systems – pathogen and host - who have evolved and further evolve to survive in the face of the other one imposes many new challenges to theoretical and experimental systems biology and systeomic analyses. Systems biology is considered as a discipline at the edge of different life sciences supposed to construct and analyze large networks and as a field producing mathematical models of small and large networks. For host-pathogen interaction, we need networks of higher dimensionality than hitherto considered since they must display the changing conditions while host and pathogen react on each other. For the yeast *S. cerevisiae*, for example, we know many effects of individual proteins and of pairs of proteins (e.g. through synthetic lethality [6] or on the level of proteinprotein interaction [7,8] to a change in abundance. This will, presumably, hold soon for certain pathogens, too. But how far do we understand the mutual

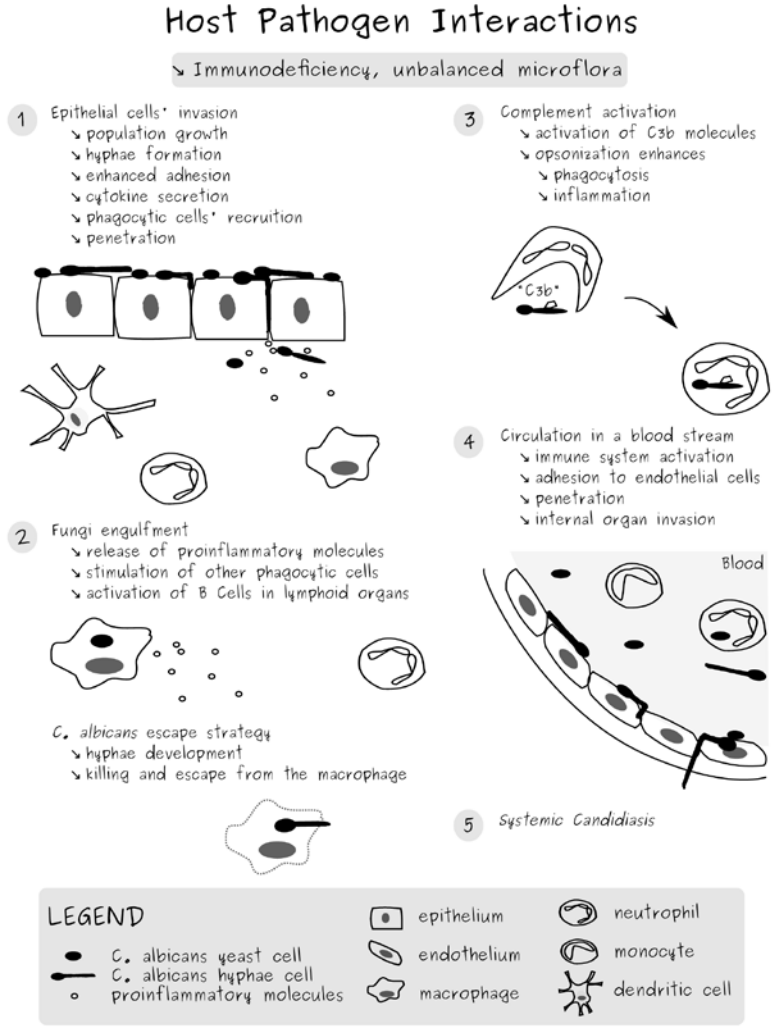

Figure 1: Host - pathogen interactions. Immunodeficient individuals or patients with unbalanced micro flora are susceptible to *C. albicans* invasion. The *C. albicans* population growth and increased germ tube formation enhance the adhesion to epithelium (1). Epithelial cells in turn secrete the pro-inflammatory molecules, chemoatractants to phagocytic cells. Macrophages, present at the site of infected tissue engulf the pathogen (2) and release other pro-inflammatory molecules. The engulfed microbe is able to form hyphae within the macrophage, break it and get free. Phagocytic cells die. Neutrophils, in contrast, are successful phagocytes. Turning on the complement pathway results in activation of special molecules, so called C3b, which bind the surface of the fungi becoming a signal for other phagocytic cells (3). In the blood stream (4), the fungi must again fight diverse immune cells. Because host is immunocompromised the hyphae *C. albicans* cells are successfully attaching to the endothelium and penetrating it inducing their own endocytosis. Because of circulation in a blood stream *C. albicans* cells are able to disseminate over internal organs leading to systemic disease (5).

effect of gene knockouts, knock downs, over expression in the host and in the pathogen? At which step of infection or defense will a certain alteration become decisive? How much does nutrition contribute or is the mutual interplay largely nutrient-independent? An important challenge is that pathogens are frequently studied under laboratory conditions, which are very different from host conditions. In the host, conditions are changing, like pH or osmolarity due to localization in different host tissues or liquids, temperature due to fever and many more. For example, historically signaling pathways have been studied in isolation which might be appropriate as a first view, but also led to the assumption that cells would prevent signal pathway crosstalk [9] which is questionable in the context of changing environments. To understand the complex interaction mechanisms of host and pathogen, we must take into account the entirety of signaling pathways ensuring together the full and fine-tuned response to the requirement of either surmounting host defense - or combating the invader. Models are powerful if they can be used for making predictions, especially with respect to drug treatment and its effect on the biological system. Developing models like host invasion by the pathogen can help us to access the key elements responsible for the success of the microbe. Very detailed models are going to be used to examine the effect of specific drug treatment not only affecting the pathogen but also the host. Complex models will thus be used to avoid negative side effect on the host during the elimination process of the invading microbe. In the next section we present only a cartoon for such a model, where the pathogen of interest is *C. albicans* and the host is the human. We model the early interaction step of the pathogen with human oral epithelial cells using an agent-based modeling approach, a formalism that facilitates the modeling process and allows to run simulations easy to track and greatly increasing our intuition on the system.

Human and *Candida albicans* as an example for host pathogen interactions: The *C. albicans* is a human commensal fungus that is able to act as a pathogen under certain circumstances. It is normally found in gut and gastrointestinal flora. The population growth of *C. albicans* is limited due to the human immune system and other microorganisms inhabiting human microflora. The commensal yeast state of *C. albicans* is tolerated and no specific defense mechanisms are activated in order to eliminate the fungi. However immunocompromised individuals are susceptible to *C. albicans* invasion. Weakened organism is not able to protect itself from the fungi invasion resulting in systemic disease at last [10]. Before that happens however, *C. albicans* must cross different host barriers and overcome many defense strategies of the host what we illustrate in the next section [11], See also (Figure 1). Over the course of evolution *C. albicans* has developed many strategies allowing it to adapt to many different environmental conditions (e.g. pH of oral and vaginal mucosa) and live as a commensal ready to switch to pathogenic mode whenever host had weakened. It is known already for many years that the ability of *C. albicans* to switch from yeast cells to hyphae cells plays an important role in virulence [12]. At the commensal stage *C. albicans* cells are in constant contact with epithelium as they are normal habitants of mucosal and vaginal flora. The host epithelial cells are thus the first layers they have to penetrate during the invasion. Induction of hyphae seems to be crucial at this point, moreover the hyphae form of *C. albicans* is considered to be the invasive form [13,14]. Because of that many studies have been done on that property and different signals triggering morphological switch are documented in e.g. [15,16]. At an early stage the disruption of friendly flora facilitates the population growth of *C. albicans* and stimulates it to act as a pathogen. Apparently there are different recognition mechanisms, first phase and second phase, activated depending on whether epithelial cells are in contact with the yeast form or hyphae form of the fungus [13] (Figure 2). Secondary phase activation results in inflammatory response, this in turn activates host immune system and starts the battle with the microbe. Endothelial cells, lining all the types of blood vessels, are another host layer *C. albicans* has to cross in order to establish deep-seated infection. In order to disseminate over different organs and cause systemic disease *C. albicans* has developed strategies allowing it to attach to endothelial cells [17] despite of flowing with the bloodstream. The attachment to endothelial cells induces *C. albicans* endocytosis which is common strategy for fungi invading normally non-phagocytic host cells [18]. There are also other strategies considered for invasion of both cell types as described in [18]. During fungi invasion the host does not remain unresponsive. The host immune system becomes aware of the dangerous hyphae form of the fungi from the very beginning. Secondary phase activation results in secretion of cytokines. These are in turn chemoattractants, in first place, for innate immune system cells that start the migration toward the site of infected tissue. Patients with cancer or human immune defficiency virus (HIV) suffer however from compromised immune system and are thus particularly susceptible to *C. albicans* infections.

Model of *Candida albicans* infection cycle: The most common fungal infection is oral candidiasis in majority of the cases caused by *C. albicans*. The yeast form of *C. albicans* itself is however not invasive. The harmless commensal yeast form of the fungus is tolerated by the individual. Sick patients (AIDS, cancer, etc) obtain different therapy strategies (chemo, anti-fungal drug treatment), which result firstly in weakening the immune system of the host and secondly in disruption of friendly flora. The fungus *C. albicans* takes an advantage of the unbalanced microflora resulting in population growth and more uptakes of available nutrients. Nutritional conditions regulate the activity of Tor signaling pathway [19]. Sparse nutrient sources inactivate Tor1 protein kinase and thus suppress its negative effect upon transcription factors Bcr1 and Efg1, enhancing expression of different adhesin genes (ALS1, ALS3, ECE1, HWP1 all of them being hyphae specific). It was already reported that *C. albicans* germination enhances adhesion to epithelial cells (oral and vaginal). The adhered hyphal fungi cells can penetrate the host tissue and the weak host is not able to fully suppress the invasion. Invasion of epithelium activates inflammatory response, some pro-inflammatory cytokines are produced (e.g. IL8) working as chemoattractants recruiting phagocytic cells (macrophages, neutrophils, dendritic cells) to the site of infection. The most exposed part of the fungus is its cell wall. The proteome of cell wall changes upon exposure to different conditions in the environment, response to stresses or defect in cell wall components. Host has to be able to recognize the invading pathogen as not itself and activate the appropriate defense response. It is achieved by special pattern-recognition receptors (PRRs), which are able to identify so called pathogen-associated molecular patterns (PAMPs). These PAMPs are highly conserved microbial signatures. Different PRRs involved in recognition of *C. albicans*, present on the surface of diverse immune cells, are extensively described in [20]. After *C. albicans* engulfment dendritic cells activate T_{-H}-Cells resulting in the production of IL17 cytokine. This further enhances the recruitment of neutrophils (PMNs), which are considered to be crucial in the fight with the microbe. For the illustration of T-Cells' and B-Cells' activation see (Figure 3). Innate immune system alone successfully blocks the fungal invasion, since tissue penetration is possible only when immune system is impaired or the barriers are breached. The *C. albicans* is able

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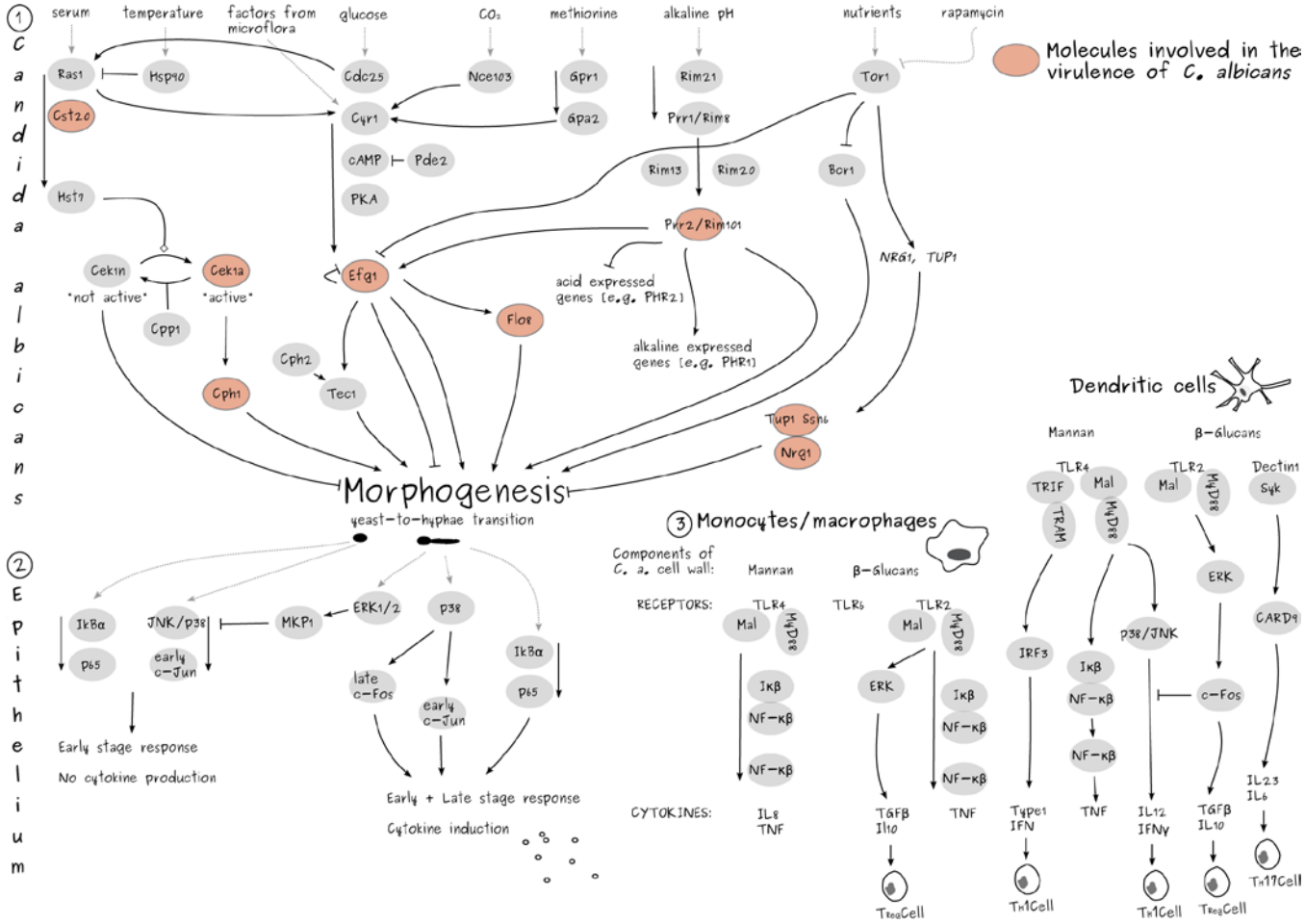

Figure 2: Selected signaling pathways activated during mutual interactions. Different environmental cues stimulate diverse signaling pathways (1) in *C. albicans*. Many proteins involved in the signaling play a role in the virulence of the fungus (marked with orange color). The yeast to hyphae transition results in the activation of some pathways in an epithelium (2; adapted from [14]). The epithelium secretes cytokines that recruit phagocytic cells to the site of infection. Within immune cells upon contact with *C. albicans* cell wall different signaling pathways are activated as indicated in (3; adapted from [20]).

to enter the bloodstream in two ways, via gastrointestinal mucosa or intravascular catheter (or a cut). Once present in the bloodstream it has to adapt quickly to the new environment. It is exposed to new pH (≈7.4) and new nutritional conditions. Serum and glucose activate Ras1-Cph1 and Ras1-Efg1 signaling pathways (Figure 2). Both Cph1 and Efg1 are considered to be the major transcription factors (TFs) responsible for induction of genes necessary for hyphae formation. The hyphae is immediately sensed by the innate immune system cells and *C. albicans* once again must activate own defense mechanisms strategies in order to evade the host attack. Some percent of the population is able to activate an immune evasion strategy. Production of molecules like secreted aspartic proteinases (Saps), changes the environment on the surface of *C. albicans* to become more proteolytic, what facilitates not only the penetration of host barriers but also strengthen immune evasion and degrades host defense. Looking at the host side during the infection in an early phase, other then phagocytic cells recruitment and recognition of the fungi results in complement activation. Signal processing results in the activation of C3b molecules binding the surface of *C. albicans* (i.e. opsonization, [21]). These molecules act as a signal for macrophages to phagocytize the microbe. Phagocytic cells are key components in the fight against the invading fungus but *C. albicans* has evolved to survive this attack [22]. In contact with different phagocytic cells (macrophages, PMNs) yeast can be exposed to reactive oxygen species (ROS) or reactive nitrogen intermediates (RNIs). It responds then by activation of appropriate detoxification mechanisms [23]. Following the model described e.g. in [24] the fungus inside the macrophage experiences oxidative stresses and has to alternate carbon utilization. Genes responsible for hyphae formation (e.g. HWP1, GPR1 [25]) are induced and fungi undergo morphological switches that enables *C. albicans* to escape from the macrophage (but not from PMNs). The macrophage is killed, *C. albicans* switches on glycolysis and the growth is back to normal. Free *C. albicans* can be again targeted for phagocytosis. After entering the circulation the pathogen has to cross endothelium, in parallel constantly fighting the immune system. Hyphae form, specifically secretion of special molecules on hyphae ends, is necessary here for the adhesion to endothelial cells [17]. It appears that the length of the hyphal germ tube also plays a role in adhesion capacity, the most efficient being in the range between 3-7 μm [17]. The attached hyphae cells (but not yeast cells) induce then endothelial cells endocytosis. Thus in spite of circulating in a bloodstream *C. albicans* is able to cross endothelial cells which enables it to disseminate all over the organism attacking different body parts

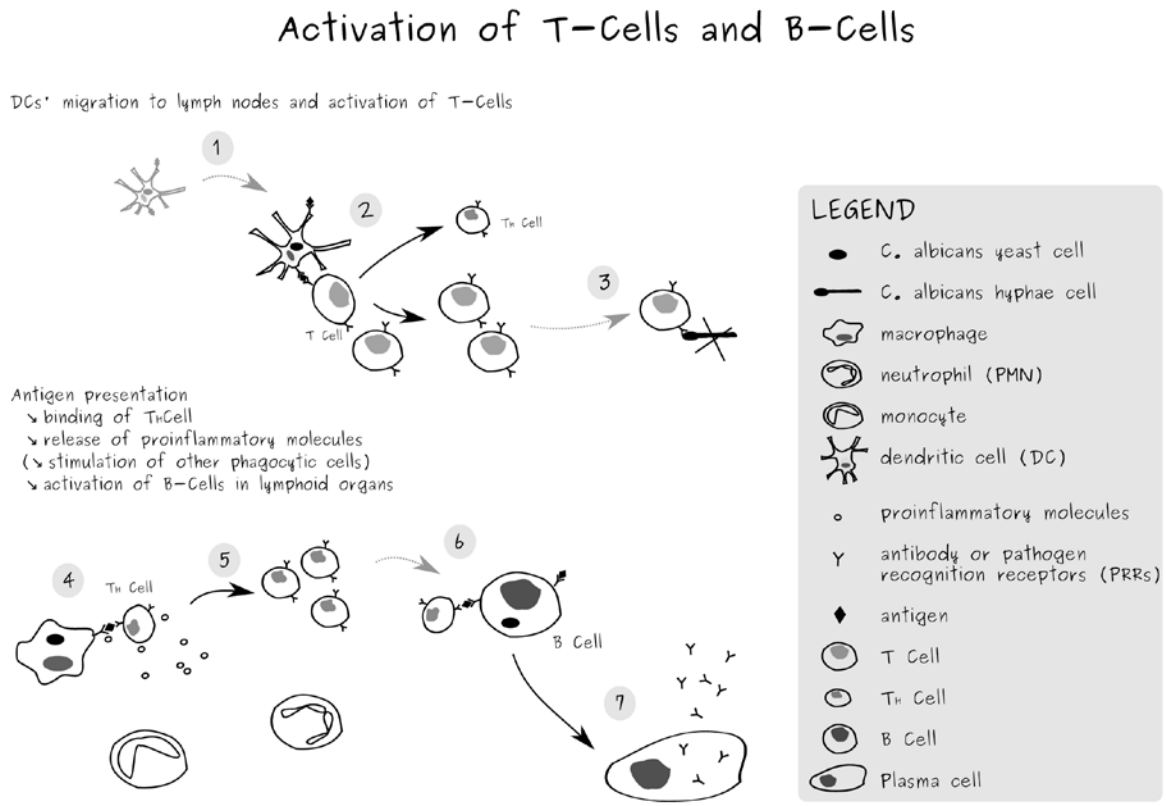

Figure 3: Activation of T-Cells and B-Cells. After phagocytosis dendritic cells present an antigen to their surface. In the next step, they migrate to lymph nodes (1), where they can attach to a specific T-Cell, it means with the proper receptor (2) and activate it. This results in T-Cell proliferation and also production of specific T_{H}-Cells (with the correct antigen-recognizing receptor). The activated T-Cell migrates to the site of infection and destroys the invading pathogen. The specific T_{H}-Cell binds the antigen, this time presented by a macrophage (4). This binding activates the T_{H}-Cell and stimulates further proinflammatory cytokine production (for instance IL17) that attracts other phagocytic cells. Activated T_{H}-Cells replicate (5), migrate toward lymph nodes and bind B-Cells presenting the antigen (6). The B-Cells mature to plasma cell producing the specific antibodies (7) that will now bind the surface of the pathogen, thereby stimulating many processes: activation of complement, enhanced phagocytosis and enhanced inflammation.

and organs. Another feature of the fungus is its ability to change phenotypically from white to opaque cells in strains homozygous for mating type-like locus (MTL). Both cell types differ in capability to adhere, formation of hyphae, size and shape, survival upon exposure to neutrophils. White cells are more successful in systemic infection model while opaque cells are more successful in a cutaneous infection model what can suggest that different phenotypic form of *C. albicans* attacks different sites of the host. The model of *C. albicans* infection cycle is a very complex system of mutual interactions and as such it is a challenge to describe it within one mathematical framework. It could become even more complex if we would like to incorporate all the signaling and regulatory pathways activated during the infection cycle, on both sides (See Figure 2 for some examples). It is therefore a good approach to divide it into small sub-models and focus on a specific stage of infection. These probably will be even further reduced in order to be able to work with the model. We are focusing on the early stage of the infection and looking for mathematical description of the *C. albicans* population dynamics while invading the host epithelial layer. For that purpose it was convenient to choose the agent based modeling approach briefly described in the next section.

ABM: Agent-based modeling approach: A set of ODEs is the most common approach used for modeling dynamics of biological systems [26] and one can use tools like COPASI [27], CellDesigner [28], XPPAUT [29] or many others. However, depending on the amount of available data and the question we want to address, alternative techniques can be applied [30]. Complex systems like fungi dissemination within a host and consequent progress of disease potentially could be modeled by partial differential equations (PDEs). They must be however supported with great amount of time course data in order to set the kinetic parameters that are very often not available in the literature. As a solution, another type of mathematical modeling formalism was introduced [31]: the agent-based modeling (ABM), more and more often applied in biology and medicine [32,33]. The modular structure of ABM facilitates the description of the model and is a very good starting point, at least to gain an intuition on the system and plan the experiments appropriately to obtain necessary and relevant information. There are many applications of ABM modeling [34] and we use this technique to model the very first interaction steps of the pathogen with the host oral epithelial cells. As a tool we choose NetLogo freely available from [31] but others can also be used and are listed in [35]. The advantage of ABM is that we can hide the complexity of such a system considering only the `system-level' interaction without entering too much details of microbiology. The nature of ABM will allow us to run simulations that will greatly improve our intuition. The visual interface of NetLogo consists of an `observer' where we set the rules defining every agent interacting in the model (here *C. albicans*

and immune cells); the `turtles' that are actually our agents behaving as specified by the `observer'; the `patches' establishing the world our agents are living in; and `links' that are features that can connect two `turtles'. The world is divided into a grid of squares, where each square is a single `patch' the `turtles' can move around. The simulations are easy to understand because of the visual interface of NetLogo and as such ABM models can also be used as educational tools. We present here a model of mutual interactions between *C. albicans* and PMNs (see Additional file 1 in Supplementary Information) and give simulation results influenced by different doses of drug treatment. The parameters in the model are freely chosen and no fitting to the experimental data was performed. The model is based on the following assumptions: *C. albicans* can switch from the yeast to the hyphae form and only the hyphae form can cause damage to the host. However dead hyphae or the one with too long hyphal germ are not harmful and we call them inactive hyphae. The model we implemented consists of three agent sets: yeast, hyphae and PMNs. Hyphae can be either active or inactive (Figure 4 A). The inactive hyphae can be seen in the simulation as yellow cells. The active hyphae, i.e. the one that cause damage are gray in the simulations. Active hyphae are immediately sensed by the epithelium (which is the patches). Presence of hyphae at an epithelium patch induces inflammation or cytokine secretion, which is here represented by diffusion of molecules along a concentration gradient. In the model it can be seen as different scales of green that gradually appear (Figure 4 C). This event recruits PMNs to the site of infection. We let run the simulation for 1500 arbitrary time units. In Figure 4 we present the situation without drug treatment and show four screen shots of the simulation at different time points (0, 400, 500, 1500). We can observe the overgrowth of *C. albicans* population because with a given set of parameters the PMNs are not able to control the fungi growth. As a next step, we consider treatment with some anti fungal drug that is supposed to inhibit the fungal growth. We keep the parameter set and we notice that application of drug results in complete elimination of invading fungi population (See Figure 5 A). Already 100 time units after application of the drug we note diminished hyphae load (Compare Figure 4 C and Figure 5 B; time point 500) and on a longer scale the gray hyphae disappear completely (Figure 5 B; time point 1500). This result however is highly dependent on the effciency of the drug. If the

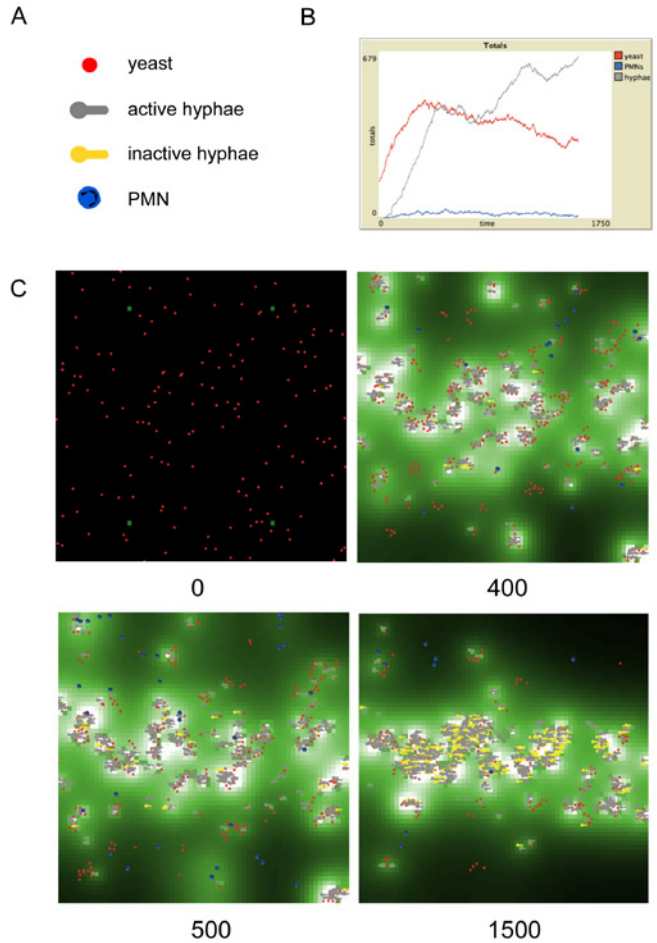

Figure 4: Model simulation with no drug treatment. (A) Agents in the model. We distinguish between the harmless yeast form of the fungus (red) and the pathogenic hyphae state (gray, yellow). We suppose that only `young' hyphae can cause damage to the host (where young hyphae is understood as hyphae with certain length of the hyphal germ). The ones that are too long or dead do not cause damage to the host (yellow cells in the model). Gray cells cause inflammation (green gradient in the simulation) which recruits the neutrophils (blue cells) to the site of infection. (B) Temporal simulation with arbitrary time units. On the Y-axis we count total number of cells as given by the legend. (C) Screen-shots of the model at different time points as given under each of the figure. At 0 time we can also see 4 green patches which play a function of portals for PMNs entering the system.

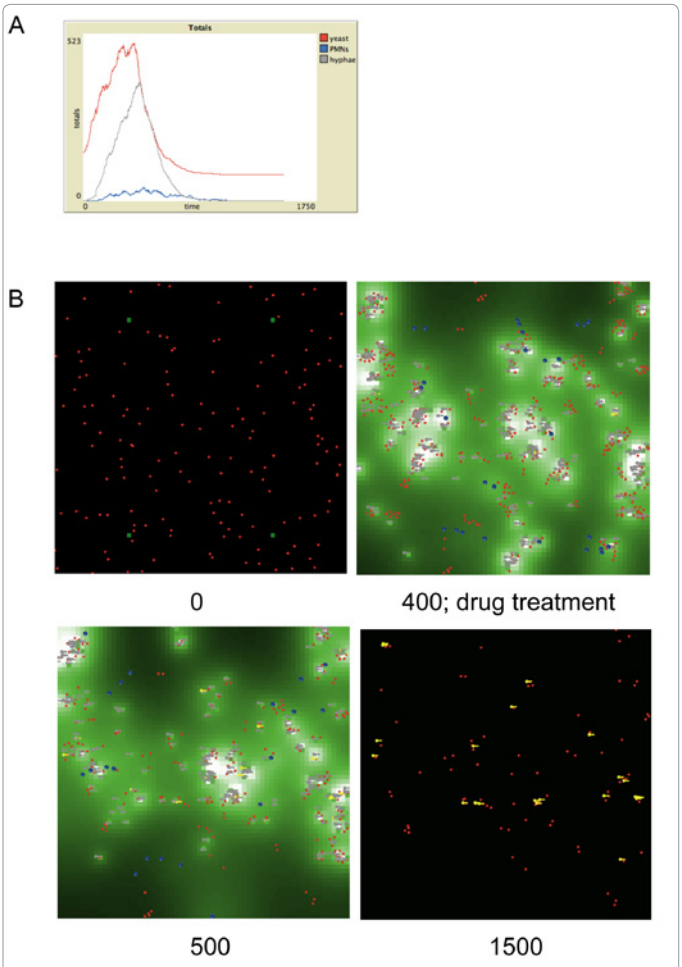

Figure 5: Model simulation. Treatment with a drug dose 8 at time point 400. The drug we apply reduces cell growth. We notice the reduction of the infection already 100 time units after drug application (time 500) and elimination of gray fungi at time 1500. See legend of the (Figure 4) for more details.

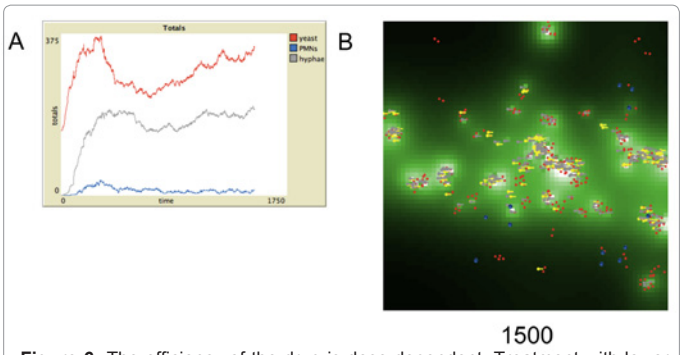

Figure 6: The efficiency of the drug is dose dependent. Treatment with lower drug dose (equal to 1.3) leads to incomplete removal of infection. This could be a typical scenario for acquirement of resistance. See legend of the (Figure 4) for more details.

drug is not strong enough PMNs can only keep the fungi population at certain level and do not succeed in full elimination, at least within 1500 time units (Figure 6). In this simulation, we assume that the drug is not degraded. However, we could now use the simulation environment to test different scenario, e.g. with degraded drug. We could ask how long the drug is actually active, how many times it has to be applied to completely eliminate the fungi from the system. What are the optimal intervals between two successive applications. Do we always have to apply the drug with the same dose? Or can it be reduced such that it does not have unnecessary side effects? These and other questions can be easily assessed using ABM models. In addition, simulations we run could be also compared to in vivo situations without raising any ethical issues.

Conclusions

High granularity models, for instance describing the infection progress, are extremely important. The predictive model that can actually give us a clue about the outcome of specific types of (multi-) drug treatment is currently the aim and there is a huge potential for pharmaceutical companies to support research in that area. In order to establish such models there must be more collaboration between experimentalists, computer scientists and theoreticians. Systeome projects need highly detailed data describing the host-pathogen interactions, not only regarding the harmless commensal state but also when the pathogen causes damage to the host leading to disease.

"(...) the knowledge of the genome of the human host and the use of host microarrays, (...) will allow us to look simultaneously at both the host and the fungus, providing fascinating insights into the complex process of pathogenesis, and the transition from commensalism to parasitism of *C. albicans*, This knowledge will ultimately enable us to develop new treatments or strategies in the fight against fungal infections [11]". In summary, systems biology has developed into a vibrant field being able to describe processes on the level of individual cells to more and more detail and accuracy, allowing to ask relevant questions and to predict essential cell properties. Host-pathogen interactions establish a new challenge. Not only the individual cell and its stress responses have to be understood, but also cell-to-cell mutual signaling and impact, their invading and evading strategies, and so on. This can essentially be considered as communication. The future challenges comprise a systematic application of tools and techniques developed for isolated organisms and, moreover new approaches such as analysis of the spatial facets of interactions, application of game theoretical concepts, investigation of mutually changing environments in space and time. A challenge worth to take.

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