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Review article: Streptomyces life cycle and cluster genes activation

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Abstract: Streptomyces is the go-to bacterium for making bioactive compounds. Some 70% of all antibiotics and numerous other pharmaceuticals, industrial chemicals, and food products are produced by Streptomyces. The development of resistance to antibiotics highlights the urgent need for alternative treatments. Secondary metabolite production is dependent on differentiation, however differentiation as a stimulant for antibiotic production has yet to be discovered. This genus is still crucial since it has several cryptic secondary metabolite pathways not expressed in the lab and weak and quiet antibiotic-producing genes not expressed without environmental circumstances, notably biological elicitor. I discuss differentiation-based approaches to increasing secondary metabolite production and stimulating cryptic pathways for antibiotic manufacture.

Keywords: Actinomycete, streptomyces, antibiotics, antimicrobial, cryptic pathway

1. INTRODUCTION

1.1. *Streptomyces* survival and development in solid

On solid-grown cultures, the life cycle of streptomyces is a complicated process. Microorganisms living in soil are subjected to multiple types of stress, including biological, chemical, physical, and nutritional stress [1]. Spores are the latent reproductive structures of several bacteria and fungus. During the process of spore formation, the cells put a stop to their normal rate of growth and their metabolism slows down [2]. Sporas have a thick hydrophobic wall and a low water content, which gives them the ability to withstand high temperatures and harsh circumstances without being damaged. Trehalose has the ability to preserve and maintain the integrity of dehydrated molecules, such as denaturalized proteins. Because macromolecules were formed before dormancy, this reduced metabolism can result in spores that are capable of germinating [2]. Spores can be dispersed by the wind, water, or insects, but they remain dormant until conditions are ripe for their growth [3, 4]. For germination to occur, optimal hydration conditions are required [2, 5, 6].
Streptomyces spores germinate in stages: darkening, swelling, germ tube emergence, and growth [7, 8].

The first stage, known as obscuring or darkening, occurs when spores admit water into latent cells in order to activate their metabolism. This step is caused by physical processes such as osmosis. After a few minutes, spores transition from latency cells to metabolic cells, which require energy stores, Ca+2, Mn+2, Mg+2, Fe+2, and Zn+2. Enzymes, in addition to

resuscitation-promoting substances, can breakdown the cell membrane, which opens the door for access to nutrients from the outside [7, 9, 10].
Second stage, includes enzymatic activities which recovered during swelling. Spores increased in size due to increase water absorbing, glucose level increase gradually, then trehalose dramatically hydrolysis [11]. An important step for germination is by decrease trehalose concentrations (main energy source) and return to functional conformations and new proteins can be translated and fully functional (during one hour) [6, 11, 12, 13, 14, 15].
Third stage germ tube, starts with DNA Replication when spores start metabolic pathways by detecting external sources of nutrients [2]. Started by the accumulation of the protein, SsgA causes an opposite effect if overexpressed or reduces the germ tubes number in each spore if it is absent [3].

Last is growth, a complex and highly regulated stage that regulates water entering spores. The spore swelling gradually reduces due to a peptidoglycan cross-link involving a carboxypeptidase gene like SCO4439 in the Streptomyces coelicolor genome. If this gene is removed, the spores continue swelling until 5 m after germ tube emission [8].

Germination includes morphological changes like degradation of peptidoglycan, which increases metabolic activity, and after the germ tube. The expression of DivIVA protein, which is located at the apex of the hyphae and plays an important role in vegetative growth [2, 6,16, 17, 18]. The germination phase ends with the expression of cell division (ftsZ) and growth (FilP) genes. During germination, secondary metabolites are produced, including the antibacterial terpenoid albaflavenone and the germination-inhibiting polyketides germicidin A and chancone. These compounds are produced de novo during germination [2, 19].

After germination, the first mycelium, also known as MI, which is a multinucleated stage of the Streptomyces mycelium, grows apically [20]. This stage is transient, and within the same hyphae you will find both dead and living segments. During MI, the septa that separate the segments can be one of two different types: one type contains peptidoglycan, and the other type does not [20, 21]. Septation occurs when dead segments are separated from living segments, allowing living segments to continue apical development. FtsZ is involved in septation, but its role is not necessary. At this time, the growth has already branched out [18].
After the branching growth of the early stage, a secondary mycelium (MII) emerges. This mycelium is a producer of secondary metabolites and has septa that are positioned in a haphazard and seemingly random manner [22]. This mycelium, which branches on surfaces and is called substrate mycelium, is distinct from aerial mycelium, which extends into the air without producing branches [18]. bald (bld) mutants, which are faulty in aerial growth, are responsible for regulating this system [23]. The sky-pathway is responsible for regulating the expression of genes that encode hydrophobic proteins that cover aerial hyphae, such as rodlins, chaplins, and ramS [25].

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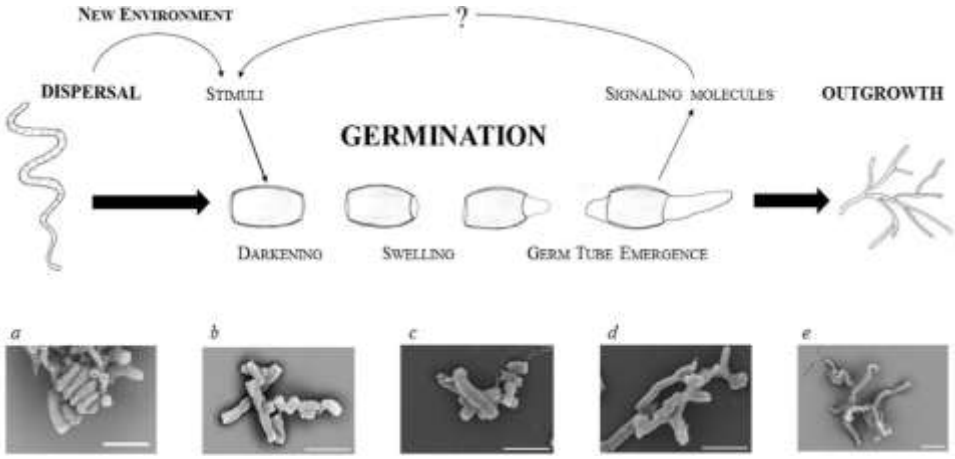
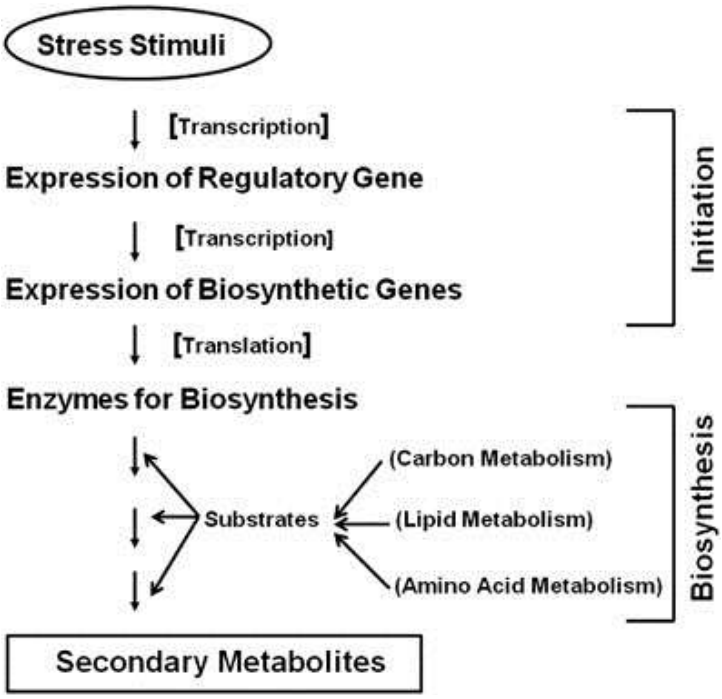


FIGURE 1. Streptomycete germination is key. A schematic of a germinating spore is shown, along with electron microscopic images of dormant (a, b) and germinating (c-e) S. coelicolor spores: the remnant of an aerial hypha with a twisted chain of mature spores is shown in (a), dormant spores are shown in (b), and time-lapse imaging of germinating spores after 2, 4, and 6 hours of [26,27,28].

1.2. *Streptomyces* life cycle and antibiotic production

The vast majority of secondary metabolites used in industry are produced in flasks or bioreactors. The behavior of Streptomyces is significant under these circumstances. Optimizing Streptomyces liquid cultures has been a focus of researchers' efforts for decades [29]. In spite of the fact that fewer compounds are being discovered and/or the fact that there are unknown biosynthetic pathways, the scientific community needs to pay attention to this. Media composition, mycelium pellet/clump analysis, and bioreactor design are the three factors that are used to discriminate strains of Streptomyces grown in liquid cultures. During the course of the life cycle, secondary metabolism depends on the differentiation of hyphae [30]. According to some studies, clumps are superior, while others support the use of pellets [31]. Analysis and improvement of industrial fermentation processes are made more difficult by the absence of a valid developmental model in Streptomyces' liquid medium.

At the conclusion of the period of proliferation, the substrate mycelium is responsible for the production of antibiotics. In spite of the fact that there is a mycelium that is dedicated to the manufacture of antibiotics (the second mycelium), the production of secondary metabolites does not start until the second mycelium differentiates. Additional restrictions apply to the production of antibiotics, and each strain of Streptomyces does not fully express its secondary metabolic capability in a particular developmental environment [27, 30]. Schematic representation of the pathways involved in the creation of secondary metabolites, including the start of transcription and biosynthesis [32].



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