Sertraline Modulates a Novel Isoform of the SR Protein Kinase in the Dermatophyte Trichophyton rubrum

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Introduction: The increased incidence of fungal infections in humans, particularly among immunocompromised individuals, is a major public health issue. Dermatophytosis, a prevalent fungal infection of keratinized tissues, is primarily caused by the filamentous fungus *Trichophyton rubrum*. Treating fungal diseases is generally protracted and expensive, with the risk of developing antifungal resistance. In fungi, differential gene expression and alternative splicing (AS) facilitate fungal adaptations to various environmental conditions. In previous studies, we demonstrated that sertraline (SRT), an antidepressant with antifungal activity. Understanding its effects may help elucidate both its mechanism of action and the fungal response to drug exposure. **Objectives:** This study aimed to investigate intron retention (IR) events in transcripts encoding serine/arginine protein kinases (SRPKs) in *T. rubrum* 118892, obtained from a patient with onychomycosis. **Materials and Methods:** RNA-seq data from cultures exposed to sub-inhibitory concentrations of SRT were analyzed to identify AS events, and the relative expression of canonical and alternative isoforms was further evaluated by RT-qPCR. Using the BLAST tool, we searched for sequence similarity between the SRPK isoforms. Then, the domains within the two isoforms were identified using the InterPro database. To predict and align the three-dimensional models of the two isoforms, we used AlphaFold2 and PyMOL, respectively. **Results:** RNA-seq analysis revealed that SRT affected transcriptional and post-transcriptional events in numerous *T. rubrum* genes, including those encoding transcription factors, kinases, and efflux pumps. Among the AS events, IR was predominant. *TERG_07061*, which encodes a serine/arginine protein kinase, exhibited distinct behavior among the protein kinase-encoding genes. RNA-seq data revealed that this gene was repressed in response to SRT exposure (log2 fold change = -1.61). In contrast, the intron-3 retention (IR3) was induced after 3 (log2 fold change = 1.43) and 12 h (log2 fold change = 2.50) of SRT treatment. The IR3 variant levels were significantly higher after 12 h of SRT exposure than in the control without SRT. InterPro analysis indicated that the IR3 isoform retains the core SRPK domains. When intron 3 was retained, a premature stop codon (UAA) was generated at bases 997–999 downstream of the start codon, resulting in an alternative isoform with 333 amino acids. This truncation affects the phosphotransferase domain, leading to partial loss of its C-terminal region, which is likely to impact protein conformation and substrate interaction. **Discussion:** AS events are associated with many biological processes, including development,

drug resistance, and adaptation. Different pre-mRNA isoforms may coexist in *T. rubrum*, and in the presence of SRT, the fungus modulates the expression of each isoform according to cellular requirements. We suggest the induction of the SRPK IR3 isoform in *T. rubrum* in response to SRT is an adaptive strategy to counteract the repression of this gene caused by the drug. **Conclusions:** SRT affects both transcriptional and post-transcriptional events in *T. rubrum*. Our study confirmed the existence of a new isoform of the SRPK gene containing IR3. This isoform could assume distinct functionalities, such as gene regulation or altered kinase activity.

Agradecimentos: FAPESP (2019/22596-9), CNPq (307871/2021-5 and 307876/2021-7), CAPES—Finance Code 001, and FAEPA. We thank V.M. Oliveira, M. Mazzucato, and M.D. Martins for their invaluable technical assistance.