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Repurposing the fungicide ciclopirox olamine for cancer therapy

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Ciclopirox olamine (CPX), an off-patent fungicide, has been clinically used to treat mycoses of the skin and nails for over two decades. Recently, we have observed that CPX exhibited anticancer activity *in vitro* and *in vivo* by inhibiting proliferation and inducing apoptosis of solid tumor cells, such as human rhabdomyosarcoma (Rh30) and breast carcinoma (MDA-MB231) cells. CPX inhibited cell proliferation by arresting cells in G1/G0 phase of the cell cycle, which is related to inhibition of cyclin dependent kinases (CDKs), leading to hypophosphorylation of retinoblastoma (Rb) protein. CPX induced apoptosis by downregulating expression of Bcl-xL and survivin and increasing cleavage of Bcl-2. In addition, we found that CPX inhibited lymphangiogenesis in an *in vitro* model (tube formation). This effect was in part associated with inhibition of VEGFR-3 expression, as overexpression of VEGFR-3 conferred partial resistance to CPX inhibitory effect on tube formation in LECs. It appears that CPX did not alter mRNA level, but inhibited protein synthesis and promoted protein degradation of VEGFR-3. Furthermore, we identified that CPX inhibited LEC tube formation in part through inhibiting VEGFR-3-mediated extracellular signal-related kinase 1/2 (ERK1/2) signaling pathway. This is supported by the findings that ectopic expression of constitutively active MKK1 resulted in activation of ERK1/2, and partially prevented CPX inhibition of LEC tube formation. Therefore, the results suggest that CPX has a great potential to be repurposed for cancer treatment and prevention.

Biography

Shile Huang received his Ph.D. from University of Salzburg (Austria) and did his postdoctoral training with Dr. Peter J. Houghton at St. Jude Children's Research Hospital, Memphis, Tennessee. Currently he is an Associate Professor in the Department of Biochemistry and Molecular Biology, and a Member of the Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, LA. His research interests include mTOR signaling in tumorigenesis and metastasis, anticancer mechanisms of small molecules, and neurotoxicity of the heavy metal cadmium. He has published more than 80 papers in reputed journals and serving as an editorial board member of *International Journal of Biochemistry and Molecular Biology.*

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