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Natural products targeting RNA-binding protein Musashi

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Musashi-1 (MSI1) is an RNA-binding protein that acts as a translation activator or repressor of target mRNAs. The best-characterized MSI1 target is NUMB mRNA, whose encoded protein negatively regulates Notch signaling. Additional MSI1 targets include the mRNAs for the tumor suppressor protein APC that regulates Wnt signaling and the cyclin-dependent kinase inhibitor $P21^{WAF-1}$. We hypothesized that increased expression of NUMB, P21 and APC, through inhibition of MSI1 RNA-binding activity might be an effective way to simultaneously down-regulate Wnt and Notch signaling, thus blocking the growth of a broad range of cancer cells. We used a fluorescence polarization assay to screen for small molecules that disrupt the binding of MSI1 to its consensus RNA binding site. One of the top hits was (-)-gossypol (Ki=476±273 nM), a natural product from cottonseed, known to have potent anti-tumor activity and which has recently completed Phase IIb clinical trials for prostate cancer. Surface Plasmon resonance and nuclear magnetic resonance studies demonstrate a direct interaction of (-)-gossypol with the RNA binding pocket of MSI1. We further showed that (-)-gossypol reduces Notch/Wnt signaling in several colon cancer cell lines having high levels of MSI1 with reduced SURVIVIN expression and increased apoptosis/autophagy. Finally, we showed that orally administered (-)-gossypol inhibits colon cancer growth in a mouse xenograft model. Our study identified (-)-gossypol as a potential small molecule inhibitor of MSI1-RNA interaction and suggests that inhibition of MSI1's RNA binding activity may be an effective anti-cancer strategy.

Biography

Liang Xu has completed his Post-doctorate training at Stanford University and started his own Lab at University of Michigan working on cancer drug discovery. He is a Co-Inventor of the first natural product Bcl-2 inhibitor that entered into clinical trials. He has more than 25 patents with four INDs in advanced clinical trials. He is a Professor of Cancer Biology at University of Kansas and has been funded by NIH, DOD and Komen Foundation. He is currently working on cancer drug discovery targeting the so far undruggable oncoproteins such as RNA-binding proteins.

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