

DOCTORAL THESIS

Developing new immuno-oncology drugs from traditional Chinese medicine

Li, Yang

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Abstract

The most exciting area in current cancer research is immuno-oncology, which aims to develop immunotherapy that activates the human immune system to attack cancers. However, we still lack broadly effective drugs and drug targets for this promising new cancer treatment modality. In an attempt to seek new immuno-oncology drugs that particularly target the antitumor innate immunity, our lab had previously screened traditional Chinese herbal medicine and found that water extract from a medicinal plant, *Alocasia Cucullata* (AC), has strong anticancer activity in mouse solid tumor models and acts partly by promoting antitumor, proinflammatory macrophages. However, the active components responsible for this exciting immuno-oncology activity and the corresponding immune targets are unknown. Therefore, the aim of my PhD study is to develop chemical biology strategies to isolate and purify the active components of AC from the crude water extract and identify the corresponding cellular targets and mechanisms. Results from my study identified two separable activities and active components, one smaller than 3K and the other larger than 100K, which work synergistically to simulate antitumor macrophages. Further analysis revealed the >100K active component is a large polysaccharide that binds to multiple Toll-like Receptors (TLRs) critical for activating proinflammatory M1-type macrophages. Identity of the <3K active component is not completely resolved due to the difficulty of purifying this highly hydrophilic small molecule using conventional chromatography

techniques. Nonetheless, I was able to clean up this fraction by 50 fold and perform RNAseq to examine the innate immune targets of this intriguing drug lead and found it acts to differentiate monocytes to macrophages. Overall my PhD thesis has explored new chemical biology strategies to purify and characterize active components from traditional Chinese medicine towards new drug development and developed a variety of cell-based immune activity assays for identifying and characterizing novel innate immune drug targets and mechanisms.

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