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Targeting host signaling pathways to protect against pathogen induced vascular damage

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A number of bacterial and viral pathogens have developed mechanisms to injure the host endothelial barrier and induce vascular leakage, edema, hemorrhagic fever or shock-like symptoms. Taking advantage of our expertise in vascular signaling pathway analysis using the zebrafish model, we developed host-endothelium directed studies showing a conservative use of homologous genes and signaling pathways. As a surrogate host, the zebrafish provides embryonic transparency and an accessible vascular system. Our studies have defined distinct differences between anthrax lethal toxin and the hemolytic phospholipase C of *P. aeruginosa* on endothelial cell function *in vivo*. While lethal toxin increased vascular permeability without inducing endothelial cell death, the hemolytic phospholipase is selectively cytotoxic to the same cells. Our work on the lethal toxin action established an important role for the MEK/ERK signaling pathway using loss-of-function or gain-of-function assays. Using a selective chemical MEK1/2 inhibitor, or a transgenic zebrafish line overactivating the MEK/ERK pathway, we were able to either mimic or protect against lethal toxin action, respectively. By defining host components that regulate vascular integrity, we will be able to develop drugs that selectively enhance endothelial resilience and protect against vascular damage. By establishing reliable assays to assess endothelial damage, we will be able to launch a large-scale chemical library screen using the zebrafish model to identify drugs that can improve vascular resilience and preserve circulatory function that may be therapeutically useful as host-targeted treatments against a number of pathogens.

Biography

Joanne Chan completed her postdoctoral training in the laboratory of Dr. Thomas M. Roberts at the Dana-Farber Cancer Institute, where she introduced the use of the zebrafish model to cancer-relevant studies. Using a preclinical anti-angiogenic drug, she demonstrated that overactivation of AKT can override an upstream inhibition of the vascular endothelial growth factor receptors (VEGFRs). She was recruited to the Vascular Biology Program at Boston Children's Hospital where she studies vascular signaling pathways underlying human diseases.

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