REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

Microtubules, Microtubule Associated Proteins (MAPs) and Cancer Therapy

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Abstract

Cancer is one of the leading causes of death worldwide. A major cellular target for cancer drugs are microtubules, which are crucial for many cellular processes involved in cell division, polarization and movement. The dynamic behaviour of microtubules and their interactions with other cellular components are to a significant extent controlled by proteins that bind to microtubules termed Microtubule Associated Proteins (MAPs). Understanding how the microtubule drugs behave in physiologically relevant concentrations is important to design better anticancer drugs and also to design therapeutic strategies that reduce the toxicity to normal tissues.

During my doctoral thesis work at the Indian Institute of Technology, Bombay, India, I was involved in the discovery and evaluation of new small molecule inhibitors of microtubule dynamics. My study helped to identify sulfonamides, nitroalkenes and organometallic compounds as potent anticancer agents and also to decipher the mechanism of action of these compounds. With my expertise on the microtubule drugs, I joined the lab of Dr. Anna Akhmanova, Utrecht University, Netherlands to understand the interaction of microtubules with + TIPs (the proteins that specifically bind to the growing ends of the microtubules). I focused my study on the End Binding (EB) proteins, the master player of the +TIP network. Using nanomolar concentrations of the MTAs, we found that these drugs have an entirely different, but stronger effect on microtubules in the presence of EB proteins. My study showed that irrespective of the different binding sites on tubulin and different mechanisms of action at higher concentrations, at low nanomolar concentrations, all the tested MTAs behave similiarly in the presence of EB proteins. Based on my postdoctoral research, I strongly believe that the effects of microtubule drugs are modulated by the proteins that associate with the microtubules. The subtle changes in microtubule dynamics are highly important for cell physiology, and therefore the consequences of the MAP-mediated modification of drug activity can be exploited for the development and improvement of microtubule targeted drugs.

Through my research I aim to acquire fundamental insight in the mechanisms of microtubule recognition by microtubule associated proteins, the general importance of this process in cell migration and proliferation and its potential as a drug target.