**Abstract**

Rab GTPases are the main regulators of eukaryotic intracellular trafficking events. In the last decade, many Rab GTPases and their related proteins have been linked to cancer. In this research, attempts have been made to develop small molecules that interfere with Rab GTPase function by selective inhibition of the essential post-translationally modifying enzyme, RabGGTase. These inhibitors are used as tools to verify RabGGTase as a potential anti-cancer target and could be used in a chemical biology approach to further study Rab-mediated processes.

RabGGTase and its related enzymes FTase and GGTase I together represent the human prenyltransferases, involved in prenylation of the superfamily of small Ras GTPases. The most potent RabGGTase inhibitor known, BMS3, was originally designed as FTase inhibitor. Since BMS3 lacks selectivity with respect to FTase, both in vitro and in cells, its pro-apoptotic effect could only be attributed to RabGGTase inhibition indirectly. In order to study the effects of selective RabGGTase inhibition on cancer cell proliferation and, more generally, Rab-mediated cellular processes, the main challenge was the design and synthesis of potent and selective RabGGTase inhibitors with cellular activity. Several approaches have been used in order to obtain such inhibitors. Using a structure-guided design, the scaffold of BMS3 was decorated with additional groups to gain selectivity for RabGGTase. Going through iterative cycles of design, synthesis and biochemical and biological evaluation, several selective RabGGTase inhibitors were obtained, the most potent being inhibitor 126. Other strategies to obtain selective RabGGTase inhibitors were evaluated with mixed success. The in vitro screening based on a fluorometric RabGGTase assay led mainly to identification of false positives, whereas a scaffold hopping approach resulted in a quick generation of a few prenyl transferase inhibitors with mixed activity toward RabGGTase, FTase or GGTase I.
In order to verify the potential of selective RabGGTase inhibitors and to inspire drug discovery, several cancer cell lines were treated with 126. It could be shown that 126 selectively inhibited cancer cell line proliferation without being generally cytotoxic to PBMC cells, thereby verifying RabGGTase as potential anti-cancer target. The iterative effort of design, X-ray structure determination, synthesis and biological evaluation successfully allowed to convert a non-selective inhibitor into a potent, selective, not generally cytotoxic inhibitor. Selective RabGGTase inhibitors may be used as valuable chemical biology tools for further research on Rab mediated processes.
Zusammenfassung

führte zu Inhibitoren mit wechselnder Selektivität gegenüber RabGGTase, FTase oder GGTag I.