β-Glucuronidase Activated Prodrugs in ADEPT Strategy

ABSTRACT:
The majority of anticancer drugs are anti-proliferative agents that preferentially kill dividing cells. However, the use of these cytotoxic agents in chemotherapy is limited by the damage they cause to normal cells. Advances in cancer research provide better understanding of differences between tumor and normal cells. Design of new chemotherapy utilizing the unique properties of tumors led to research in targeted therapy. The first carriers of tumor-specific toxins were monoclonal antibodies. By using antibodies that specifically target antigens expressed on the tumor cell surface, researchers were able to target the delivery of cytotoxins to a tumor site. However, due to limitations of immunotoxins, another strategy in targeted therapy emerged. Antibody Directed Enzyme Prodrug Therapy (ADEPT) is an adaptation of immunotoxin therapy. In ADEPT, selective activation of cytotoxic agents at the tumor site decreases systemic toxicity and increases the therapeutic window of cytotoxic agents. Beta-glucuronidase, a member of glycosylhydrolase, is one of the enzymes used in ADEPT to activate glucuronide prodrugs at the tumor site. Several glucuronides of anti-proliferative agents, such as doxorubicin, have been reported. The glucuronides are considered to be good candidates for anticancer prodrugs because the sugar moiety provides selectivity and improved pharmacokinetics. Recent development in the design of glucuronides of camptothecin, a cytotoxic agent isolated from Camptotheca acuminate, gave promising results in vitro. Such compounds have promising potential for application in ADEPT as well as prodrug monotherapy (PMT).

References: