Is an Inhibitor or Blocker of Inactivation of Glycogen Synthase Kinase-3β (GSK-3β) a Reliable Agent for Cancer Chemotherapy?

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Inhibitor of GSK-3β

Lithium ion (Li⁺) is the simplest GSK-3β inhibitor and blocks activity in a non-competitive manner by interacting with the substrate protein. Actually, Li⁺ competes with magnesium ions (Mg²⁺) at the ATP-binding site by direct binding. When the Li⁺ concentration is maintained near the Ki value of GSK-3β (2 mM), physiologically essential enzymes such as inositol monophosphatase (Ki: 0.8 mM), inositol polyphosphate 1-phosphatase (0.3 mM), and fructose 1,6-bisphosphatase (0.3-0.8 mM) are strongly inhibited [6]. According to a more specific inhibitor of GSK-3β with a much higher affinity is needed. Because the structures of the ATP-binding site in Ser/Thr kinases are different from those in Tyr kinases, some adenine-like compounds may be candidates for specific and effective GSK-3β inhibitors (e.g., 6-bromoindirubin 3′-oxime: BIO). However, compounds such as BIO may also inhibit CDK [7]. As we described above, GSK-3β is involved in multiple signaling pathways, and the pharmacological action of an inhibitor is a combined result of its multifunctional properties. For example, BIO is a potent inhibitor of GSK-3β and has anti-proliferative activity on cancer cells. GSK-3β down-regulates the cell cycle by suppressing cyclin D production after degradation of β-catenin, because the complex of cyclin D and
Conclusion

Recently, GSK-3β has been considered a target protein for the development of novel anti-cancer agents. GSK-3β is a kinase that is involved in various signaling pathways. Because GSK-3β plays a crucial role in cell proliferation, inhibition of cell cycle progression is expected to be a main mechanism of action of such anti-cancer agents. Cell cycle progression is a complicated process that is regulated by numerous factors such as cyclins and kinases including CDKs, PI3K, Akt, DDK, and ATR in combination or individually. Anti-proliferative activities have been found in both inhibitors and an inhibitor of activation of GSK-3β. These contradictory observations suggest that small molecules interact with many intracellular components in addition to the biochemical effectors that have been characterized. Recently, celecoxib was reported to inhibit NF-kB (via I-κB degradation after COX-2 inhibition) as well as Akt [10]. This finding leads to the controversial result that celecoxib suppresses apoptosis via inhibition of NF-kB and directs cells toward death via inhibition of Akt. Accordingly, no clear direction exists regarding whether to choose up- or down-regulation of GSK-3β for developing novel anti-cancer agents. However, because GSK-3β is thought to be an incidental factor in Alzheimer’s disease and type II diabetes, up-regulation of the enzyme may enhance the risks of these diseases. On the other hand, BIO, which is a GSK-3β inhibitor, suppresses phosphorylation of amyloid precursor protein and tau and may be therapeutically useful in neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, and bipolar disorder. Furthermore, BIO has anti-hyperglycemic potential in addition to anti-inflammatory potential and promotion potential in osteogenesis [11, 12]. Although the mechanism is unclear, GSK-3β inhibitors with anti-proliferative activity are anticipated for development of novel anti-cancer agents.

Competing Interests

The authors declare that they have no competing interests.

References


