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

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Tyrosine kinase inhibitors such as imatinib (Glivec®) and sunitinib (Sutent®) are useful drugs in cancer chemotherapy and are called "molecular targeting agents" [1]. Kinase inhibition is thus considered a promising anti-cancer mechanism. Two categories of kinases are present in cells; one class called tyrosine (Tyr) kinases phosphorylates tyrosine residues in the target protein, and the other class called serine/threonine (Ser/Thr) kinases phosphorylates serine or threonine residues. Although the leading molecular targeting agents target Tyr kinases, a new drug called palbociclib (Ibrance®) targets cyclin-dependent kinase (CDK), which is a Ser/Thr kinase [2]. Glycogen synthase kinase-3β (GSK-3β) is a proline-directed Ser/Thr kinase and a key enzyme in the cell cycle along with CDK. GSK-3β was originally identified as a key regulatory enzyme in the glycogen synthesis pathway, which inactivates glycogen synthase by phosphorylation [3]. Subsequently, several important physiological roles for GSK-3β have been identified in embryogenesis, neural differentiation, and cell division. In these processes, GSK-3β regulates the activities of transcription factors and cell signaling pathways such as Wnt/β-catenin signaling and PI3K/Akt signaling. GSK-3β transfers a phosphate molecule onto β-catenin, NF-κB, NFAT, Snail, c-Myc, p53, tau protein, and CRMP-2 in multiple physiological signaling pathways [4]. In the kinase cascade, GSK-3β is also a substrate of several kinases and the enzyme activity is regulated. Phosphorylation at Tyr-219 of GSK-3β by PyK2 and FYN up-regulates GSK-3β activity. In contrast, phosphorylation at Ser-9 of GSK-3β by PI3K, Akt (PKB), and $p90^{RSK}$ down-regulates GSK-3β activity [5]. Because the expression of these kinases is regulated by extracellular factors such as growth factors, hormones, and cytokines, GSK-3β activity is significantly influenced by the physiological state of the whole body. Accordingly, modulation of the enzymatic activity of GSK-3β is considered important in pharmacotherapeutics for diseases such as neurological disorders and cancer.

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 (Mg^{2+}) 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]. Accordingly, a more specific inhibitor of GSK-3β with a much high 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 CDK4/6 drives G1 phase progression in the cell cycle. Because GSK-3β catalyzes degradation of β-catenin by phosphorylation, inhibition of GSK-3β leads to promotion of the cell cycle. However, anti-proliferative effects are due to inhibition of cell cycle progression. These contradictory data suggest that BIO inhibits CDKs as well as GSK-3β in anti-proliferative pathways. We determined the anti-proliferative activity to evaluate the biological significance of newly developed indirubin derivatives as anti-cancer agents. We successfully developed an effective compound (IC_{50}: 1.7 μM) with anti-proliferative activity that is comparable with that of cis-platin, a powerful anti-cancer agent [8].

From another viewpoint, GSK-3β down-regulates glycogen synthesis by phosphorylation of its synthase. When GSK-3β is inhibited over the long term, ATP production is suppressed due to depletion of free glucose after elevation of glycogen synthesis. This assumption suggests that one possible mechanism of the anti-proliferative activity of GSK-3β inhibitors is deterioration of cell viability by starvation of cellular ATP.

Blocker of the inactivation of GSK-3β

Celecoxib, a useful non-steroidal anti-inflammatory drug and a selective inhibitor of cyclooxygenase-2 (COX-2), shows anti-proliferative activity on cancer cells due to suppression of progression through the G1 phase of the cell cycle. In this case, production of cyclin D is suppressed by depletion of β-catenin,the degradation of which is catalyzed by GSK-3β [9]. However, celecoxib promotes neither GSK-3β expression nor activation directly. As we described above, GSK-3β is down-regulated by phosphorylation at Ser-9 by several kinases including Akt and PI3K. Surprisingly, celecoxib inhibits Akt, and therefore, the inactivation of GSK-3β is suppressed. Because overexpression of cyclin D is observed in various types of cancer cells, up-regulation of GSK-3β may be valuable in cancer therapy.

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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-κB (*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-κB 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.

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