Deregulated GSK3β activity in colorectal cancer: its association with tumor cell survival and proliferation *

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GSK3β is a multifunctional serine/threonine kinase that regulates various cellular pathways, depending on its substrates for phosphorylation. It is evident that regulation of Wnt/β-catenin signaling is only one of its diverse functions. Since oncogenic transcription factors (e.g., c-Jun, c-Myc) and proto-oncoproteins (i.e., β-catenin, Gli proteins) are putative GSK3β substrates for phosphorylation-dependent inactivation, it is hypothesized that GSK3β interferes with cellular neoplastic transformation and tumor development, as exemplified by its activity in Wnt/β-catenin signaling. However, only a few studies have addressed its role(s) in human cancer, and these studies have reported differing effects of GSK3β on cancer cells. Using GSK3β deficient mouse embryonic fibroblasts, it was shown that GSK3β plays a crucial role in cell survival mediated by the nuclear factor-kappaB (NF-κB) pathway (Nature 2000; 406:86-90). Interestingly, we have recently shown that the Wnt/β-catenin and NF-κB pathways were co-activated in colorectal cancer by dysregulation in the ubiquitin system (J Natl Cancer Inst 2004; 96:1161-70). Thus, these observations bring forward apparently opposing notions regarding the functions of GSK3β in neoplastic cells on the one hand, removing a neoplastic trigger by phosphorylation-dependent degradation of β-catenin oncoprotein in the ubiquitin system, and on the other, contributing to a cell proliferation and survival pathways by regulating NF-κB. The present study was therefore undertaken to clarify the role of GSK3β in cancer by analyzing expression and activity of this kinase in colon cancer cells and clinical colorectal cancers and by investigating its effects on cancer cells. In colon cancer cell lines and colorectal cancer patients, levels of GSK3β expression and its active form were higher in tumor cells than in their normal counterparts; these findings were independent of nuclear accumulation of β-catenin oncoprotein in the tumor cells. Inhibition of GSK3β activity by its Ser9 phosphorylation was defective in colorectal cancers but preserved in non-neoplastic cells and tissues. Strikingly, inhibition of GSK3β activity by chemical inhibitors and its expression by RNA interference targeting GSK3β induced apoptosis and attenuated proliferation of colon cancer cells *in vitro*. Our findings demonstrate an unrecognized role of GSK3β in tumor cell survival and proliferation and warrant proposing this kinase as a novel and potential therapeutic target in colorectal cancer.

*Reference: Shakoori A, Ougolkov A, Yu ZW, Zhang B, Modarressi MH, Billadeau DD, Mai M, Takahashi Y, Minamoto T. Deregulated GSK3β activity in colorectal cancer: its association with tumor cell survival and proliferation. Biochem Biophys Res Commun 334: 1365-1373, 2005.