Location, Location, Location: FoxM1 Mediates β-Catenin Nuclear Translocation and Promotes Glioma Tumorigenesis

Angela Bowman[1] and Roel Nusse[1,*]
[1]Department of Developmental Biology, Howard Hughes Medical Institute, Lorry I. Lokey Stem Cell Research Building, 265 Campus Drive, Room G2143B, Stanford University, School of Medicine, Stanford, CA 94305-5458, USA
*Correspondence: rnusse@stanford.edu
DOI 10.1016/j.ccr.2011.10.003

Genetic alterations in the Wnt/β-catenin/TCF-signaling pathway are commonly found in human tumors, but not in glioblastomas. In this issue of *Cancer Cell*, Zhang et al. report that FoxM1 mediates β-catenin nuclear translocation in glioblastoma, suggesting a novel mechanism for glioblastoma progression in the absence of conventional Wnt/β-catenin pathway activation.

The role of the Wnt/β-catenin pathway in normal development, including the control of stem cell self-renewal and proliferation, is well established (Clevers, 2006). Not surprisingly, mutations in this pathway result in aberrant activation of target genes, such as *MYC* and *CCND1*, and often lead to cancer (Clevers, 2006). Pathway disruptions commonly include mutations to adenomatous polyposis coli (APC), a negative regulator of the pathway, or to β-catenin itself, the fundamental signaling effector. However, glioblastoma multiforme (GBM), the most common and aggressive glioma, rarely shows these genetic abnormalities, though increased β-catenin activation is present (Paraf et al., 1997). Here, Zhang et al. (2011) describe a surprising mechanism for Wnt/β-catenin signaling activation in GBM and, more fundamentally, explain a mechanism for β-catenin nuclear translocation via binding to the transcription factor, FoxM1.

FoxM1 is a forkhead box (Fox) transcription factor with known roles in regulating cell cycle progression by controlling the G2/M transition, exit from the cell cycle, and the stability of the mitotic spindle. An expanding body of work has linked FoxM1 upregulation to a variety of cancers, including breast, gastric, and lung cancer (Wang et al., 2010), marking it as a proto-oncogene. Importantly, its expression is often correlated with poor prognosis (Wang et al., 2010). The fact that FoxM1 interacts with numerous signaling pathways and is associated with many solid tumors makes it an attractive molecular target for anticancer therapies.

In the present study, Zhang et al. (2011) probe the relationship between FoxM1 and β-catenin. Although it is known that β-catenin nuclear translocation is important for Wnt target gene regulation, the mechanism by which this movement happens has been surprisingly hard to define. Notably, β-catenin lacks a nuclear localization signal (NLS) and does not depend on importins or Ran for nuclear translocation (reviewed in Henderson and Fagotto, 2002). Rather, Zhang et al. (2011) demonstrate that FoxM1 is required for β-catenin nuclear translocation because β-catenin fails to accumulate in nuclei of FoxM1$^{-/-}$ cells. The authors further validate that translocation depends on the binding of β-catenin to FoxM1, which is mediated by armadillo repeats 11–12 of β-catenin, and the Fox domain of FoxM1. Moreover, this interaction is maintained in nucleus, where both proteins form a complex with TCF transcription factors on the promoters of Wnt/β-catenin target genes.

Zhang et al. (2011) go on to demonstrate that the nuclear translocations of both β-catenin and FoxM1 and their interaction drive the formation of gliomas. Knockdown of either protein decreased the self-renewal of glioblastoma-initiating cells (GICs) in vitro and induced the expression of differentiation markers. These results are consistent with a known role for Wnt/β-catenin signaling in regulating the cell cycle and cell fate choices of mouse neural progenitor cells (Chenn and Walsh, 2002), but whether FoxM1 plays a role in this nontumor context is unknown. Additionally, reduction in FoxM1 in GICs resulted in a loss of tumor formation in vivo. Interestingly, the tumor-promoting ability of FoxM1 depended completely on β-catenin because the absence of β-catenin abolished the potency of FoxM1 to generate brain tumors. Furthermore, the authors find that high FoxM1 and nuclear β-catenin are correlated in a panel of human GBMs, demonstrating the relevance of these studies for human disease. These results suggest that targeting FoxM1, which is usually absent from noncycling cells (Wang et al., 2010), might effectively inhibit glioma progression by excluding β-catenin from the nucleus, and by extension, blocking the activation of Wnt/β-catenin target genes. In fact numerous small molecules, including the antibiotic siomycin A, have already been demonstrated to reduce FoxM1 expression in various tumor contexts (Wang et al., 2010).

The findings of Zhang et al. (2011) in glioblastoma are interesting to compare with medulloblastoma, a pediatric tumor of the cerebellum. In agreement with the current study, a recent report by Priller et al. (2011) demonstrated that high FoxM1 expression correlates with poor prognosis in medulloblastoma. Additionally, the molecular subgroup of medulloblastoma with Wnt/β-catenin pathway activation expresses high levels of FoxM1 protein (Priller et al., 2011). However, in medulloblastoma high levels of nuclear β-catenin are largely due to activating mutations in the *CTNNB1* gene itself (Fattet et al., 2009), whereas β-catenin mutations are usually absent from GBM. Interestingly, unlike the current study

(Zhang et al., 2011), in medulloblastoma high nuclear β-catenin is an established predictor of increased patient survival (Ellison et al., 2005). How, then, does a β-catenin/FoxM1 interaction function in medulloblastoma, if it exists at all? Do mutations to β-catenin at key regulatory residues, which are common in medulloblastoma, alter the armadillo repeat-mediated interaction of β-catenin with FoxM1? It will be interesting to see what a more thorough examination of the FoxM1/β-catenin interaction in medulloblastoma can elucidate concerning this discrepancy.

A further point that the current study (Zhang et al., 2011) highlights is the potential for a widespread interaction between Fox proteins and the Wnt/β-catenin signaling pathway. Previous studies in *C. elegans* and mammalian cells demonstrated a physical interaction between β-catenin and multiple FOXO proteins (Essers et al., 2005). Similar to the results of Zhang et al. (2011), these interactions were mediated by the armadillo repeats of β-catenin and the portion of the FOXO protein containing the forkhead DNA-binding domain (Essers et al., 2005). Additionally, there is precedence for Wnt/β-catenin signaling in the regulation of Fox proteins. This is the case for FoxN1, the protein that is mutated in nude mice, resulting in athymic and hairless animals (Balciunaite et al., 2002). In the thymus and the hair follicle, Wnt/β-catenin pathway stimulation leads to activation of FoxN1, which possesses Wnt Response Elements (WREs) in its promoter (Balciunaite et al., 2002). In fact there may also be a reciprocal relationship between Wnt/β-catenin and FoxM1 because FoxM1 can directly bind to the promoter of human β-catenin and regulate its expression in endothelial cells. However, the frequency of cross-regulation between these two pathways, in both normal and tumor environments, remains to be seen. Additionally, whether FoxM1 can regulate β-catenin nuclear translocation in other cell contexts has yet to be established. In any case this study illuminates the potential for Wnt/β-catenin pathway control by an unusual source, FoxM1, and the role for these proteins in glioblastoma progression.

REFERENCES

Balciunaite, G., Keller, M.P., Balciunaite, E., Piali, L., Zuklys, S., Mathieu, Y.D., Gill, J., Boyd, R., Sussman, D.J., and Holländer, G.A. (2002). Nat. Immunol. *3*, 1102–1108.

Chenn, A., and Walsh, C.A. (2002). Science *297*, 365–369.

Clevers, H. (2006). Cell *127*, 469–480.

Ellison, D.W., Onilude, O.E., Lindsey, J.C., Lusher, M.E., Weston, C.L., Taylor, R.E., Pearson, A.D., and Clifford, S.C.; United Kingdom Children's Cancer Study Group Brain Tumour Committee. (2005). J. Clin. Oncol. *23*, 7951–7957.

Essers, M.A.G., de Vries-Smits, L.M.M., Barker, N., Polderman, P.E., Burgering, B.M.T., and Korswagen, H.C. (2005). Science *308*, 1181–1184.

Fattet, S., Haberler, C., Legoix, P., Varlet, P., Lellouch-Tubiana, A., Lair, S., Manie, E., Raquin, M.A., Bours, D., Carpentier, S., et al. (2009). J. Pathol. *218*, 86–94.

Henderson, B.R., and Fagotto, F. (2002). EMBO Rep. *3*, 834–839.

Paraf, F., Jothy, S., and Van Meir, E.G. (1997). J. Clin. Oncol. *15*, 2744–2758.

Priller, M., Poschl, J., Abrao, L., von Bueren, A.O., Cho, Y.J., Rutkowski, S., Kretzschmar, H.A., and Schuller, U. (2011). Clin. Cancer Res. Published online September 14, 2011. 10.1158/1078-0432.CCR-11-1214.

Wang, Z., Ahmad, A., Li, Y., Banerjee, S., Kong, D., and Sarkar, F.H. (2010). Cancer Treat. Rev. *36*, 151–156.

Zhang, N., Wei, P., Gong, A., Chiu, W.-T., Lee, H.-T., Colman, H., Huang, H., Xue, J., Liu, M., Wang, Y., et al. (2011). Cancer Cell *20*, this issue, 427–442.

RAIDDing ER Stress for Oncolytic Viral Therapy

David J. McConkey[1,2,*]
[1]Department of Cancer Biology
[2]Department of Urology
The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
*Correspondence: dmcconke@mdanderson.org
DOI 10.1016/j.ccr.2011.10.002

Oncolytic viruses exploit molecular differences between normal and cancer cells to selectively kill the latter. Results of a synthetic lethal screen described in this issue of *Cancer Cell* demonstrate that components of the unfolded protein response (UPR) limit virus-induced tumor cell killing and identify a strategy to utilize this knowledge.

Productive viral infection mimics oncogenic transformation in several respects, and some of the same molecular mechanisms are employed by viruses and cancer cells to disrupt key homeostatic mechanisms. These similarities serve as the foundation for the development of "oncolytic" viruses that are designed to specifically target and kill cancer cells (Parato et al., 2005). Although some targeting strategies involve engineering viruses so that they bind specifically to cancers, an even more attractive approach involves developing viruses that can only replicate in cancer cells that contain specific defects in homeostatic control. For example one of the products of the adenovirus E1B