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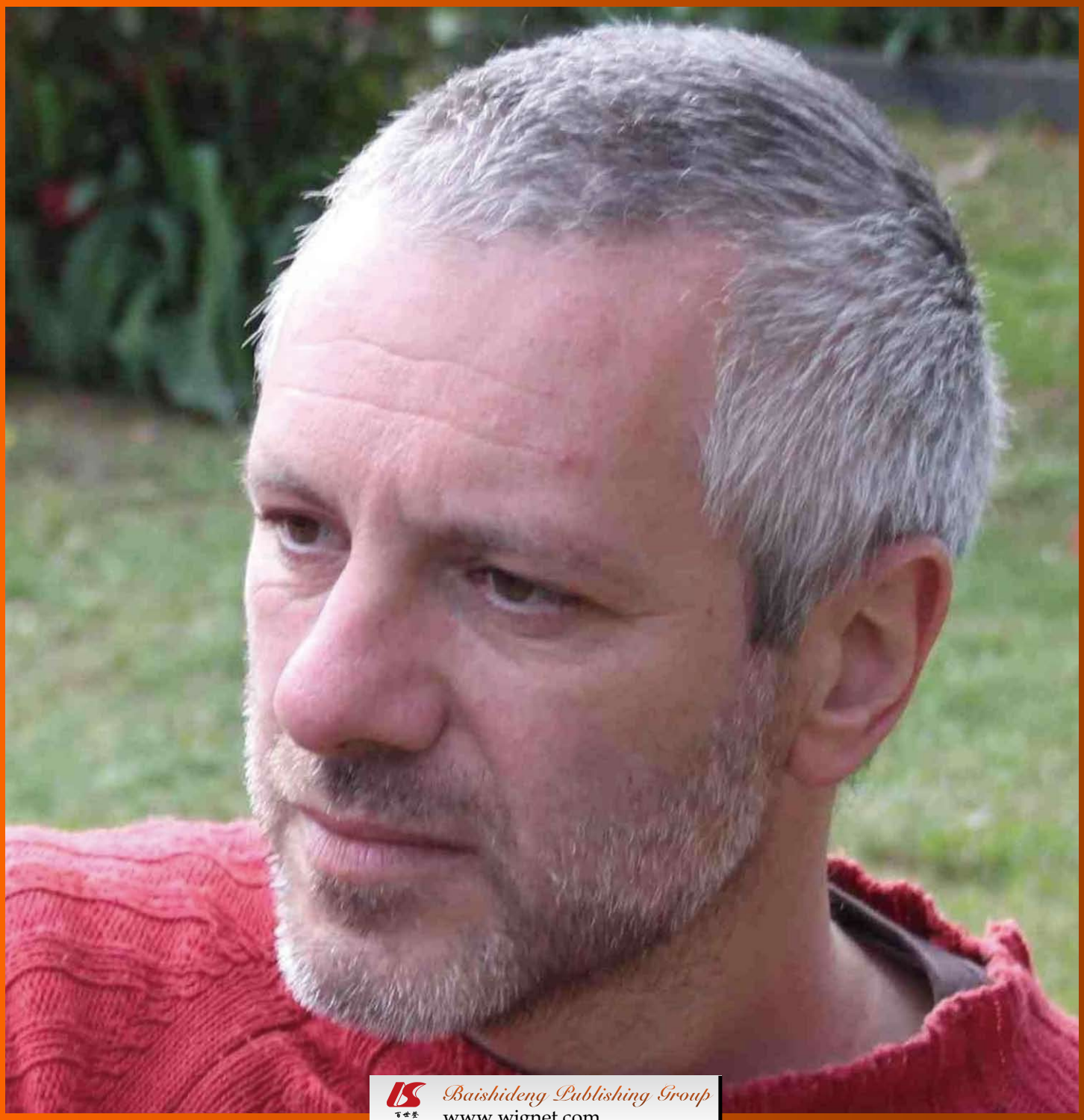

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FIELD OF VISION

Nuclear accumulation of β-catenin and forkhead box O3a in colon cancer: Dangerous liaison

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Abstract

The WNT/β-catenin and phosphoinositide 3-kinase (PI3K/AKT) signaling cascades both have been implicated in the formation and progression of colorectal cancer. Oncogenic PI3K/AKT signaling suppresses the activity of forkhead box O3a (FOXO3a) transcription factor through phosphorylation leading to its nuclear exclusion. Inhibition of the PI3K/AKT signaling by PI3K or AKT inhibitors results in the translocation of FOXO3a to the nucleus, and is considered to be a promising therapeutic strategy for many cancers including colon cancer. Now, however, a new study in *Nature Medicine* has revealed a nuclear interaction of β-catenin with FOXO3a as a promoter of metastatic progression in colon cancer. The work has important implications for the treatment of colon cancers, suggests a companion biomarker strategy to enable a personalized medicine approach, and offers an alternative therapeutic strategy to overcome resistance to PI3K and AKT inhibitors.

Key words: Colon cancer; β-catenin; Forkhead box O3a; Metastasis; Drug resistance; PI3k/AKT inhibitors; Tankyrase inhibitors; Personalized medicine; Xenopatient

Peer reviewer: Dr. Sung H Kim, Professor, Cancer Preventive Material Research Center, Kyunghee University, 1 Hoegidong Dongdaemungu, Seoul 130-701, South Korea

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INVITED COMMENTARY ON HOT ARTICLES

Colon cancer is a leading cause of cancer mortality in western countries[1]. Early detection allows the tumor to be removed by surgery which, along with the appropriate adjuvant chemotherapy, eliminates the disease in a high percentage of cases. However, despite recent progress in colon cancer screening and treatment, in the advanced stages, colon tumors are resistant to a broad spectrum of antitumor drugs, added to which the cancerous cells are capable of dispersing throughout the body, giving rise to metastasis. At present, there are no effective treatments for slowing down the progression of colon cancer in these late stages, and most patients die as a result of disease progression. In recent years new drugs have been designed that are targeted at blocking the activity of certain molecules responsible for promoting the growth and dissemination of tumor cells. Some of these drugs, which are currently in the clinical trial stage, are showing very good results in certain patients, while others show no improvement at all.

Now, a report in *Nature Medicine* has identified the molecular mechanisms that determine patients' response to certain drugs used in the treatment of colon cancer[2].

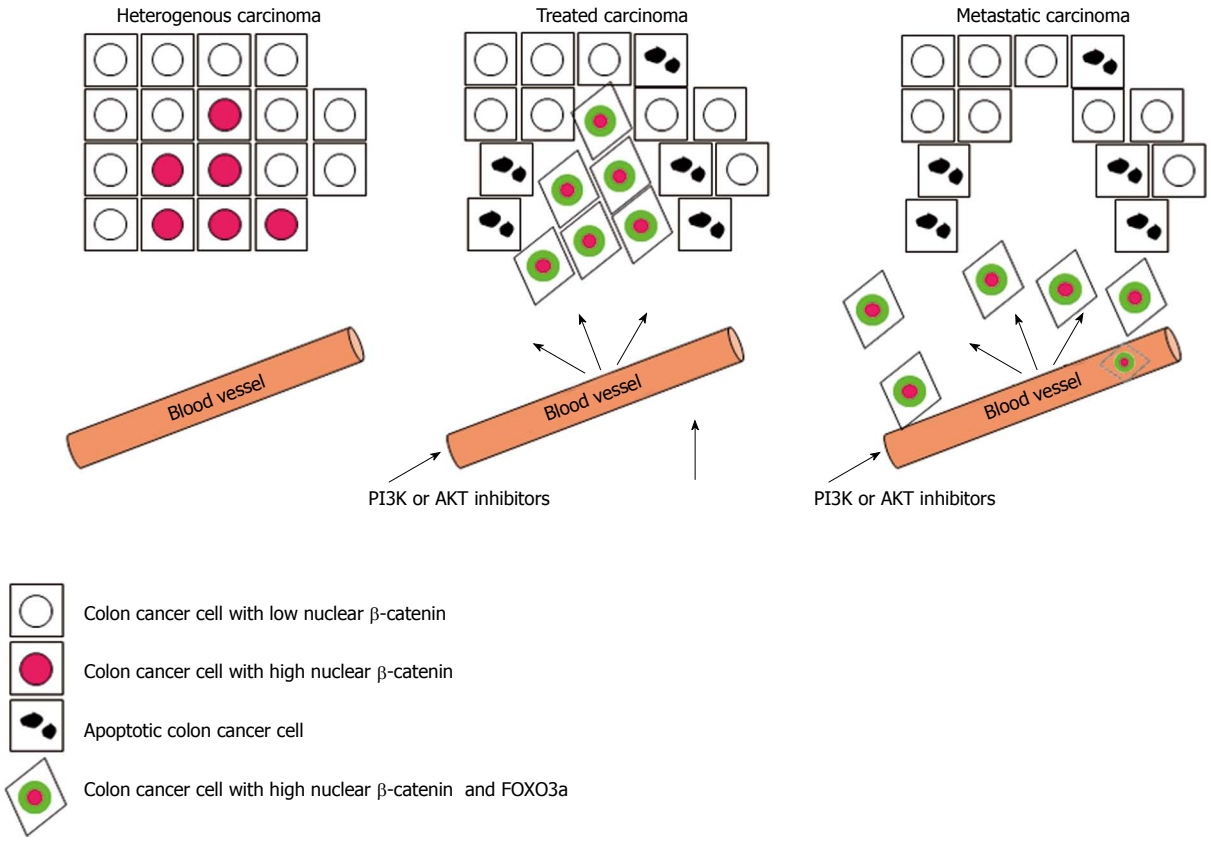

Figure 1 Nuclear accumulation of β-catenin and forkhead box O3a drives metastatic tumor progression in colon cancer. Human primary colon carcinoma cells are heterogeneous in terms of their nuclear level of β-catenin. Agents capable of inducing the nuclear translocation of forkhead box O3a (FOXO3a) transcription factor, for example, PI3K or AKT inhibitors promote apoptosis in those colon cancer cells with low nuclear β-catenin. Conversely, the cells with high level of β-catenin are resistant to those agents and specifically express metastasis-promoting genes induced by the nuclear β-catenin/FOXO3a complex. PI3K/AKT: Phosphoinositide 3-kinase.

The authors took a top-down approach based on their clinical observation that the coincidence of nuclear β-catenin and forkhead box O3a (FOXO3a) in samples from patients with colon cancer correlated with shorter survival time and metastasis stage (Figure 1). Most cases of colon cancer are initiated by nuclear accumulation of β-catenin protein due to its own mutation, or inactivation of the adenomatous polyposis coli (APC) tumor suppressor that controls the stability of the β-catenin protein[3-8]. β-catenin, the mammalian homolog of Drosophila Armadillo is a multifunctional oncogenic protein that is found at the plasma membrane of epithelial cells where it is implicated in the formation of adherens junctions[9-11]. β-catenin has been shown to be a key component of the Wnt signaling pathway[12]. β-catenin is phosphorylated by the glycogen synthase kinase 3β: adenomatous polyposis coli [glycogen synthase kinase (GSK)-3β:APC] complex leading to its ubiquitination and proteosome-mediated degradation. Upon binding of Wnt to its receptor, frizzled (Fz), disheveled (Dsh) is recruited to the membrane and inactivates GSK-3β. Thus, increased Wnt signaling results in diminished phosphorylation and reduced degradation of β-catenin. Stabilization and nuclear translocation of β-catenin allows its association with several transcriptional regulators such as T cell factor (TCF), lymphoid enhancer and transcription factors that promote the perpetual activation of Wnt target genes even in the absence of any extracellular signals. In addition, several alternative interaction partners of β-catenin have been reported including the androgen receptor[13], vitamin D receptor[14], the homeodomain factor Prop1[15] and FOXO transcription factors[16]. Many Wnt/β-catenin target genes have been shown to be involved in oncogenic growth and cellular transformation[17].

Conversely, members of the mammalian FOXO family of proteins have emerged as tumor suppressors[18,19]. FOXO factors are evolutionarily conserved proteins implicated in several fundamental cellular processes[18-20]. The mammalian members of FOXO subclass of forkhead transcription factors FOXO1, FOXO3A, FOXO4 and FOXO6 function as transcriptional regulators in the cell nucleus[21]. FOXO transcription factors bind as monomers to their consensus DNA binding sequence TTGTTTAC and activate or repress multiple genes such as Bim and FasL involved in apoptosis[22,23], p27kip[24] and cyclin D[25] in cell cycle regulation, GADD45a in DNA damage repair[22,23,26,27], manganese superoxide dismutase (MnSOD) in stress response[28], Foxp3 in T-cell regulation[29,30], atrogin 1 in skeletal muscle atrophy[31], and glycogenolytic gene glucose-6-phosphatase (G6pc) in metabolism[32]. Recent studies also reveal the importance of FOXOs in preserving the self-renewal capacity of

hematopoietic stem cells[33,34] and pluripotency of human embryonic stem cells[35]. FOXO factors can undergo AKT mediated phosphorylation, which promotes binding to 14-3-3, nuclear export through the export receptor CRM1 and cytoplasmic sequestration. Under stress conditions or in the absence of growth or survival factors, when the PI3K/AKT pathway is inhibited, FOXO proteins translocate to the cell nucleus, where their transcriptional functions can be executed. FOXO proteins are inactivated *via* cytoplasmic mislocalization by oncogenic signaling in a broad variety of human cancers including colon cancer[18]. Accordingly, reactivation of FOXO factors based on their tumor suppressor properties is considered as a very attractive anticancer strategy.

The current work by Tenbaum *et al*[2] however establishes FOXO3a as a Janus-faced protein that, dependent on the nuclear β-catenin status, can reduce cell proliferation *via* inducing apoptosis or cell cycle arrest, or promote cell scattering and metastasis[36]. The work provides physiological relevance to the previous observation that β-catenin can bind to FOXO proteins, thereby enhancing FOXO-dependent and inhibiting TCF transcriptional activity[16,37]. In this context, the present work provides some intriguing evidence. The authors have shown that FOXO3a and β-catenin co-regulate metastasis-relevant genes including genes that are involved in cytoskeleton remodeling and cell shape and motility. These findings raise the question whether the expression of metastatic genes is part of an intrinsic FOXO3a-driven transcriptional program that is over-ridden by the predominant expression of proapoptotic target genes in the absence of β-catenin, or whether β-catenin drives the recruitment of FOXO3a specifically to promoters of metastasis-relevant genes. The authors reveal IQGAP2 as a new target gene of the FOXO3a/β-catenin complex that is required for destabilizing E-cadherin-containing adherens junctions. Given that specific inhibition of the PI3K/AKT signaling pathway has become one of the most sought after goals of pharmaceutical applications, the implications of this work for targeted cancer therapy are extremely important. At least 16 class I PI3K and > 12 AKT inhibitors are in clinical development aimed at the inhibition of the PI3K/AKT signaling, thereby restoring nuclear localization of FOXO3a. Using patient-derived sphere cultures and xenograft models, the authors present striking evidence that the treatment of colon cancer cells harboring high level expression of nuclear β-catenin with the small molecule AKT inhibitor API-2 known to relocate FOXO3a to the nucleus promoted cell scattering *in vitro* and metastasis *in vivo*. Hence, therapeutic inhibition of PI3K/AKT signaling in colon cancer might have deleterious long-term effects because β-catenin renders the cells resistant to FOXO3a-mediated apoptosis and converts FOXO3a into a metastasis-promoting factor. This scenario clearly illustrates the need to select carefully a biomarker-defined population that will benefit from treatment with PI3K/AKT inhibitors, or to identify other therapeutic solutions for patients who will not respond well to the treatment and avoid the risk of administering ineffective drugs. In the context of a personalized medicine setting, patients with low nuclear β-catenin levels would probably best respond to therapeutic inhibition of oncogenic PI3K/AKT signaling. Most importantly, this study demonstrates that β-catenin is not only a predictive biomarker that correlates with the response to treatment with PI3K or AKT inhibitors, but is intimately involved in the molecular mechanism that renders colon cancer cells resistant to these agents. Accordingly, the study further reveals that tankyrase inhibition by the small molecule compound XAV-939, which increases degradation of β-catenin and reduces its nuclear concentration[38], sensitizes resistant cells specifically to PI3K and AKT inhibitors. Hence, the combined use of agents that target the Wnt signaling pathway together with PI3K or AKT inhibitors may be effective in colon cancer patients with high nuclear β-catenin and oncogenic PI3K/AKT signaling. XAV-939 has failed to be active *in vivo*, therefore, clinical proof-of-concept has to await the development of a new generation of tankyrase inhibitors with potent *in vivo* activity.

Given that FOXO3a has been shown to be the target of a broad variety of post-translational modifications that fine-tune its intracellular localization, it is not surprising that many different agents (tool compounds and approved drugs) capable of inducing the nuclear accumulation of FOXO3a have been reported. The growing list of FOXO3a regulators includes Ca^{2+}/calmodulin inhibitors, nuclear export inhibitors, MEK1/2 inhibitors, IKK inhibitors, and a diverse spectrum of anticancer drugs, such as paclitaxel, doxorubicin, lapatinib, gefitinib, imatinib and cisplatin[21,39-41]. According to the data presented by Tenbaum *et al*[2], those agents should be "red flagged" for the treatment of colon cancer and carefully assessed for their metastasis-promoting properties in the presence of high nuclear β-catenin concentrations. It remains to be established whether the spatial coincidence of the two proteins in the cell nucleus is sufficient to assemble the FOXO3a/β-catenin complex or whether this interaction is regulated by post-translational modifications that might be blocked pharmacologically. The results of the study by Tenbaum *et al*[2] are in accordance with the notion that the tumor suppressor functions of FOXO proteins are context dependent[42]. FOXO factors regulate a broad variety of cellular functions, some of which seemingly oppose their therapeutic activation or inhibition, which may lead to undesirable clinical outcomes. Therapeutic interference with FOXO functions might have both beneficial effects in one disease setting while having deleterious effects in another[43]. A fascinating aspect of this work is the use of a model system based on the sequential inoculation of patient-derived tumor cells that are capable of regenerating the disease with the same distinctive characteristics as in the individual patient, retaining its original genetic, clinical and pathological alterations. This "xenopatient" system might prove to be an excellent tool to predict individual response to experimental drugs before subjecting

the patient to new treatments. It might also be useful to pinpoint the specific molecular effectors that mediate the resistance to apoptosis and the metastatic phenotype triggered by the FOXO3a/β-catenin complex and thereby provide potential drug targets against metastatic progression of colon cancer. An exhaustive survey of clinical samples of patients with different cancers is required to establish a causal relationship between FOXO3a activation and metastasis for non-colon cancers. Future work might reveal that β-catenin is not the only binding partner capable of undermining the tumor suppressor functions of FOXO3a.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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