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E2F transcription factors and digestive system malignancies: How much do we know?

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Abstract

The E2F proteins comprise a family of 8 members that function as transcription factors. They are key targets of the retinoblastoma protein (RB) and were initially divided into groups of activators and repressors. Accumulating data suggest that there is no specific role for each individual E2F member. Instead, each E2F can exert a variety of cellular effects, some of which represent opposing ones. For instance, specific E2Fs can activate transcription and repression, promote or hamper cell proliferation, augment or inhibit apoptosis, all being dependent on the cellular context. This complexity reflects the importance that these transcription factors have on a cell's fate. Thus, delineating the specific role for each E2F member in specific malignancies, although not easy, is a challenging and continuously pursued task, especially in view of potential E2F targeted therapies. Therefore, several reviews are continuously trying to evaluate available data on E2F status in various malignancies. Such reviews have attempted to reach a consensus, often in the simplistic form of oncogenes or tumor suppressor genes for the E2Fs. However they frequently miss spatial and temporal alterations of these factors during tumor development, which should also be considered in conjunction with the status of the regulatory networks that these factors participate in. In the current "Letter to the Editor", we comment on the flaws, misinterpretations and omissions in one such review article published recently in the *World Journal of Gastroenterology* regarding the role of E2Fs in digestive system malignancies.

Key words: E2F; Hepatocellular carcinoma; Pancreatic ductal adenocarcinoma; Gastrointestinal tract; Digestive system; p53; p73; Cancer; Apoptosis; Proliferation

Core tip: The roles of the E2F transcription factors can vary significantly in malignancies of the digestive system, often dictating different outcomes in separate compartments of the gastrointestinal tract. Knowledge of the molecular status of the regulatory networks that E2Fs participate in is imperative to define their role. Therefore the use of proper molecular analysis to investigate these networks, complemented also by functional analysis in cellular and animal models, is essential. All in all, such an approach can define chronologically and provide a wider and more accurate view on the exact roles that E2Fs may exhibit in the development of specific digestive system malignancies.

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TO THE EDITOR

We read with great interest the review article of Xanthoulis and Tiniakos[1] commenting on the role of the

E2F family of transcription factors in the malignancies of the gastro-intestinal tract, published recently in the *World Journal of Gastroenterology*. With all due respect to the opinion of our colleagues, we would like to reply to the aforementioned article. We have found inaccuracies regarding a series of scientific information on data presented, as well as flaws in the interpretation of published experimental findings upon which the authors relied on to reach a consensus regarding the role(s) of these transcription factors in the various compartments of the digestive system.

Given that accuracy is important for the readers but also to provide a more in depth presentation on this subject, we would like to bring these issues to the attention of the *World Journal of Gastroenterology* audience. Specifically, regarding the detected inaccuracies, we would like to note the following issues: (1) Among the E2F members, the authors refer that only E2F3 and E2F7 exhibit different isoforms through alternative splicing. Notably, however, different isoforms for E2F6 have also been identified as a result of alternative splicing, leading to four distinct protein products[2]; and (2) the authors state that E2F1-3 members have nuclear localization signal (NLS) domains adjacent to their cyclin-A binding domains. Also, in Figure 1 of the article, the NLS domain of each E2F member is depicted at a 5' position relative to the cyclin-A binding domain. According to the originally published data[3-8], the cyclin-A binding domain is larger in all E2F1-3 members (aa 67-108 for E2F1), therefore incorporating the narrower NLS domain (aa 85-91 for E2F1) (see also URL: http://atlasgeneticsoncology.org/Genes/E2F1ID40382ch20q11.html). For certain E2F members, such as E2F3a/b, this positioning is asymmetric; the NLS is located exclusively in exon 2 while the cyclin-A binding domain covers a wider area that comprises the majority of exon 1 and part of exon 2 of the gene[5,7]. Therefore, Figure 1 is inaccurate and it seems that the authors perpetuated previous misleading information from other reviews, and quoted such in their article, without consulting the originally published research data.

More important is the approach on the interpretation given by the authors on the role of the E2F members in the various digestive tract malignancies. An increasing body of evidence clearly indicates that the E2Fs can act in a bimodal fashion during cancer development, sometimes even within the same type of tumor[9-11]. This behavior is often dictated by the status of vital cell cycle regulators, like pRb, p53, $p16^{INK4A}$ and others, with many of which the E2F factors create intricate loops[8,10-13]. Yet, the authors have not provided adequate molecular explanations or insights, especially for apparent contradictory results, in certain parts of the digestive system. The most prominent ones concern the role of E2F1 in pancreatic cancer and hepatocellular carcinoma (HCC), which we would like to present.

In the pancreatic cancer section, it is mentioned that Yamazaki *et al*[14] found an inverse relationship between E2F1 immunopositivity and histological grade and disease-associated survival (ref 119 in manuscript). This is inaccurate as Yamazaki *et al*[14] clearly demonstrate a direct statistical relationship in their report. In addition, the data from only this study seems to be sufficient to infer a tumor-promoting role for E2F1 in pancreatic ductal adenocarcinoma (PDAC) (as mentioned also in Table 1 of Xanthoulis and Tiniakos[1]). Nevertheless, a series of reports in the review of Xanthoulis and Tiniakos clearly show that E2F1 exhibits a pro-apoptotic activity in pancreatic cancer cell lines and contributes to chemosensitivity (Ref. 120-122, according to the in-text citation)[15-17]. This conclusion is generalized and contradicts the deductions made by authors in refs 120[15] and 122[17]. In the first reference, the analysis of human tumors has demonstrated the causative relation between pRb overexpression and PDAC development, while the *in vitro* studies indicate that high E2F1 expression due to loss of pRB increases chemotherapy induced apoptosis-sensitivity. It should also be noted that Yamazaki *et al*[14] did not perform E2F1-Ki67 immunohistochemical (IHC) analysis at single cell level in serial sections or double IHC analysis within the same section. Furthermore, the authors have not examined the pRB status along with total E2F1 expression levels. Therefore, the issue whether E2F1 possesses tumor promoting activity in vivo is still debatable in pancreatic cancer. The second reference proposes that there is an E2F1/p73-dependent pathway halting the initiation of PDAC tumorigenesis, which can be therapeutically exploited[17]. Although the study by Rödicker *et al*[17] has been cited, the arguments of the aforementioned publication are not discussed at all. Additionally, as presented in ref 43 of Xanthoulis and Tiniakos, in E2F1/$E2F2^{-/-}$ animal models, S-phase entry is not properly regulated leading to endoreduplication and thus polyploidy in the exocrine pancreas, suggesting a rather tumor-suppressive effect for these members[18]. Finally, publications quoted in the elegant review article by Chen *et al*[10] (ref 17 of Xanthoulis and Tiniakos) report on the frequent loss of the 1p36 chromosomal region encompassing the E2F2 locus, data which further pinpoints to potential anti-tumor effects of E2F1/E2F2 in this tumor type.

Regarding the HCC, there is a series of previous studies providing evidence of an oncogenic role of E2F1 in HCC (ref. 109-112 according to the in-text citation)[19-22]. However only one cited self-published work (ref 108 in the manuscript)[23] providing some hints for a pro-apoptotic role of E2F1, is judged to be sufficient to infer a putative oncosuppressive role of E2F1 in HCC. This is a rather unsafe generalization which has also been quoted in the "Abstract". This generalization stems from the misinterpretation of raw *in situ* analysis data which need to be supplemented by more conclusive evidence from cell systems and mechanistic details regarding E2F1-induced apoptosis, as those comprehensively provided by Rödicker *et al*[17]. As E2F1 is known to stimulate the expression of anti-apoptotic genes such as PEG10 (ref.

111 in the manuscript)[21] and it is well-established that the control of apoptotic networks is a key determinant for E2F1's role with regard to tumorigenesis[12], the conclusion in favour of a tumor-suppressive role of E2F1 in HCC merits further investigation in order to be unequivocally supported.

For instance, Wang *et al*[21] found that in clinical specimens there is a correlation among elevated expression of E2F1 and PEG10 and this is functionally associated with the repression of apoptosis. In addition, they reported that in hepatocellular carcinoma cells BEL-7404, PEG10 inhibits apoptosis *via* up-regulating the antiapoptotic molecule BCL-X_L. On the other hand, it has been reported that E2F1 can trigger apoptotic cell death *via* engaging both p53 family-dependent and p53 family-independent pathways[24], or even the DDR (DNA damage response) pathways such as ATM/NBS1/Chk2-[25] or even ATM/p73-dependent routes[9]. Conceivably, the immunohistochemical experiments in ref. 108[23] - which is considered as a nodal publication by the authors allowing them to reach their conclusions - could benefit if accompanied by a more scrutinous IHC examination of E2F1 in relation to different molecules, which mediate the regulation that E2F1 exerts over apoptosis such as PEG10, BCL-X_L, p-T68 Chk2 (a marker of activated Chk2) or p73. Moreover, the use of different human HCC cell lines, with different molecular backgrounds (*e.g.,* BEL-7404, BEL-7402 or SMMC-7721) for investigating whether pro-apoptotic pathways are indeed operative, while anti-apoptotic pathways are shut-off, through employment of functional analyses could further clarify this issue.

Finally, Xanthoulis and Tiniakos omitted the work of Jiang *et al*[26] who demonstrated that up-regulation of E2F5 has a potential role in HCC.

In the paragraph "CONCLUSIONS AND PERSPECTIVES" the conclusion that the opposing roles of E2Fs in oncogenesis are explained by its tissue-specific activities, constitutes a rather self-negation with what authors have formerly stated. Specifically, as referred by the cited studies, E2F1 behaves in a bimodal fashion in HCC, exhibiting both a tumor-promoting (ref. 109-112 according to the in-text citation)[19-22] and a tumor-suppressive role (Ref. 108 in the manuscript)[23]. Nevertheless, Xanthoulis and Tiniakos suggest a putative oncosuppressive role of E2F1 in HCC, but in the concluding remarks they support the opposing roles that E2Fs exerts in tissues. To explain the dual function of E2F1 in oncogenesis, more attention should have been paid to the findings reported in various analyses that include cell lines and animal models, always taking into consideration the status of vital cell regulators. Furthermore, for the interpretation of E2F1's pro-apoptotic activity, there is an inadequate discussion of the previously reported, well-confirmed more than one signaling pathways which E2F1 can engage to trigger apoptosis[9,24,25].

But how is the observed duality in E2F1's behavior towards cancer biology explained? And how does a putative explanation apply in the case of gastrointestinal cancer? In another review on E2F1 by Engelmann and Pützer[12], preceding that of Xanthoulis *et al*[1], an elegant model is proposed whereby upon the concomitant ectopic expression of E2F1 and loss of functional pRb the tumor-suppressive, pro-apoptotic p53/p73-dependent duties of E2F1 can be switched to tumor-promoting activities depending on the integrity of cell death signaling networks. Consequently, in the cells where proapoptotic signals outweigh the prosurvival ones, E2F1 carries out its oncosuppressive task, therefore promoting their apoptotic elimination. On the contrary, when the apoptotic machinery harbors defects, deregulated pRb/E2F1 signaling induces cancer progression. This is achieved *via* a self-sustained circuit where E2F1 upregulates the expression of its own co-factors which are required to stimulate the transcription of oncogenic *E2F1* gene targets. In this way, the proapoptotic *vs* prosurvival balance is the key determinant of configuring E2F1's oncosuppressive or oncogenic behavior. Interestingly though, this model seems to apply in the case of PDAC and HCC where E2F1 exerts seemingly opposing effects.

In PDACs, with aberrant pRb/E2F1 pathway status[27,28] and mutant p53[29], E2F1 has been reported to engage a p53-independent, p73-dependent apoptotic pathway to oppose tumorigenesis[17]. Hence, it rather seems that in this case, the E2F1/p73-dependent pathway operates as a failsafe antitumor route with p53 being dispensible for the induction of apoptosis.

In HCC, where E2F1 is commonly overexpressed[30] and the INK4A/pRb pathway is deregulated[30,31], due to aberrant methylation of $p16^{INK4A}$ gene, E2F1 is not likely to employ an apoptotic route given that the ARF/p53 axis is disrupted because of either mutational inactivation of p53 or epigenetic silencing (promoter methylation) at INK4A-ARF locus[31]. In addition, in HCC p53 is frequently inactivated by mutagens such as AFB_1 or alternatively, p53 functions can be attenuated by viral HBx proteins[32]. P73 does not seem to compensate for the loss of p53 functions, since *TP73* is aberrantly targeted by LOH in an appreciable number of HCC cases[33]. Moreover, there is evidence that in HCC, E2F1 prevents Myc-induced apoptosis[34], while the anti-apoptotic protein Bcl-xL is found to be overexpressed in the majority of HCC clinical samples and is associated with poor overall and disease-free survival[35]. Collectively, the data suggests that in HCC, E2F1 cannot fulfil its pro-apoptotic, tumor-suppressive tasks due to the fact that both the p53- and the p73-pathways have been compromised. Rather, it seems that it functions to impede apoptosis, at least the Myc-driven one. Hence, E2F1- and Bcl-xL-dependent prosurvival signals, either alone or in synergy, seem to surmount the antitumor barrier of apoptosis and to fuel cancer progression. Therefore, we would suggest caution on deducing the role of E2F1 in PDAC and HCC, as presented in Table 1, by Xanthoulis and Tiniakos[1].

In conclusion, it is clear that the roles of E2Fs can significantly vary, depending on the specific cellular envi-

ronment. As they participate in crucial cell-fate regulatory networks, E2Fs appear to be able to modulate seemingly contradictory outcomes, including cellular proliferation and apoptosis. Elucidation of these relations provides vital information, as the E2F status is often associated with tumor kinetics and clinical evolution. In view of the new drugs designed to target E2F activity, the study of E2F function in cancer and its expression in various histologic subtypes could prove to be beneficial.

REFERENCES

1 **Xanthoulis A**, Tiniakos DG. E2F transcription factors and digestive system malignancies: how much do we know? *World J Gastroenterol* 2013; **19**: 3189-3198 [PMID: 23745020 DOI: 10.3748/wjg.v19.i21.3189]

2 **Kherrouche Z**, De Launoit Y, Monté D. Human E2F6 is alternatively spliced to generate multiple protein isoforms. *Biochem Biophys Res Commun* 2004; **317**: 749-760 [PMID: 15081404 DOI: 10.1016/j.bbrc.2004.03.099]

3 **Müller H**, Moroni MC, Vigo E, Petersen BO, Bartek J, Helin K. Induction of S-phase entry by E2F transcription factors depends on their nuclear localization. *Mol Cell Biol* 1997; **17**: 5508-5520 [PMID: 9271426]

4 **Verona R**, Moberg K, Estes S, Starz M, Vernon JP, Lees JA. E2F activity is regulated by cell cycle-dependent changes in subcellular localization. *Mol Cell Biol* 1997; **17**: 7268-7282 [PMID: 9372959]

5 **Leone G**, Nuckolls F, Ishida S, Adams M, Sears R, Jakoi L, Miron A, Nevins JR. Identification of a novel E2F3 product suggests a mechanism for determining specificity of repression by Rb proteins. *Mol Cell Biol* 2000; **20**: 3626-3632 [PMID: 10779352 DOI: 10.1128/MCB.20.10.3626-3632.2000]

6 **Adams MR**, Sears R, Nuckolls F, Leone G, Nevins JR. Complex transcriptional regulatory mechanisms control expression of the E2F3 locus. *Mol Cell Biol* 2000; **20**: 3633-3639 [PMID: 10779353 DOI: 10.1128/MCB.20.10.3633-3639.2000]

7 **He Y**, Cress WD. E2F-3B is a physiological target of cyclin A. *J Biol Chem* 2002; **277**: 23493-23499 [PMID: 11980909 DOI: 10.1074/jbc.M202629200]

8 **Tsantoulis PK**, Gorgoulis VG. Involvement of E2F transcription factor family in cancer. *Eur J Cancer* 2005; **41**: 2403-2414 [PMID: 16213134 DOI: 10.1016/j.ejca.2005.08.005]

9 **Liontos M**, Niforou K, Velimezi G, Vougas K, Evangelou K, Apostolopoulou K, Vrtel R, Damalas A, Kontovazenitis P, Kotsinas A, Zoumpourlis V, Tsangaris GT, Kittas C, Ginsberg D, Halazonetis TD, Bartek J, Gorgoulis VG. Modulation of the E2F1-driven cancer cell fate by the DNA damage response machinery and potential novel E2F1 targets in osteosarcomas. *Am J Pathol* 2009; **175**: 376-391 [PMID: 19541929 DOI: 10.2353/ajpath.2009.081160]

10 **Chen HZ**, Tsai SY, Leone G. Emerging roles of E2Fs in cancer: an exit from cell cycle control. *Nat Rev Cancer* 2009; **9**: 785-797 [PMID: 19851314 DOI: 10.1038/nrc2696]

11 **Conner EA**, Lemmer ER, Omori M, Wirth PJ, Factor VM, Thorgeirsson SS. Dual functions of E2F-1 in a transgenic mouse model of liver carcinogenesis. *Oncogene* 2000; **19**: 5054-5062 [PMID: 11042693 DOI: 10.1038/sj.onc.1203885]

12 **Engelmann D**, Pützer BM. The dark side of E2F1: in transit beyond apoptosis. *Cancer Res* 2012; **72**: 571-575 [PMID: 22298593 DOI: 10.1158/0008-5472.CAN-11-2575]

13 **Olson MV**, Johnson DG, Jiang H, Xu J, Alonso MM, Aldape KD, Fuller GN, Bekele BN, Yung WK, Gomez-Manzano C, Fueyo J. Transgenic E2F1 expression in the mouse brain induces a human-like bimodal pattern of tumors. *Cancer Res* 2007; **67**: 4005-4009 [PMID: 17483310 DOI: 10.1158/0008-5472.CAN-06-2973]

14 **Yamazaki K**, Yajima T, Nagao T, Shinkawa H, Kondo F, Hanami K, Asoh A, Sugano I, Ishida Y. Expression of transcription factor E2F-1 in pancreatic ductal carcinoma: an immunohistochemical study. *Pathol Res Pract* 2003; **199**: 23-28 [PMID: 12650514 DOI: 10.1078/0344-0338-00348]

15 **Plath T**, Peters M, Detjen K, Welzel M, von Marschall Z, Radke C, Wiedenmann B, Rosewicz S. Overexpression of pRB in human pancreatic carcinoma cells: function in chemotherapy-induced apoptosis. *J Natl Cancer Inst* 2002; **94**: 129-142 [PMID: 11792751 DOI: 10.1093/jnci/94.2.129]

16 **Elliott MJ**, Farmer MR, Atienza C, Stilwell A, Dong YB, Yang HL, Wong SL, McMasters KM. E2F-1 gene therapy induces apoptosis and increases chemosensitivity in human pancreatic carcinoma cells. *Tumour Biol* 2002; **23**: 76-86 [PMID: 12065845 DOI: 10.1159/000059708]

17 **Rödicker F**, Stiewe T, Zimmermann S, Pützer BM. Therapeutic efficacy of E2F1 in pancreatic cancer correlates with TP73 induction. *Cancer Res* 2001; **61**: 7052-7055 [PMID: 11585734]

18 **DeGregori J**, Johnson DG. Distinct and Overlapping Roles for E2F Family Members in Transcription, Proliferation and Apoptosis. *Curr Mol Med* 2006; **6**: 739-748 [PMID: 17100600]

19 **Chen YL**, Uen YH, Li CF, Horng KC, Chen LR, Wu WR, Tseng HY, Huang HY, Wu LC, Shiue YL. The E2F transcription factor 1 transactives stathmin 1 in hepatocellular carcinoma. *Ann Surg Oncol* 2013; **20**: 4041-4054 [PMID: 22911364 DOI: 10.1245/s10434-012-2519-8]

20 **Simile MM**, De Miglio MR, Muroni MR, Frau M, Asara G, Serra S, Muntoni MD, Seddaiu MA, Daino L, Feo F, Pascale RM. Down-regulation of c-myc and Cyclin D1 genes by antisense oligodeoxy nucleotides inhibits the expression of E2F1 and in vitro growth of HepG2 and Morris 5123 liver cancer cells. *Carcinogenesis* 2004; **25**: 333-341 [PMID: 14604889 DOI: 10.1093/carcin/bgh014]

21 **Wang C**, Xiao Y, Hu Z, Chen Y, Liu N, Hu G. PEG10 directly regulated by E2Fs might have a role in the development of hepatocellular carcinoma. *FEBS Lett* 2008; **582**: 2793-2798 [PMID: 18625225 DOI: 10.1016/j.febslet.2008.07.009]

22 **Pascale RM**, Simile MM, De Miglio MR, Muroni MR, Calvisi DF, Asara G, Casabona D, Frau M, Seddaiu MA, Feo F. Cell cycle deregulation in liver lesions of rats with and without genetic predisposition to hepatocarcinogenesis. *Hepatology* 2002; **35**: 1341-1350 [PMID: 12029619 DOI: 10.1053/jhep.2002.33682]

23 **Palaiologou M**, Koskinas J, Karanikolas M, Fatourou E, Tiniakos DG. E2F-1 is overexpressed and pro-apoptotic in human hepatocellular carcinoma. *Virchows Arch* 2012; **460**: 439-446 [PMID: 22450712 DOI: 10.1007/s00428-012-1220-4]

24 **Croxton R**, Ma Y, Song L, Haura EB, Cress WD. Direct repression of the Mcl-1 promoter by E2F1. *Oncogene* 2002; **21**: 1359-1369 [PMID: 11857079 DOI: 10.1038/sj.onc.1205157]

25 **Powers JT**, Hong S, Mayhew CN, Rogers PM, Knudsen ES, Johnson DG. E2F1 uses the ATM signaling pathway to induce p53 and Chk2 phosphorylation and apoptosis. *Mol Cancer Res* 2004; **2**: 203-214 [PMID: 15140942]

26 **Jiang Y**, Yim SH, Xu HD, Jung SH, Yang SY, Hu HJ, Jung CK, Chung YJ. A potential oncogenic role of the commonly observed E2F5 overexpression in hepatocellular carcinoma. *World J Gastroenterol* 2011; **17**: 470-477 [PMID: 21274376 DOI: 10.3748/wjg.v17.i4.470]

27 **Schutte M**, Hruban RH, Geradts J, Maynard R, Hilgers W, Rabindran SK, Moskaluk CA, Hahn SA, Schwarte-Waldhoff I, Schmiegel W, Baylin SB, Kern SE, Herman JG. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. *Cancer Res* 1997; **57**: 3126-3130 [PMID: 9242437]

28 **Rozenblum E**, Schutte M, Goggins M, Hahn SA, Panzer S, Zahurak M, Goodman SN, Sohn TA, Hruban RH, Yeo CJ, Kern SE. Tumor-suppressive pathways in pancreatic carcinoma. *Cancer Res* 1997; **57**: 1731-1734 [PMID: 9135016]

29 **Morton JP**, Timpson P, Karim SA, Ridgway RA, Athineos

D, Doyle B, Jamieson NB, Oien KA, Lowy AM, Brunton VG, Frame MC, Evans TR, Sansom OJ. Mutant p53 drives metastasis and overcomes growth arrest/senescence in pancreatic cancer. *Proc Natl Acad Sci USA* 2010; **107**: 246-251 [PMID: 20018721 DOI: 10.1073/pnas.0908428107]

30 **Huynh H**, Do PT, Nguyen TH, Chow P, Tan PH, Quach TH, Van T, Soo KC, Tran E. Extracellular signal-regulated kinase induces cyclin D1 and Cdk-2 expression and phosphorylation of retinoblastoma in hepatocellular carcinoma. *Int J Oncol* 2004; **25**: 1839-1847 [PMID: 15547725]

31 **Tannapfel A**, Busse C, Weinans L, Benicke M, Katalinic A, Geissler F, Hauss J, Wittekind C. INK4a-ARF alterations and p53 mutations in hepatocellular carcinomas. *Oncogene* 2001; **20**: 7104-7109 [PMID: 11704835 DOI: 10.1038/sj.onc.1204902]

32 **Hussain SP**, Schwank J, Staib F, Wang XW, Harris CC. TP53 mutations and hepatocellular carcinoma: insights into the etiology and pathogenesis of liver cancer. *Oncogene* 2007; **26**: 2166-2176 [PMID: 17401425 DOI: 10.1038/sj.onc.1210279]

33 **Mihara M**, Nimura Y, Ichimiya S, Sakiyama S, Kajikawa S, Adachi W, Amano J, Nakagawara A. Absence of mutation of the p73 gene localized at chromosome 1p36.3 in hepatocellular carcinoma. *Br J Cancer* 1999; **79**: 164-167 [PMID: 10408709 DOI: 10.1038/sj.bjc.6690027]

34 **Ladu S**, Calvisi DF, Conner EA, Farina M, Factor VM, Thorgeirsson SS. E2F1 inhibits c-Myc-driven apoptosis via PIK-3CA/Akt/mTOR and COX-2 in a mouse model of human liver cancer. *Gastroenterology* 2008; **135**: 1322-1332 [PMID: 18722373 DOI: 10.1053/j.gastro.2008.07.012]

35 **Watanabe J**, Kushihata F, Honda K, Sugita A, Tateishi N, Mominoki K, Matsuda S, Kobayashi N. Prognostic significance of Bcl-xL in human hepatocellular carcinoma. *Surgery* 2004; **135**: 604-612 [PMID: 15179366 DOI: 10.1016/j.surg.2003.11.015]

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