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RE: HABP2 G534E Mutation in Familial Nonmedullary Thyroid Cancer

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In a recent report, Zhang et al. (1) investigated families affected by nonmedullary thyroid cancer (FNMTC) and detected G534E mutations in the Hyaluronan-Binding Protein 2 (HABP2) in 13.8% of the kindreds. None of the normal subjects or patients with benign thyroid neoplasms were found to carry the G534E mutation. Germline *HABP2* mutations were previously identified in hereditary FNMTC (2). Such HABP2 polymorphism was indicated to cause loss of function and higher transforming capacity. These studies were met with criticism as HABP2 G534E prevalence in control populations was found to be close to that in affected individuals. Moreover, frequency variation across human populations (cancergenome.nih.gov) appeared just as large as that across experimental subgroups (1,2). It should also be pointed out that even in kindreds where *HABP2* G534E appeared associated to FNMTC (1,2) only a fraction of patients carried the mutation. Taken together, these findings indicated that factors other than the *HABP2* G534E mutation played a role in FNMTC.

We argue that the impact of *HABP2* on cancer does not depend on protein sequence mutations.

Disregulation of expression of *HABP2*, ie, downregulation or upregulation vs normal tissue levels, is associated with several cancer histotypes (www.proteinatlas.org/ENSG00000148702-HABP2/cancer) (Figure 1). Both deletion and amplification of the *HABP2* gene were found in pancreatic cancer (3). Next-generation transcriptome sequencing defined a core set of 12 cellular signaling pathways, which were altered in 67% to 100% of the tumors. Convergent evidence indicated highest impact of HABP2 on PI3K-driven networks (3). HABP2 was downregulated by miRNA in colon cancer. Similar findings were obtained in non–small cell lung cancer (4). Either up or downregulation in cancer vs normal tissues is found in breast, endometrium, ovary, pancreas, testis, and thyroid (Figure 1). The Cancer Genome Atlas investigators found a three-fold lower expression of HABP2 in gliomas (cancergenome.nih.gov). High levels of HABP2 are most frequently observed in ovarian, prostate, gastric, and pancreatic cancer (Figure 1).

Wild-type *HABP2* expression in cancer is altered through multiple distinct mechanisms. *HABP2* mRNA levels were found divergently regulated vs corresponding protein levels (Figure 1, left), suggesting post-transcriptional and post-translational regulation. HABP2 transcripts were shown to take part to mRNA chimeras in tumors (5). Most such chimeras possess transforming activity (6,7). mRNA chimeras cause altered mRNA stability and protein translation capacity. This is key to acquisition of transforming ability and is not related to oncogene-like protein mutations (6). Further, *HABP2* was found to be epigenetically disregulated by H3K27Me3 and H3K4Me3 (cancergenome.nih.gov). Mutations in HABP2 intron 7 were then found in breast cancer (cancergenome.nih.gov), consistent with a transformation ability beyond protein coding sequence mutations. Notably, the very same protein codon mutations can lead to reduced mRNA half-life ([6] and references therein).

In summary, disregulation of *HABP2* expression is heavily associated with cancer whereas the *HABP2* G534E mutation is not. We argue that investigation of the functional impact of *HABP2* disregulation in cancer and of the control mechanisms identified above may provide key insights on the role of *HABP2* in FNMTC and in other solid tumors.

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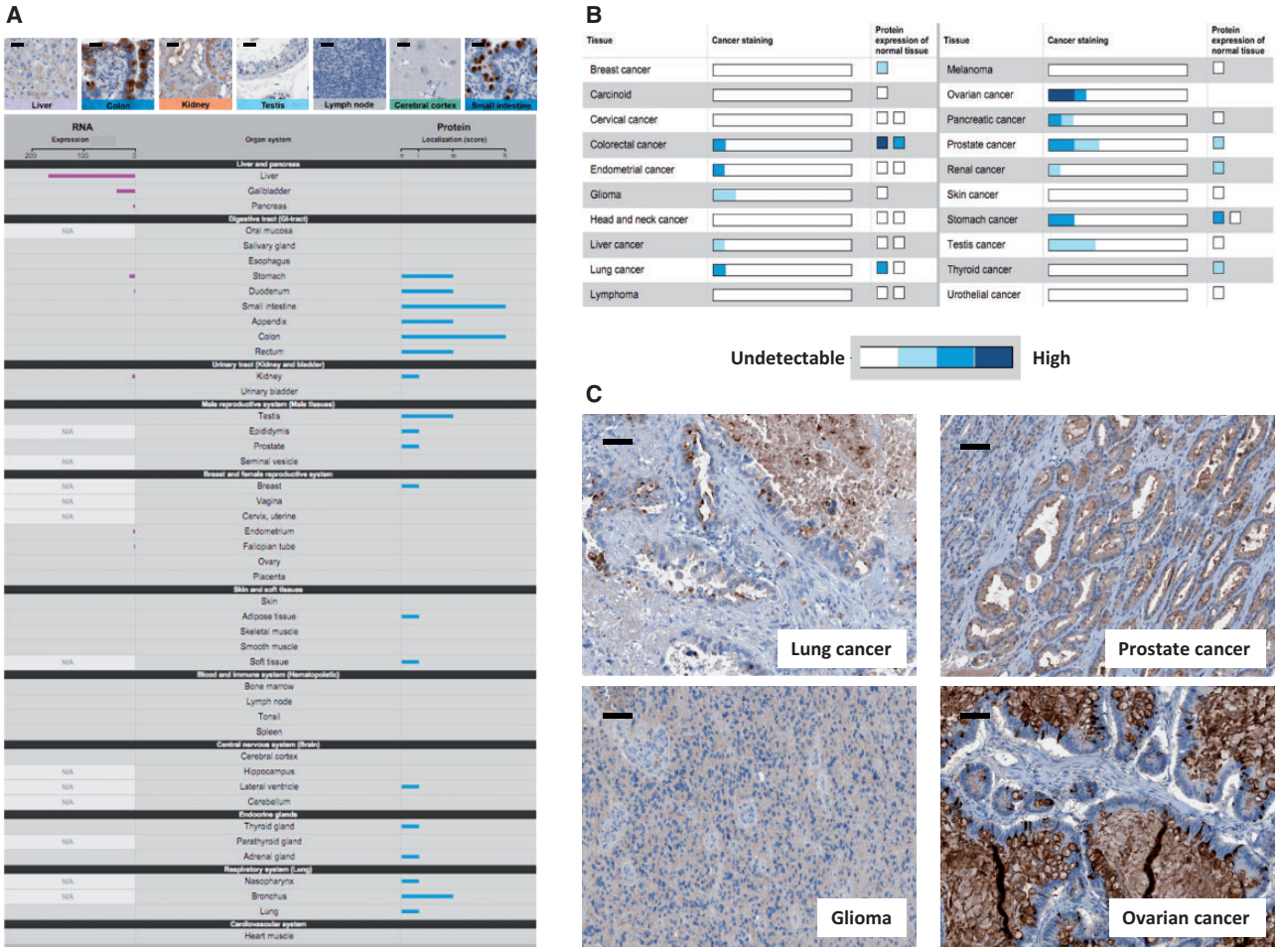

Figure 1. HAPB2 expression in normal and transformed tissues (www.proteinatlas.org/ENSG00000148702-HABP2/cancer). **A)** Expression in normal tissues at the mRNA (**left, ~~red~~ bars**) and protein levels (**right, ~~blue~~ bars**). Bars: 15 μm. **B)** Comparative levels of expression of the HABP2 protein in normal organs and corresponding cancers. Expression levels were color-coded as indicated. **C)** HABP2 protein expression in lung, prostate, brain, and ovary tumors, as detected by immunohistochemistry (www.proteinatlas.org/ENSG00000148702-HABP2/antibody). Bars: 30 μm.

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Notes

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