Editorial

BIRC3 as a yet underestimated prognostic marker of malignancies?

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Working in the field of human genetics since >20 years the announcement and publication of a discovery of a new candidate gene for a specific genetic disorder is not that unusual to me. In contrary, even though the whole exome of human was announced to be sequenced in 2001 already (1), candidate genes for inborn as well as acquired diseases were not becoming less since that time (*Figure 1*). Knowing the field, this is not surprising. Even though human genome project (HUGO) told us where genes may be located within the 46 human chromosomes, HUGO per se was never able to tell us what the function of all these genes is. To find out about this, studies in patients are necessary to identify which genes are impaired in connection with which disorder or disease; and such studies need to be followed or accompanied by functional studies.

The study of Gressot and coworkers published in the present issue of *Oncotarget* (2) is a good example for this kind of so-called 'post-genomic' research. Using a combination of clinical studies, database analyses, meta-analyses and functional studies they could nicely provide evidence that *Baculoviral IAP Repeat Containing 3* gene (*BIRC3*, also earlier denominated as apoptosis inhibitory protein *IAP2*) seems to play a crucial role in malignant transformation of low grade gliomas to glioblastoma, as also recently found by others (3). Besides it seems to be new prognostic marker of glioblastoma.

As Gressot and coworkers (2) also mentioned, *BIRC3* being a negative regulator of the non-canonical NF-κB protein, has yet been shown to play a role also in other malignancies, too.

It was known already since 2012 that *BIRC3* disruption can be observed in fludarabine refractory chronic lymphocytic leukemia (4), and just recently we could show that it is also involved either as deletion or duplication event in a subset of acute lymphocytic leukemia patients (5); *BIRC3* is a translocation partner in MALT lymphoma (6); altered expression of *BIRC3* was recently seen in breast (7,8) as well as pancreatic cancer (9); *BIRC3* amplification and or upregulation of its expression were observed in gastrointestinal stromal tumors (10), and bladder cancer (cell lines) (11); involvement of *BIRC3* is suggested in melanoma (12), colorectal cancer (13,14) and nasopharyngeal carcinoma (15); interestingly, a predictive value of *BIRC3* has been postulated in oesophageal adenocarcinoma patients, as well (16).

Besides, *BIRC3* also is suspected to play a role in childhood asthma (17), in human herpesvirus 6 (HHV-6) infection and associated neurologic diseases (18), as well as in age-related macular degeneration (19).

In conclusion the study of Gressot and coworkers (2) is one more puzzle stone which highlights the importance of *BIRC3* in tumor development and progression. Still, it remains surprising that *BIRC3* alterations were recognized already in 2004 e.g., in neuroblastoma (20), but most studies involving this gene came out just lately (*Figure 2*). It seems *BIRC3* somehow escaped from the focus of research attention until recently. Overall, it remains true what Yamato *et al.* stated in 2015 (21) for *BIRC3*: "*BIRC3 mutations are present in a wide range of epithelial tumors and most nonsense or frameshift mutations confer direct transforming potential.*" Besides, amplification and deletions were observed recently. "*This oncogenic function of BIRC3 mutants is largely independent of their ability to activate NF-κB signaling. In addition to the BIRC3-NIK-*

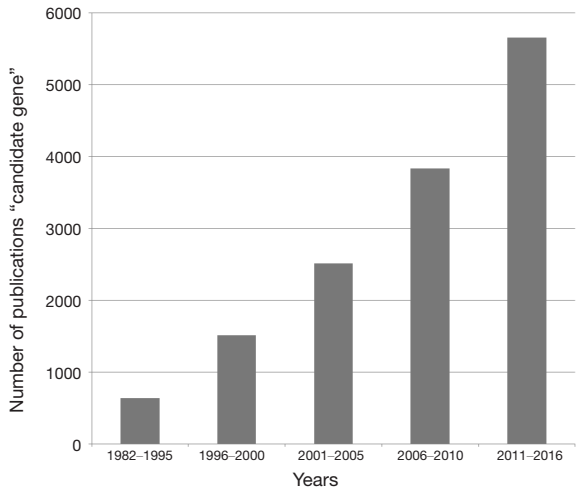

Figure 1 Number of publications containing the words "candidate gene" between 1982 and August 2016. Acc. to http://www.ncbi.nlm.nih.gov/pubmed

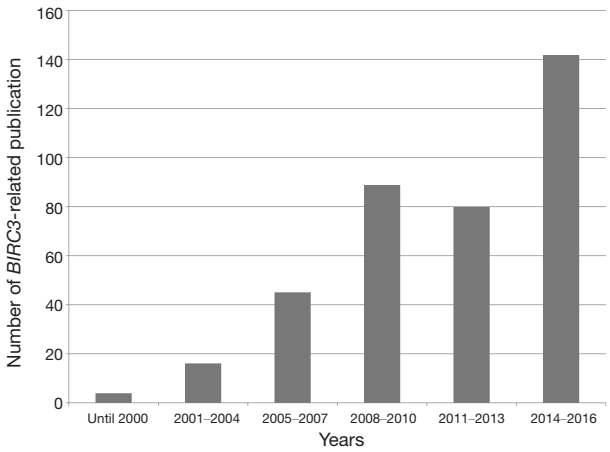

Figure 2 Number of *BIRC3* related publications between 1997 and August 2016. Acc. to http://www.ncbi.nlm.nih.gov/pubmed

NF-κB signaling pathway, BIRC3-NIK signaling targets effectors other than NF-κB and thereby contributes directly to carcinogenesis. Identification (and further characterization) of these effectors may provide a basis *for the development of targeted agents for the treatment of lymphoid malignancies and other cancers with BIRC3 alterations.*" Finally, for practical patient care, the potential of *BIRC3* as a prognostic marker should be delineated for more detail in near future.

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Footnote

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