Editorial

Asb genes in vertebrates and its function in gastrointestinal cancer

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One of the most important and defining processes during development is the pattern formation of the various compartments in embryos; cancer represents aberrant use of these processes. In an effort to discover the participants involved in regulating compartment size, Zivkovic *et al*. earlier reported a differential display designed to isolate genes that are downregulated upon cell differentiation in *Danio rerio* (zebrafish) embryos (1). Zebrafish biological characteristics make it a valuable model organism for studies of vertebrate development and gene function allowing the identification of many genes involved in embryogenesis and human diseases. The full-length sequence of one of the down-regulated fragments revealed a gene homologous to the mammalian ankyrin repeat and suppressor of cytokine signaling (SOCS) box-containing protein 11 (*ASB11*). Loss of function experiments resulted in premature neuronal differentiation and reduced cell proliferating compartment in embryos, whereas forced expression prevented neuronal differentiation and maintained precursor cell fate *in vivo* and *in vitro*. Thus, *d-asb11* first emerged as an essential gene responsible for maintaining proliferation of progenitors during zebrafish embryogenesis. In the article of Sartori *et al*. in the current issue of TGC (2), the authors provide evidence that other vertebrate *Asb* genes may fulfill comparable functions and especially highlight a role for Asb9 in gastrointestinal cancer.

The *d-Asb11* is a member of the ASB family, which constitutes a conserved chordate-unique gene family characterized by variable numbers of N-terminal ankyrin repeats and a C-terminal SOCS box domain. Although still very little is known about ASB proteins, ASBs have been reported to regulate the turnover of protein substrates by interacting with and targeting them to degradation via the ubiquitin-proteasome pathway. ASB association with components of Cullin-based ubiquitylation complexes via the SOCS box domain is well established; however, ASB proteins seemed to be varied in the ubiquitylation complexes formation and may act by additional regulation pathways (3). Furthermore, in the present study in TGC (2), analysis of ASB transcripts levels revealed a tissue-specific expression pattern, indicating tissue-specific functions. In this regard (tissue-specificity), Wilcox *et al*. have shown that *Asb6* expression appears to be restricted to adipocytes (4). Also, Meijer *et al*. and Queiroz *et al*. have shown that human adipocytes are the *bona fide* source of huge number of cytokines and many other proteins involved in signaling pathway such as hedgehog signaling (5,6), which plays an important role in embryo development. It is then very interesting to study ASB protein family in adipocytes and other cells as well. ASB proteins were firmly implicated in the regulation of cell proliferation and differentiation, important to maintain controlled cell growth and prevent tumor formation. Consistently, abnormal ASB expression was now found in different cancer types. Therefore, more studies are necessary to investigate ASB proteins function and to define specific substrates by which ASBs interact with as well as to provide important information as the control of normal and pathological (i.e. cancer) compartment size in

various systems during gastrointestinal cancer.

Although the expression data is suggestive for roles of Asb proteins in cancer, the lacking provides insight into the importance of their specific domains in targeting substrates. In this sense a previous study of Sartori *et al*. is important, where these authors explored the biological functions of the cullin box domain of the *d-Asb11* (7). For that, they isolated a zebrafish mutant lacking the Cul5 box domain (*Asb11*^{Cul}) and found that homozygous zebrafish mutants for this allele were defective in Notch signaling as indicated by the impaired expression of Notch target genes. Importantly, *asb11*^{Cul} fish were not capable to degrade the Notch ligand Delta-A during embryogenesis, a process essential for the initiation of Notch signaling during neurogenesis. Accordingly, proper cell fate specification within the neurogenic regions of the zebrafish embryo was impaired. In addition, *asb11*^{Cul} mRNA was defective in the ability to transactivate a *her4-gfp* reporter DNA when injected in embryos. Thus that study reported the generation and the characterization of a metazoan organism mutant in the conserved cullin binding domain of the SOCS-box demonstrates a hitherto unrecognized importance of the SOCS-box domain for the function of this class of cullin-RING ubiquitin ligases and establishes that the *d-Asb11* cullin box is required for both canonical Notch signaling. From the present study now reported it might be inferred that colon cancer is the relevant pathological condition to which these findings might apply.

Indeed were initiated to identify further *in vivo* functions of *d-Asb11*, demonstrating expansion of the gastrointestinal system, highlighting the role of *Asb* genes outside the neuronal system and prompting more comprehensive analysis of its role in gastrointestinal cancer. Whether *d-asb11* is important for compartment size in the endodermal lineage, however, is questionable as *Asb9* is the main differentially expressed gene here and the authors present an evolutionary explanation to this phenomenon. Although these results provide important new insight on the action and function of ASB proteins in gastrointestinal cancer, further investigations remains to be done.

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