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Editorial

Sprouty Proteins and Cancer

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Sprouty proteins are inducible modulators of mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway that regulate key cellular functions, including cell vitality, differentiation and motility. Owing to their critical regulatory functions, Sprouty proteins are well documented to participate in developmental and adult physiological processes and, consistently, to be implicated in the regulation of pathological conditions, including cancer. Since discovery in Drosophila in 1998 [1], four human homologs of Sprouty have been identified, among which Spry1, Spry2 and Spry4 have been reported to be deregulated in a variety of malignant conditions. A growing body of evidence shows that the expression of Sprouty inhibits cancer cell proliferation, migration, invasion and survival. Since these cellular functions are central to growth and development of malignancies, the clinicopathological significance of the Sprouty expression has been studied by different investigators for the past decade [2]. Accordingly, the following clinical applications are among those suggested for the expression of Sprouty proteins in malignant tumors:

1. Spry2 as an independent predictor of a more favorable outcome in breast cancer [3].
2. Spry2 as a biomarker for stratifying patients with breast cancer for trastuzumab therapy [3].
3. Spry2 as an independent predictor of recurrence in hepatocellular carcinoma [4]
4. Spry4 as a reliable marker of the imatinib-responsive treatment in patients with gastrointestinal stromal tumors [5]
5. Spry1 and Spry2 as independent prognostic factors for overall and disease-free survival in ovarian cancer (our recent, unpublished data)
6. Spry2 as an independent predictor of post-treatment ascites (our recent, unpublished data)

As follows, however, facts and factors impacting Sprouty-mediated regulation need to be taken into account when interpreting the biological outcomes and clinical relevance of the Sprouty expression. Sprouty proteins are versatile regulators with complex functionality in different cell types. Initially described as inhibitors of growth factor signaling, they have shown to affect known targets beyond MAPK/ERK to mediate the crosstalk among different pathways required for the maintenance of balanced cellular responses. For this purpose, on the other hand, Sprouty proteins themselves are under a tight, multilayered control at transcriptional and post-translational levels. This also includes the regulation of subcellular localization and availability of these proteins, as well as the regulation of receptor tyrosine kinase (RTK) activity and stability. Moreover, regulatory functions of Sprouty indicate growth factor dependency as well as pathway sensitivity. Structural variation and functional divergence of the Sprouty isoforms despite structural and/or functional interactions further add to the complexity of the Sprouty-mediated regulation. Taken together, it is believed that Sprouty activity, while showing isoform specificity, is cell type- and context-dependent.

On this basis, it is not surprising that role of Sprouty in malignant conditions, where physiological homeostasis is altered in favor of neoplastic growth and progression, is fraught with more intricacy and even controversy. Therefore, while down regulation of Sprouty, as anticipated, is evident in a variety of cancers and Sprouty has been argued to serve as a tumor suppressor or a biomarker of a more favorable outcome or treatment sensitivity, there are contradictory reports of Sprouty upregulation in some cancer types and its opposite role as a tumorigenic factor or a biomarker of poor outcome or resistance to a given treatment. In this regard, the presence of accompanying mutations, such as oncogenic RAS,

has been shown to be an important determinant of the Sprouty expression status and/or its mode of action. In agreement, Spry1 upregulation along with aberrant activation of MAPK/ERK downstream of the Sprouty action point was reported in oncogenic RAS mutants of embryonal rhabdomyosarcoma [6]. We have reviewed the expression status of Sprouty proteins in different cancers and its biological and/or clinical consequences elsewhere [2].

Thus, for a better understanding of the role and putative clinical applications of the Sprouty expression in a particular cancer, in-depth investigation on Sprouty gene and protein and likely underlying aberrations in relation to malignant behavior of cancer cells in suitable in vitro and in vivo models is essential. This could give rise to the development of novel biomarkers for subclassification of disease and stratification of patients for personalized treatment as well as identification of new targets for cancer therapy.

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