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Current topics

The use of insulin like-growth factor II messenger RNA binding protein–3 in diagnostic pathology

Jennifer J. Findeis-Hosey MD, Haodong Xu MD, PhD*

Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, USA

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Summary The histologic distinction between reactive processes and malignant neoplasms and between low-grade and high-grade tumors is not always straightforward and is sometimes extremely challenging. This is especially the case when the diagnostic material is a small biopsy specimen or a cytology specimen with scant cellularity. In addition, suboptimal processing and crush artifact may limit accurate diagnosis. A reliable diagnostic biomarker that preferentially highlights malignant processes and high-grade tumors would be very valuable in segregating these entities from reactive processes and low-grade lesions. Recent extensive studies have shown that an oncoprotein, insulin like-growth factor II messenger RNA binding protein–3, is not only a prognostic biomarker but also a diagnostic molecule. This review focuses on discussing the value of insulin like-growth factor II messenger RNA binding protein–3 in diagnostic pathology, with a focus on utilization of insulin like-growth factor II messenger RNA binding protein–3 in the discrimination of benign effusions from malignant effusions, malignant mesothelioma from mesothelial hyperplasia, carcinoids from high-grade neuroendocrine carcinomas, low-grade dysplasia from high-grade dysplasia, hepatocellular carcinoma from hepatic adenoma, cholangiocarcinoma and metastatic pancreatic ductal carcinoma from benign bile duct lesions, melanoma from nevi, and follicular thyroid carcinoma from follicular adenoma of the thyroid, as well as examining insulin like-growth factor II messenger RNA binding protein–3 expression in lymphomas of germinal center origin.

1. Introduction

Insulin-like growth factor II messenger RNA binding protein–3 (IMP3), also known in the literature as IMP-3, K homology domain containing protein overexpressed in cancer, KOC, IGF2BP3, and L523S, is a 580–amino acid oncofetal RNA-binding protein containing 2 RNA recognition motifs and 4 K homology domains [1]. IMP3 is a member of the IMP family, which is composed of IMP1, IMP2, and IMP3 [2]. The IMP family has additionally been aggregated within the VICKZ (Vg1 RBP/Vera, IMP, CRD-BP, KOC, and ZBP-1) RNA-binding protein family [3]. This classification highlights IMP3 as a member of a family of highly conserved RNA-binding proteins that are present in a multitude of organisms with similar identities and functions [3].

Cancer research has implicated IMP3, a cytoplasmic protein that binds to the 5′ untranslated region of the insulin-like growth factor II (IGF-II) leader-3 messenger RNA (mRNA), as a translational activator of IGF-II leader-3

* Corresponding author. Department of Pathology and Laboratory Medicine, Box 626, University of Rochester Medical Center, Elmwood 601, Rochester, NY 14642, USA.
E-mail address: haodong_xu@urmc.rochester.edu (H. Xu).

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Table 1 IMP3 expression in human neoplasms

Organ/disease process	IMP3 positivity (% cases)	References
Pancreas		
Pancreatic adenocarcinoma	49-100	[12,19-24]
Gastrointestinal tract		
Esophageal adenocarcinoma	66-94	[25,26]
Gastric adenocarcinoma	60	[27]
Colorectal adenocarcinoma	65-74	[28,29]
Hepatobiliary		
Hepatocellular carcinoma	63-68	[6,30]
Cholangiocarcinoma	47[a]-87	[24,31]
Gallbladder carcinoma	82[a]	[31]
Gynecologic		
Endometrial clear cell carcinoma	25-71	[32,33]
Endometrioid carcinoma	7-56	[33-35]
Serous endometrial carcinoma	73-100	[32,33, 35-37]
Cervical adenocarcinoma in situ	93	[38]
Ovarian carcinoma, overall	47-70	[11,39-41]
Ovarian carcinoma, mucinous subtype	87	[11]
Ovarian carcinoma, clear cell	52-78	[11,39,41]
Ovarian carcinoma, high-grade serous carcinoma	50	[11]
Ovarian carcinoma, endometrioid subtype	25-27	[11,39]
Ovarian serous papillary carcinoma	92	[36]
Lung/pleura		
Non–small cell lung cancer	52-68	[42,43]
Squamous cell carcinoma lung	75-90[b]	[9,42-44]
Adenocarcinoma of the lung	27-55	[9,43,45]
Bronchioloalveolar carcinoma	25-40	[42,45]
Large cell neuroendocrine carcinoma of the lung	100	[46]
Small cell lung carcinoma	100	[46]
Malignant pleural mesothelioma	36-91	[47-50]
Lymphoid		
Hodgkin lymphoma	100	[16,51]
Burkitt lymphoma	83	[16]
Follicular lymphoma	80-100	[16,51]
Diffuse large B-cell lymphoma	85-100	[16,51]
Cutaneous		
Melanoma, primary	40-85	[34,52,53]
Merkel cell carcinoma	90	[14]
Thyroid		
Papillary carcinoma, conventional	11-66.7	[34,54,55]
Papillary carcinoma, follicular variant	38-66.7	[54,55]
Follicular carcinoma	62.5-69	[54,55]
Hürthle cell carcinoma	21	[54]
Poorly differentiated carcinoma	59	[56]
CNS		
Meningioma	7	[57]
Pituitary adenoma	31	[15]
Pituitary carcinoma	36	[15]
Genitourinary		
Renal cell carcinoma, overall	13-16	[34,58,59]
Renal cell carcinoma, clear cell	14-30	[58-60]
Renal cell carcinoma, chromophobe	15-35	[58,59,61]
Renal cell carcinoma, papillary	9-65	[58,59,61]
Noninvasive papillary urothelial carcinoma	10-16	[62-64]
Urothelial carcinoma in situ	36-48	[63,64]
Invasive urothelial carcinoma	34-59	[63,64]
Breast		
Mammary carcinoma	8-33	[34,65-67]
Oropharynx		
Laryngeal squamous cell carcinoma	35	[68]
Bone and soft tissue		
Osteosarcoma	17-96	[69,70]
Other		
Squamous cell carcinomas of the upper aerodigestive tract	92	[71]
Extrapulmonary small cell carcinoma	94	[13]

NOTE. All results, unless otherwise indicated, are number of IMP3-positive cases, as determined by immunohistochemical studies.
Abbreviation: CNS, central nervous system.
[a] Strong immunohistochemical expression [31].
[b] RT-PCR.

mRNA, which normally controls cell proliferation [4]. Liao et al [4] demonstrated that IMP3 knockdown by short interfering RNA slowed K562 human leukemia cell proliferation by inhibiting translation of IGF-II leader-3 mRNA without affecting mRNA levels of IGF-II. In addition, studies have shown that IMP1 and IMP3 exert profound effects on cellular adhesion and formation of invadopodia by stabilizing CD44 mRNA, indicating that expression of IMPs in cancer cells may promote their invasive capacity [5]. The *Xenopus* IMP3 orthologue has been demonstrated to be localized to the leading edge of migrating neural crest cells, and the antisense suppression of this orthologue resulted in inhibition of migration of these cells [3]. In a study of IMP depletion in the human hepatocellular carcinoma cell line HA22T, depletion of IMP3 resulted in the inhibition of tumor cell motility and invasion [6]. Meanwhile, overexpression of IMP3 in the CL-1-0 lung adenocarcinoma and MDA-MB-231 breast cancer cell lines increased the invasive properties of these cell lines [6]. Similarly, in the human melanoma cell line 1205LU, si-RNA–mediated knockdown of IMP3 resulted in a substantial decrease in in vitro cellular invasion [7].

As an oncogene, IMP3 is ubiquitously expressed during the early stages of embryogenesis, with only limited normal expression in postembryonic stages [8,9]. During embryogenesis, the greatest expression of IMP3 occurs in the gut, pancreas, kidney, and brain [8]. Expression of IMP3 in adults is normally limited to placental intermediate trophoblasts, with limited expression in lymph node germinal centers, ovary, testis, brain, the internal root sheath of hair follicles, and intestinal and endocervical mucosa [2,8,10-16].