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Original contribution

Expression analysis of Ubc9, the single small ubiquitin-like modifier (SUMO) E2 conjugating enzyme, in normal and malignant tissues

Stergios J. Moschos MD[a,*], Drazen M. Jukic MD, PhD[b,d], Charalambos Athanassiou MSc[c], Rohit Bhargava MD[b], Sanja Dacic MD, PhD[b], Xiaolei Wang PhD[b], Shih-Fan Kuan MD[b], Shelley L. Fayewicz BSc[a], Csaba Galambos MD, PhD[b], Marie Acquafondata BSc[b], Rajiv Dhir MD[b], Dorothea Becker PhD[b]

[a]*Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[b]*Department of Pathology, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[c]*Department of Computational Biology, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[d]*Department of Dermatology, University of Pittsburgh, Pittsburgh, PA 15213, USA*

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Summary Unlike ubiquitination, which targets proteins for degradation, sumoylation modulates protein-protein interactions of target proteins. Although there are multiple E2 enzymes required for ubiquitination, there is only one E2-conjugating enzyme for sumoylation, which is Ubc9. In line with increasing evidence that sumoylation plays an important role in tumorigenesis, we recently demonstrated that Ubc9 is expressed at high levels in advanced melanomas and that blocking expression of Ubc9 sensitizes melanomas to the cytotoxic effects of chemotherapeutic drugs. To determine whether and to what extent Ubc9 is expressed in other malignancies and their normal tissue counterparts, we undertook a detailed analysis of colon, lung, prostate, and breast cancer tissue microarrays. The findings, presented here, document that in primary colon and prostate cancer, Ubc9 expression is increased compared with their normal tissue counterparts, whereas in metastatic breast, prostate, and lung cancer, it is decreased in comparison with their corresponding normal and primary adenocarcinoma tissues. We also provide evidence that Ubc9 expression correlates positively with Dukes' stage and negatively with the Gleason score as well as breast cancer grade and that Ubc9 expression is substantially higher in the luminal than in the nonluminal type of breast cancer.

1. Introduction

Small ubiquitin-like modifiers (SUMO) are a family of proteins that covalently and reversibly attach to target proteins. The SUMO paralog proteins are activated by a heterodimeric E1-activating enzyme (Uba2/Aos1), which

* Corresponding author.
E-mail address: moschossj@upmc.edu (S. J. Moschos).

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Table 1 Clinicopathologic characteristics of colon, lung, breast, and prostate cancer TMAs

Histologic diagnosis		Staging system		Other features			
					Present	Absent	Unknown
Colon adenocarcinoma (1.0-mm cores spotted in duplicates)							
	n	Duke's		hMLH1 status [a]			
Normal adjacent to invasive cancer	9	A	27				
Adenoma adjacent to invasive cancer	16	B	47		33	18	
Primary adenocarcinoma	168	C	46				
		D	17				
		Unknown	31				
Lung adenocarcinoma (0.6-mm cores spotted in duplicates)							
		AJCC		EGFR, K-Ras gene aberrations			
		IA	36				
Normal [b]	10	IB	31	EGFR exon 19 deletion	11	99	1
Normal adjacent to invasive cancer	49	IIA	3	EGFR exon 21 mutation	12	98	1
Primary adenocarcinoma	111	IIB	9	K-Ras mutations	56	52	3
Metastatic adenocarcinoma	14	IIIA	13				
		IIIB	12				
		Unknown	7				
Breast adenocarcinoma (1.0-mm cores spotted in quadruplicates)							
		AJCC		Hormone Receptor Status-Sorlie Classification [a]			
Normal [c]	30			Luminal A			
Primary adenocarcinoma	76	I	28	ER+PR+ her2/neu−	50		
Ductal	52	IIA	9	ER+PR− her2/neu−	5		
Lobular	21	IIB	7	Luminal B			
Other	3	IIIA	9	ER+PR+ her2/neu+	8		
Metastatic adenocarcinoma	23	IIIB	7	ER+PR− her2/neu+	2		
Lung	5	Unknown	16	Unclassified			
Lymph nodes	9			ER−PR− her2/neu+		2	
Brain	3			Basal-like			
Other	6			ER−PR− her2/neu−		9	
Prostate adenocarcinoma (0.6-mm cores spotted in triplicates)							
Normal	59	AJCC		Gleason score			
Donor normal	15	II	42				
Matched adjacent to invasive cancer	24	III	37	<7	16		
Matched adjacent to relapsed cancer [d]	20	IV	32	7	54		
PIN	22	Unknown	1	8-9	42		
Nonmatched PIN	14						
Matched adjacent to invasive cancer	8						
Primary adenocarcinoma	112						
Newly diagnosed	89						
Relapsed [d]	23						
Metastatic adenocarcinoma	62						
Locally advanced	5						
Distant metastatic							
Viscera	29						
Lymph nodes	16						
Bones	12						

Abbreviations: n, numbers of cases; hMLH1, human MutL homolog 1; EGFR, epidermal growth factor receptor; PR, progesterone receptor.

[a] Expression status is defined by immunohistochemistry as part of official pathology sign-out.

[b] Histologically confirmed normal lung tissue from children who had undergone thoracoscopic surgery for primary spontaneous pneumothorax.

[c] Normal breast containing normal breast epithelium with histologically normal terminal ductal-lobular units, which was obtained as part of benign bilateral reduction mammoplasty.

[d] Relapse is defined as prostate-specific antigen failure or metastatic disease.

results in the formation of a thiolester intermediate, which is then transferred to Ubc9, the single E2 SUMO conjugating enzyme, and thereupon, Ubc9 conjugates SUMO paralogues to the target protein. Although the process of sumoylation does not fundamentally differ from that of ubiquitination, the major difference is that ubiquitination