Gene 647 (2018) 31–38

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

Polymerase epsilon mutations and concomitant β2-microglobulin mutations in cancer

Ioannis A. Voutsadakis*

Division of Medical Oncology, Department of Internal Medicine, Sault Area Hospital, Sault Ste Marie, Ontario, Canada
Division of Clinical Sciences, Northern Ontario School of Medicine, Sudbury, Ontario, Canada

ARTICLE INFO

Keywords:
Polymerase epsilon
Neo-antigens
Genomic
cBioportal
Exonuclease domain

ABSTRACT

Mutations in the exonuclease domain of polymerase epsilon (POLE), an enzyme of DNA synthesis, are involved in a newly described syndrome of colorectal polyposis and cancer, and have been associated with a high mutation burden with or without microsatellite instability (MSI) phenotype. The exonuclease domain of POLE executes a proofreading function that decreases the mutation rate during DNA replication by an estimated of one to two orders. The high mutation burden resulting from its loss of function could create a load of neo-antigens that would put the neoplastic cells in severe disadvantage of an immune attack if properly presented to the immune system. This paper investigates the mutagenic effect of different POLE mutations in various cancers, in published genomic studies and the effect that these POLE mutations have in selecting for mutations of the β2 microglobulin (B2M) gene involved in antigen presentation.

1. Introduction

Studies of immune blockade inhibitors have revealed that tumors with elevated mutation load due to mismatch repair (MMR) defects have an increased probability of response (Le et al., 2015). Genetic lesions in one of four genes (MSH2, MSH6, MLH1 and PMS2) participating in MMR results in tumor with Microsatellite instability (MSI) which have a mutation load several (8 to 9) times higher than Microsatellite stable (MSS) tumors (Shukla et al., 2017). MSI is the characteristic of the genetic syndrome Hereditary Non-Polyposis Colorectal Cancer (HNPCC also known as Lynch syndrome) which presents with a high prevalence of colorectal cancers as well as endometrioid endometrial cancers (Carethers and Stoffel, 2015). A significant minority of sporadic colorectal cancers are also MSI although due to a different underlying mechanism, usually involving promoter methylation of the MLH1 gene.

More recently a novel genetic defect leading to tumors with high mutation load has been discovered, that involves genetic defects of the polymerase epsilon (POLE) gene (Briggs and Tomlinson, 2013). POLE and the related polymerase delta (POLD1) are polymerases of the B family executing the synthesis of the leading and lagging strand respectively during DNA replication. Genetic mutations in either of them leads to a syndrome with high prevalence of colorectal adenomas and early onset carcinomas named polymerase proofreading-associated polyposis (PPAP) (Palles et al., 2012). Mutations of POLE in cases of sporadic colorectal cancers have also been described and are usually located in a domain of POLE with 3′-exonuclease activity which effectuates proofreading activities during replication and decreases the mutation rate of newly synthesized DNA by about 100-fold (Heitzer and Tomlinson, 2014). Thus defects in this domain of the POLE may create tumors with mutation burden several times higher than even MSI tumors (Shukla et al., 2017). At the same time this high mutation number would produce an increased neo-antigen load that, if presented to the immune system, would constitute a major impediment for tumor viability, as it would make tumor cells an excellent target for immune effectors. These POLE-mutant tumors would be, as a result, at increased pressure to develop antigen presentation machinery defects in order to avoid presentation of their increased neo-antigen load to immune cells or, alternatively, to express molecules inhibiting immune cells, such as PD-L1. Indeed endometrial cancers with POLE mutations or MSI have been found to express higher levels of PD-L1 than MSS cancers, a fact that may be exploited for therapy with immune checkpoint inhibitors (Howitt et al., 2015).

This paper investigates the presence and effect of various POLE mutations in cases of published genomic studies and explores the hypothesis that certain POLE defects favor the concomitant mutation in

Abbreviations: POLE, polymerase epsilon; B2M, beta 2 microglobulin; MMR, mismatch repair; HNPCC, Hereditary Non-Polyposis Colorectal Cancer; PPAP, polymerase proofreading-associated polyposis

* Division of Medical Oncology, Sault Area Hospital, 750 Great Northern Road, Sault Ste Marie, Ontario P6B 0A8, Canada.
E-mail address: ivoutsadakis@nosm.ca.

https://doi.org/10.1016/j.gene.2018.01.030
Received 15 September 2017; Accepted 6 January 2018
Available online 07 January 2018
0378-1119/

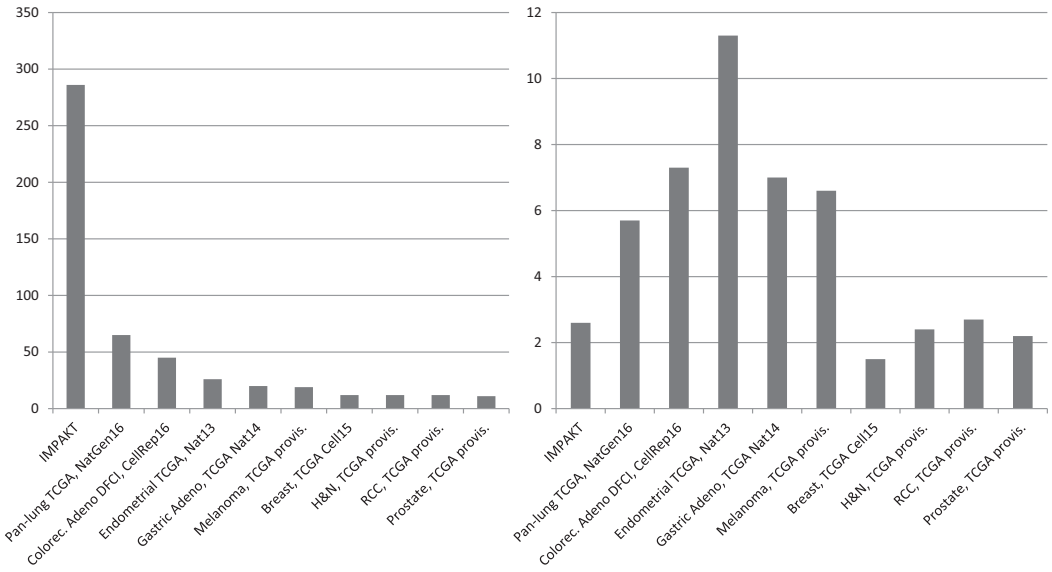

Fig. 1. Series contained in cBioportal with the most cases of POLE mutations or deletions. Left: Absolute numbers of samples with POLE defects. Right: Cases with POLE defects as a percentage of the total number of cases included in the respective series.

Table 1
Numbers and percentages of missense/truncating mutations and deep deletions of POLE and B2M truncating mutations and deletions in the studies with the higher frequencies of POLE mutations in cBioportal.

Reference	Cancer type	POLE lesions		B2M lesions		Number of samples with co-occurrence	Co-occurrence significance
		Number	%	Number	%		
Zehir et al.	Various	286	2.6	144	1.4	23	$p < .001$
Campbell et al.	Lung	65	5.7	39	3.4	4	$p = .07$
Giannakis et al.	Colon	45	7.3	44	7.1	10	$p < .001$
CGARN et al.	Endometrial	26	11.3	3	1.3	2	$p = .07$
CGARN	Gastric	20	7	18	6.3	4	$p = .04$
TCGA, provisional	Melanoma	19	6.6	13	5	4	$p = .008$

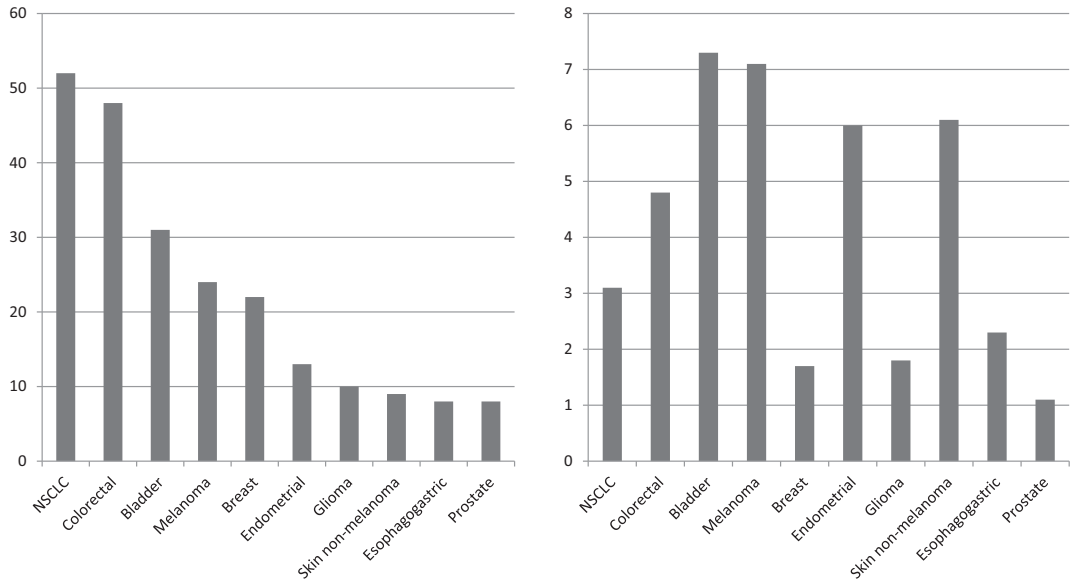

Fig. 2. Most abundant types of cancers with POLE mutations in the MSK-IMPACT series. Left: absolute numbers. Right: Percentages of the cases with POLE mutations in the respective types included in MSK-IMPACT.

the beta2-microglobulin gene (B2M), the invariant light chain of the MHC (Major Histocompatibility Complex) that presents polypeptides to the cell surface for CD8+ T effector cell recognition (Voutsadakis, 2017). Absence of B2M would neutralize the disadvantage that an increased neoantigen burden would impose to a cancer. In addition, B2M defects could be a mechanism of primary or secondary resistance to immune checkpoint inhibitors treatment (Sharma et al., 2017).