Gynecologic Oncology 140 (2016) 333–344

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review Article

Emerging strategies for targeting PI3K in gynecologic cancer☆

Amy J. Bregar, Whitfield B. Growdon *

[a] Vincent Center for Reproductive Biology, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA, United States
[b] Harvard Medical School, Boston, MA, United States
[c] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA, United States

HIGHLIGHTS

- Ovarian, endometrial and cervical cancers share activation of the PI3K pathway
- PI3K pathway inhibitors have shown promise in the pre-clinical and clinical setting
- Current clinical trials pair PI3K pathway inhibitors with other therapies to maximize response

ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form 27 September 2015
Accepted 28 September 2015
Available online 30 September 2015

Keywords:
Gynecologic cancer
PI3K pathway inhibition
mTOR inhibition
Therapeutic resistance

ABSTRACT

Ovarian, endometrial and cervical cancers are the most prevalent gynecologic cancers in the United States and account for significant mortality. Translational research into these cancers has highlighted the distinctive molecular and genomic profiles of these cancers finding that, even within a disease site, the landscapes and drivers of neoplasia are distinctive. Despite this molecular diversity, activation of the phosphatidylinositol-3-kinase (PI3K) pathway appears to be conserved in subsets of these tumors, suggesting that strategies that antagonize mediators in this signaling cascade could offer anti-tumor efficacy. Extensive pre-clinical and clinical data have demonstrated that single agent targeted therapies lead to modest single agent activity of generally limited duration, even in the setting of innate PI3K pathway activation via mutation or amplification. These findings in the laboratory and clinic have prompted investigations into resistance pathways following PI3K pathway inhibition in order to understand escape pathways and restore tumor cell sensitivity. A next generation of clinical trial investigations will focus on novel combinations in order to define how these important therapeutics can be used in the clinic. This review will present preclinical data that supports the role of the PI3K pathway in ovarian, endometrial and cervical cancers, in addition to discussing the reported clinical trial experience with PI3K pathway inhibition. A specific focus will be on the rationale behind ongoing clinical trials utilizing novel agents in concert with PI3K pathway inhibitors to reverse resistance in populations with and without gain of function alterations in this oncogenic signaling cascade.

Contents

☆ Funding: No funding was granted for this manuscript.
* Corresponding author at: Massachusetts General Hospital, Vincent Center for Reproductive Biology, Vincent Department of Obstetrics and Gynecology, THR 901, 55 Fruit Street, Boston, MA 02114, United States.
E-mail address: wgrowdon@partners.org (W.B. Growdon).

http://dx.doi.org/10.1016/j.ygyno.2015.09.083
0090-8258/

1. Introduction

Cancers of the uterus, ovary and cervix account for the majority of gynecologic cancer treated in the United States with over 90,000 new diagnoses anticipated in 2015. While ovarian cancers are the most lethal, with a 67% mortality rate, the mortality associated with endometrial and cervical cancers is significant at 18% and 31% respectively [1]. These statistics demonstrate the current limitations of available therapies and highlight the dire need for translational research to understand the molecular events that cause and promote these cancers.

In an era of targeted therapeutics that can specifically inhibit key oncogenic mediators, investigators have come to understand that the drivers of malignant transformation tend to be diverse with the three most prevalent gynecologic cancers harboring markedly different profiles. Multiple investigations have found that endometrial carcinoma harbors numerous complex, even overlapping mutations [2–6], while the hallmark of a majority of ovarian carcinomas appears to be generalized genomic instability with low frequencies of conserved mutations [7–9]. In contradistinction to both these disease sites, cervical carcinoma is known to be an acquired cancer via HPV infection [10,11]. While all arising in the female reproductive tract, these malignancies have been shown to have disparate molecular underpinnings and clinical behavior.

Despite clear differences, these gynecologic cancers share activation of the phosphatidylinositol-3-kinase (PI3K) pathway as a common signature, offering the hope that agents targeting this cascade could have therapeutic relevance [10,12,13]. The PI3K pathway consists of a network of intracellular lipid kinases involved in complex cell signaling pathways affecting cell metabolism and survival [14]. The PI3K pathway is among the most commonly altered pathways in solid tumor malignancies, thus suggesting it to be a key nodal pathway in sustaining malignancy [14]. There are many underlying mechanisms for PI3K pathway activation in cancer, including receptor tyrosine kinase activation or amplification, mutation, deletion, silencing of negative regulators of the PI3K pathway and activation or amplification of downstream kinase mediators [15]. The PI3K pathway also interacts with a complex network of other signaling cascades important for cancer growth including the mitogen activated protein kinase (MAPK) pathway, which can also be activated by similar receptor tyrosine kinases as well as by crosstalk interactions through mediator kinases [16]. Growing evidence suggest that these two pathways have redundant functions and share multiple negative feedback loops which may be important for both primary and secondary resistance to isolated inhibition of either of these pathways [17].

1.1. PI3K signaling pathway

While three classes of PI3K enzymes have been described, class IA PI3Ks have been most associated with promoting carcinogenesis [18].

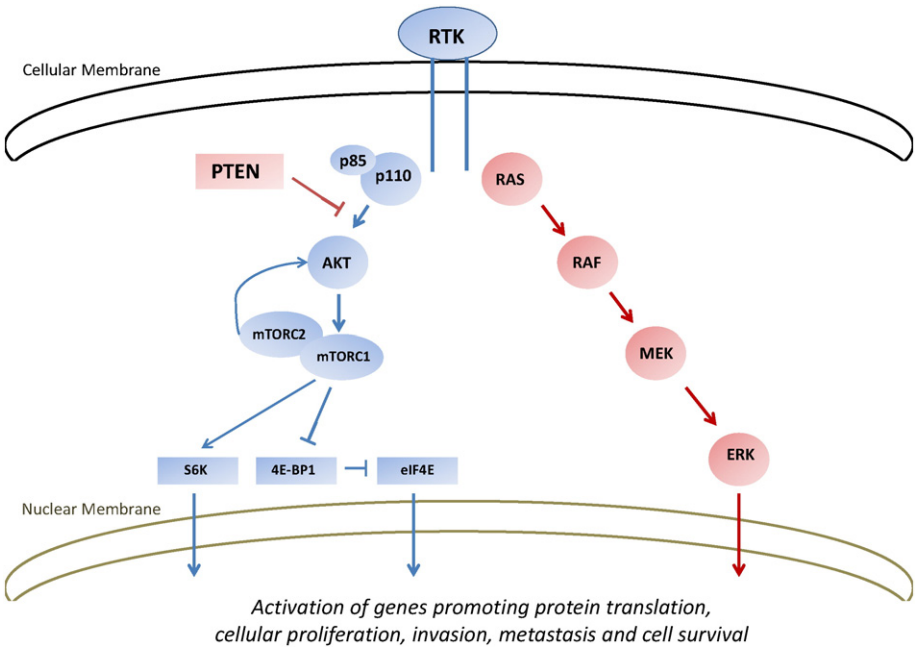

Fig. 1. The PI3K signaling cascade begins with growth factor ligand binding that leads to activation of a receptor tyrosine kinases (RTK). This leads to activation of PI3K, a heterodimer composed of a p85 regulatory subunit and a p110 catalytic subunit. PI3K induces phosphorylation and activation of AKT (protein kinase B). AKT activates the mammalian target of rapamycin (mTOR) complex via intermediaries. mTOR1 in turn interacts with ribosomal protein S6 kinase (rpS6K) and eukaryotic translation initiation factor 4E1 binding protein (4E-BP1). These proteins induce translation of genes that support proliferation, angiogenesis, survival and metastasis. PI3K is negatively regulated by phosphatase and tensin homolog (PTEN), a phosphatase that suppresses signal transduction down the PIK3/AKT/mTOR pathway. RTK: receptor tyrosine kinase; p85: regulatory subunit of class IA phosphoinositide 3-kinase; p110: catalytic subunit of class IA phosphoinositide 3-kinase; AKT: protein kinase B; rpS6K: ribosomal protein rpS6K; mTORC: mammalian target of rapamycin complex; 4E-BP1: eukaryotic translation initiation factor 4E binding protein 1; eIF4E: eukaryotic translation initiation factor 4E; RAF: rapidly accelerated fibrosarcoma; MEK; mitogen-activated protein kinase; ERK: extracellular signal regulated kinase.