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Microbial inositol polyphosphate metabolic pathway as drug development target

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ABSTRACT

Inositol polyphosphates are a diverse and multifaceted class of intracellular messengers omnipresent in eukaryotic cells. These water-soluble molecules regulate many aspects of fundamental cell physiology. Removing this metabolic pathway is deleterious: inositol phosphate kinase null mutations can result in lethality or substantial growth phenotypes. Inositol polyphosphate synthesis occurs through the actions of a set of kinases that phosphorylate phospholipase-generated IP_3 to higher phosphorylated forms, such as the fully phosphorylated IP_6 and the inositol pyrophosphates IP_7 and IP_8. Unicellular organisms have a reduced array of the kinases for synthesis of higher phosphorylated inositol polyphosphates, while human cells possess two metabolic routes to IP_6. The enzymes responsible for inositol polyphosphate synthesis have been identified in all eukaryote genomes, although their amino acid sequence homology is often barely detectable by common search algorithms. Homology between human and microbial inositol phosphate kinases is restricted to a few catalytically important residues. Recent studies of the inositol phosphate metabolic pathways in pathogenic fungi (*Cryptococcus neoformans*) and protozoa (*Trypanosome brucei*) have revealed the importance of the highly phosphorylated inositol polyphosphates to the fitness and thus virulence of these pathogens. Given this, identification of inositol kinase inhibitors specifically targeting the kinases of pathogenic microorganisms is desirable and achievable.

Contents

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1. Introduction

Cells, whether part of a multicellular organism or independent beings, must adapt to external inputs to survive and reproduce. A unicellular organism must respond to the ever-changing external environment. A metazoan or plant cell, often highly specialised, must perform unique tasks in harmony with the other cell types; thus its physiology is controlled not only by external factors, such as nutritional input, but also from signals (for example mechanical, hormonal) deriving from other cells of the organism. Signal transduction mechanisms are used to integrate the received inputs and to coordinate the appropriate physiological answers. Misfiring, causing improper physiological responses, often affects growth rate, which can lead to cancerous development, or in the case of unicellular organisms can cause decreased fitness and ultimately death. Cell biology textbooks show us numerous signal transduction pathways: protein phosphorylation cascades, nuclear receptors, cAMP signalling etc. Inositol phosphates, in their lipid-bound or cytosolic forms, represent perhaps one of the most complex systems of signalling molecules present in eukaryotic cells. The signal transduction pathways regulated by phosphorylated forms of inositol are more than the AKT phosphorylation cascade activated by synthesis of the lipid PIP_3 (Hawkins et al., 2006) or the phospholipase-C (PLC) generation of the calcium release factor $I(1,4,5)P_3$ (Yang et al., 2013). Although less well-known than their lipid counterparts, the soluble 'cytosolic' inositol polyphosphates constitute a large metabolic network of signalling molecules with unexpected features (Irvine and Schell, 2001). Starting from the calcium release factor IP_3, specific kinases generate an array of phosphorylated molecules leading to the synthesis of IP_6 (inositol hexakisphosphate, also known as phytic acid), with a fully phosphorylated inositol ring. More phosphorylated forms exist: called inositol pyrophosphates, they possess seven (IP_7, diphosphoinositol pentakisphosphate), eight (IP_8, bis-diphosphoinositol tetrakisphosphate) and likely even more phosphate groups attached to the six-carbon inositol ring (Losito et al., 2009; Pisani et al., 2014). Depleting the cell of inositol pyrophosphates, by destroying the metabolic pathways that lead to their synthesis, has vast phenotypic consequences, since these molecules control numerous cell biological processes. This pleiotropy of functions suggests that inositol pyrophosphates control some fundamental aspect of cell physiology. Indeed, these molecules are emerging as important players in regulating basic energetic metabolism (Szijgyarto et al., 2011) through their ability to control phosphate homeostasis (Wild et al., 2016) (for review see (Azevedo and Saiardi, 2017; Shears, 2017; Wilson et al., 2013)).

While the AKT signalling cascade, generated from the lipid PIP_3, is largely characteristic of metazoa, the inositol phosphate metabolic network that leads to the synthesis of the inositol pyrophosphates is present with some variance in virtually all eukaryotic cells (Livermore et al., 2016).

The simplicity of and easy genetics and biochemistry of the budding yeast *Saccharomyces cerevisiae* have been instrumental in identifying the different inositol phosphate kinases that lead to the synthesis of IP_7 and IP_8 from PLC-generated $I(1,4,5)P_3$. In budding yeast, the sequential action of Arg82 (Ipk2 or inositol phosphate multikinase IPMK), IPK1 (IP5-2K), Kcs1 (IP6K) and Vip1 (PPIP5K) leads to the conversion of $I(1,4,5)P_3$ to IP_8. Only two of the known inositol polyphosphate kinases, IP_3-3K and ITPK1, have not been identified using the budding yeast, because they are actually absent from its genome. Undiscovered kinases may also still exist: in the amoeba *Dictyostelium discoideum* the synthesis of highly phosphorylated inositol phosphates occurs directly from inositol and not from PLC-generated IP_3 (Stephens and Irvine, 1990). The metazoa specific IP_3-3K is linked to calcium signalling, since it specifically converts $I(1,4,5)P_3$ to IP_4, switching off calcium release (Schell, 2010). On the other hand ITPK1 converts a different isomer of IP_3, namely $I(1,3,4)P_3$, to IP_5. Together these two kinases create a metabolic pathway leading to highly phosphorylated inositol such as IP_5, IP_6, and inositol pyrophosphates that is absent from yeast (see below) and many protozoa.

The identification of the inositol phosphate metabolic pathway in pathogenic fungi such as *Cryptococcus neoformans* (Lev et al., 2013, 2015; Li et al., 2016a,b) and pathogenic protozoa such *Trypanosoma brucei* (Cestari et al., 2016; Cordeiro et al., 2017) revealed the importance of these signalling molecules to the fitness of these organisms. The generation of inositol phosphate kinase null mutants results in multiple defects, including lethality or substantial growth delay phenotypes. Interestingly, these pathogens possess an array of inositol phosphate kinases similar to *S. cerevisiae*, and lack the alternative metazoan-specific synthetic pathway. Furthermore, the homology between the inositol phosphate kinases in these pathogens and their human counterparts is restricted to a few key amino acids, with an identity index below 30%. These three features: 1) the importance of highly phosphorylated inositol phosphates for the fitness of pathogenic organisms; 2) the presence, in human cells, of an alternative metabolic pathway leading to IP_6 and 3) the low amino acid homology existing between the human and the pathogenic kinases, points towards the microbial inositol polyphosphate metabolic pathway as a drug development target. Developing new treatments to fight eukaryote pathogens such as fungi or trypanosomes is particularly challenging since the mammalian host is also eukaryotic and therefore with a similar cellular physiology. Targeting unique feature of each pathogen's physiology, such as the cell walls of pathogenic fungi, has led to the development of drugs that are often limited by species specificity. Drug resistance is also emerging (Prasad et al., 2016) and it has become urgent and imperative to identify novel targetable microbial pathways. Therefore, screening to identify inositol phosphate kinase inhibitors targeting specifically the kinases of pathogenic microorganisms, is not only achievable but also extremely desirable.

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