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Oocyte activation and latent HIV-1 reactivation: AMPK as a common mechanism of action linking the beginnings of life and the potential eradication of HIV-1

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ABSTRACT

In all mammalian species studied to date, the initiation of oocyte activation is orchestrated through alterations in intracellular calcium (Ca^{2+}) signaling. Upon sperm binding to the oocyte plasma membrane, a sperm-associated phospholipase C (PLC) isoform, PLC zeta (PLCζ), is released into the oocyte cytoplasm. PLCζ hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to produce diacylglycerol (DAG), which activates protein kinase C (PKC), and inositol 1,4,5-trisphosphate (IP3), which induces the release of Ca^{2+} from endoplasmic reticulum (ER) Ca^{2+} stores. Subsequent Ca^{2+} oscillations are generated that drive oocyte activation to completion. Ca^{2+} ionophores such as ionomycin have been successfully used to induce artificial human oocyte activation, facilitating fertilization during intra-cytoplasmic sperm injection (ICSI) procedures. Early studies have also demonstrated that the PKC activator phorbol 12-myristate 13-acetate (PMA) acts synergistically with Ca^{2+} ionophores to induce parthenogenetic activation of mouse oocytes. Interestingly, the Ca^{2+}-induced signaling cascade characterizing sperm or chemically-induced oocyte activation, i.e. the "shock and live" approach, bears a striking resemblance to the reactivation of latently infected HIV-1 viral reservoirs via the so called "shock and kill" approach, a method currently being pursued to eradicate HIV-1 from infected individuals. PMA and ionomycin combined, used as positive controls in HIV-1 latency reversal studies, have been shown to be extremely efficient in reactivating latent HIV-1 in $CD4^+$ memory T cells by inducing T cell activation. Similar to oocyte activation, T cell activation by PMA and ionomycin induces an increase in intracellular Ca^{2+} concentrations and activation of DAG, PKC, and downstream Ca^{2+}-dependent signaling pathways necessary for proviral transcription. Interestingly, AMPK, a master regulator of cell metabolism that is activated thorough the induction of cellular stress (e.g. increase in Ca^{2+} concentration, reactive oxygen species generation, increase in AMP/ATP ratio) is essential for oocyte maturation, T cell activation, and mitochondrial function. In addition to the AMPK kinase LKB1, CaMKK2, a Ca^{2+}/calmodulin-dependent kinase that also activates AMPK, is present in and activated on T cell activation and is also present in mouse oocytes and persists until the zygote and two-cell stages. It is our hypothesis that AMPK activation represents a central node linking T cell activation-induced latent HIV-1 reactivation and both physiological and artificial oocyte activation. We further propose the novel observation that various compounds that have been shown to reactivate latent HIV-1 (e.g. PMA, ionomycin, metformin, bryostatin, resveratrol, etc.) or activate oocytes (PMA, ionomycin, ethanol, puromycin, etc.) either alone or in combination likely do so via stress-induced activation of AMPK.

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Introduction

An increase in the intracellular concentration of calcium (Ca^{2+}) ions within an oocyte after initiation of fertilization has been characterized in all species studied to date. The competency of a mature mammalian oocyte to respond to fertilization-induced Ca^{2+} signaling is accomplished through oocyte maturation, a process in which meiosis is initiated during fetal development but is arrested at the diplotene stage of prophase I of meiosis I near the time of birth [1]. Meiosis is later reinitiated in response to a pre-ovulatory luteinizing hormone (LH) surge, with the oocyte entering and becoming arrested again at metaphase II of meiosis II until

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fertilization occurs [1]. Meiotic maturation induces changes to cytoplasmic structures and organelles that facilitate efficient generation of intracellular Ca^{2+} oscillations necessary for oocyte activation and embryonic development, including a reorganization of the endoplasmic reticulum (ER), an increase in the concentration of Ca^{2+} ions in the ER, and an increase in the number and post-translational modifications of the IP3 receptor (IP3R1) [2].

The induction and completion of oocyte activation is accomplished by sperm-induced intracellular Ca^{2+} oscillations within the oocyte upon fertilization, characterized by cortical granule exocytosis, meiotic resumption, recruitment of maternal mRNAs, and the formation of male and female pronuclei [3]. Interestingly, the failure to induce fertilization after intra-cytoplasmic sperm injection (ICSI), a procedure in which micromanipulation is used to directly inject sperm into the cytoplasm of an oocyte, has been demonstrated to be linked to oocyte activation failure [4]. Consequently, ICSI failure has led to the increased use of assisted oocyte activation (AOA) to successfully enhance fertilization and pregnancy rates. The use of various methods to artificially activate oocytes, including electrical activation, mechanical manipulation, and chemical activation (e.g. Ca^{2+} ionophores, strontium chloride) each provoke singular or multiple increases in intracellular Ca^{2+} concentrations within the oocyte cytoplasm [5–8].

The majority of global human immunodeficiency virus (HIV) infections and subsequent progression to acquired immunodeficiency syndrome (AIDS) are primarily associated with the retrovirus HIV-1 [9,10]. AIDS is an often fatal condition characterized by a reduction of $CD4^+$ T cells, loss of cell-mediated immunity, and increased susceptibility to opportunistic infections [9–11]. The reduction of viral load below the limits of detection for clinical assays (i.e. less than 50 copies per milliliter) is however achievable through the combined use of antiretroviral medications that target various stages of the HIV-1 life cycle, also known as highly active antiretroviral therapy (HAART) [9,12]. A rapid rebound in viral load often follows cessation of HAART due primarily to the presence of a long-lived latently infected $CD4^+$ memory T cell reservoir. Latently infected HIV-1 $CD4^+$ memory T cells are thus capable of evading immune system surveillance due to the selective targeting by HAART of activated $CD4^+$ T cells that harbor replicating viruses capable of inducing viral gene expression [9,13].

The reactivation of latent HIV-1 viral reservoirs through the combinatorial usage of compounds that inhibit repressive epigenetic markers, facilitate transcription factor binding, or remodel repressive nucleosomes, also known as the 'shock and kill approach', is an active area of current research to potentially eradicate HIV-1 [9,14]. Interestingly, the most effective agents capable of fully reactivating latent viral reservoirs do so via T cell activation-induced latent HIV-1 reactivation. Often used as positive controls in many HIV-1 latency reversal studies, compounds including the lectin phytohemagglutinin (PHA), the phorbol ester phorbol 12-myristate 13-acetate (PMA), the Ca^{2+} ionophore ionomycin (Io), and anti-CD3/anti-CD28 monoclonal antibodies (mAbs) have each been shown alone or in combination to efficiently reactivate latent HIV-1 viral reservoirs via T cell activation [15]. Indeed, any candidate latency reversal agent(s) incapable of inducing selective T cell activation of latently infected viral reservoirs will likely prove ineffective for clinical application. Interestingly, an increase in intracellular Ca^{2+} concentration is imperative for efficient T cell activation and PHA, PMA/Io, and anti-CD3/anti-CD28 mAbs invariably induce sufficient intracellular increases in Ca^{2+} concentration that activate signaling pathways to promote proviral transcription [15,16]. Intriguingly, PMA and Io have also been shown to induce parthenogenetic activation of mouse oocytes and PHA has been shown to promote meiotic maturation in mouse oocytes, implicating the induction of cellular stress as a common mechanism of action linking oocyte activation and latent HIV-1 reactivation [17–20].

The hypothesis

We propose the novel hypothesis that induction of cellular stress (e.g. increase in intracellular Ca^{2+} concentration, reactive oxygen species [ROS] generation, increase in AMP/ATP ratio) and the subsequent activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) represents a common mechanism of action linking the reactivation of latent HIV-1 in $CD4^+$ memory T cells (i.e. the "shock and kill" approach) and the physiological or artificial activation of mouse and human oocytes (i.e. the "shock and live" approach). Indeed, strikingly similar intracellular signaling mechanisms characterize both T cell activation-induced latent HIV-1 reactivation and sperm-induced oocyte activation, with PLC isoforms (PLCζ in sperm and PLCγ1 in T cells) hydrolyzing PIP2 to produce DAG and IP3, leading to the activation of PKC and inducing the release of Ca^{2+} from ER Ca^{2+} stores, respectively. A resulting Ca^{2+}-induced signaling cascade is initiated, leading to the activation of calmodulin (CaM) and several Ca^{2+}/CaM-dependent protein kinases that are essential for both T cell activation and oocyte activation. Additionally, compounds that have been shown to reactivate latent HIV-1 in $CD4^+$ memory T cells (e.g. PMA, ionomycin, metformin, bryostatin, resveratrol, JQ1, bortezomib) or artificially activate oocytes (e.g. PMA, ionomycin, ethanol, puromycin) alone or in combination have also been shown in various studies to activate AMPK (a master regulator of cellular metabolism) via stress-induced increases in intracellular Ca^{2+} concentrations, ROS generation, or an AMP/ATP ratio increase. Interestingly, mitochondrial function and ATP generation, which is enhanced by AMPK activation, is critical for both T cell activation and oocyte activation through mitochondrial accumulation at the immunological synapse and facilitation of Ca^{2+} oscillations through Ca^{2+} buffering, respectively. In addition to the AMPK kinase LKB1, CaMKK2, a Ca^{2+}/CaM-dependent upstream kinase of AMPK, is upregulated on T cell activation and is also present in mouse oocytes and persists until the zygote and two-cell stages, suggesting that certain cellular stress-inducing compounds and methodologies that induce latent HIV-1 reactivation and artificial oocyte activation likely do so via Ca^{2+}-induced AMPK activation. Also, because ROS has been shown to increase intracellular Ca^{2+} concentrations though modulation of ER Ca^{2+} release channels, an increase in the AMP/ATP ratio and/or subsequent ROS generation by compounds that have been shown to inhibit mitochondrial function may provide an additional mechanism through which such compounds may reactivate latent HIV-1 and facilitate oocyte activation. Interestingly, AMPK activation has also been shown to be a central mediator in the induction of meiotic resumption and maturation in mouse oocytes in preparation for oocyte activation and metformin, a mitochondrial inhibitor and AMPK activator, improves pregnancy rates during human *in vitro* fertilization procedures. As AMPK has been shown to activate PKC theta (a critical PKC isoform that activates transcription factors essential for latent HIV-1 reactivation including NF-kB, NFAT, and AP-1) on T cell stimulation, and knockdown of one of the catalytic AMPK subunits (AMPK α1) leads to a decrease in litter size and mitochondrial dysfunction in mouse oocytes, physiological or artificial induction of a cellular stress response and subsequent AMPK activation appears to represent a common mechanism facilitating both oocyte activation and latent HIV-1 reactivation.

Background discussion

AMPK, mitochondria, and oxidative phosphorylation

Expressed in a number of tissues including brain, liver, skeletal muscle, and cells of the immune and reproductive systems, AMPK

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