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Elimination of cancer stem cells and reactivation of latent HIV-1 via AMPK activation: Common mechanism of action linking inhibition of tumorigenesis and the potential eradication of HIV-1

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ABSTRACT

Although promising treatments are currently in development to slow disease progression and increase patient survival, cancer remains the second leading cause of death in the United States. Cancer treatment modalities commonly include chemoradiation and therapies that target components of aberrantly activated signaling pathways. However, treatment resistance is a common occurrence and recent evidence indicates that the existence of cancer stem cells (CSCs) may underlie the limited efficacy and inability of current treatments to effectuate a cure. CSCs, which are largely resistant to chemoradiation therapy, are a subpopulation of cancer cells that exhibit characteristics similar to embryonic stem cells (ESCs), including self-renewal, multi-lineage differentiation, and the ability to initiate tumorigenesis. Interestingly, intracellular mechanisms that sustain quiescence and promote self-renewal in adult stem cells (ASCs) and CSCs likely also function to maintain latency of HIV-1 in $CD4^+$ memory T cells. Although antiretroviral therapy is highly effective in controlling HIV-1 replication, the persistence of latent but replication-competent proviruses necessitates the development of compounds that are capable of selectively reactivating the latent virus, a method known as the "shock and kill" approach. Homeostatic proliferation in central $CD4^+$ memory T (T_{CM}) cells, a memory T cell subset that exhibits limited self-renewal and differentiation and is a primary reservoir for latent HIV-1, has been shown to reinforce and stabilize the latent reservoir in the absence of T cell activation and differentiation. HIV-1 has also been found to establish durable and long-lasting latency in a recently discovered subset of $CD4^+$ T cells known as T memory stem (T_{SCM}) cells. T_{SCM} cells, compared to T_{CM} cells, exhibit stem cell properties that more closely match those of ESCs and ASCs, including self-renewal and differentiation into all memory T cell subsets. It is our hypothesis that activation of AMPK, a master regulator of cellular metabolism that plays a critical role in T cell activation and differentiation of ESCs and ASCs, will lead to both T cell activation-induced latent HIV-1 reactivation, facilitating virus destruction, as well as "activation", differentiation, and/or apoptosis of CSCs, thus inhibiting tumorigenesis. We also propose the novel observation that compounds that have been shown to both facilitate latent HIV-1 reactivation and promote CSC differentiation/apoptosis (e.g. bryostatin-1, JQ1, metformin, butyrate, etc.) likely do so through a common mechanism of AMPK activation.

Introduction

Stem cells are endowed with both self-renewal and differentiation capabilities and are found to be smaller in number and more rare compared to fully differentiated cell types [1]. Embryonic stem cells (ESCs) are pluripotent, reside in the blastocyst, and possess the ability to self-renew and differentiate into all cell types of the developing embryo [1]. Adult or somatic stem cells (ASCs) however are undifferentiated, multipotent, typically reside in compartmentalized niches within an organ or tissue, and are capable of maintaining and repairing damaged resident tissues by giving rise to committed progenitors that later differentiate into mature functioning cell types [1]. In addition to self-renewal as a hallmark characteristic of stem cells, ASCs are often found in a quiescent (i.e. dormant state) state, likely facilitated by interactions of the stem cell with its micro-environmental niche [1].

Tumor cell populations have also been shown to exhibit significant heterogeneity and initiation of tumorigenesis has been recognized as mimicking organ formation in some aspects, implicating

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that a cellular hierarchy likely governs cancer initiation as well [2,3]. Indeed, within this heterogeneous tumor cell environment, a limited number of cells that possess variable self-renewal and differentiation capacities have been identified in several solid tumors as well as in hematologic diseases. Due to further similarities with ESCs or ASCs including the ability to produce a heterogeneous lineage of cancer cell types and to initiate new tumors that recapitulates the original tumor on serial transplantation, such cells have been termed tumor-initiating (TICs) or cancer stem cells (CSCs) [4].

CSCs (the designation adopted throughout the remainder of this manuscript) are thought to only comprise a small minority of the tumor cell population whereas the bulk of the tumor consists of non-tumorigenic cells with limited proliferative capacities [4]. Although many CSCs exhibit a potentially unlimited proliferative capacity, CSCs also utilize several cellular mechanisms characteristic of normal stem cells that render CSCs relatively resistant to chemotherapy and radiation therapy, including upregulation of anti-apoptotic genes and drug efflux transporters, enhanced DNA repair and anti-oxidative mechanisms, interactions within the CSC niche, and a slower proliferation rate [5,6]. Because mitotic cells have been shown to be more sensitive to radiation therapy than cells in the G0 or G1 phase of the cell cycle, CSC quiescence likely also imparts resistance to radiation therapy. Indeed, inhibition of self-renewal and forced differentiation of CSCs has shown some success in acute myelogenous leukemia (AML), gliomas, and glioblastoma [6,7].

Acquired immunodeficiency syndrome (AIDS), most often associated with infection by the retrovirus HIV-1, is typically a fatal condition characterized by a significant decrease in the levels of $CD4^+$ T cells, precipitating a loss of cell-mediated immunity and a resultant increase in risk for developing multiple opportunistic infections [8–10]. However, a number of anti-retroviral medications used in a combinatorial fashion (termed highly active antiretroviral therapy or HAART) have been successful in reducing the viral load of patients to below 50 copies/milliliter (i.e. below clinical assay detection limits) by targeting various stages of the HIV-1 life cycle in productively infected cells [8,11].

However, the establishment of durable and long-stating latency by replication-competent HIV-1 proviruses in $CD4^+$ memory T cells is primarily responsible for the rapid rebound in viral load after discontinuation of HAART [8,12]. Also, as HAART selectively targets replicating viruses capable of inducing viral gene expression in activated $CD4^+$ T cells, immune system surveillance, detection, and destruction of latently-infected HIV-1 $CD4^+$ memory T cells is insufficient for viral eradication, necessitating alternative means by which to reactivate latent HIV-1 reservoirs [8,12].

Such an approach, known as the "shock and kill" approach, is an active area of investigation in HIV-1 cure research. Several compounds have been developed and are in various stages of preclinical testing to selectively reactivate latent HIV-1 viral reservoirs without inducing global T cell activation. A number of signaling pathways and intracellular mechanisms that promote HIV-1 latency have been targeted by these compounds, including facilitation of transcription factor binding, remodeling of repressive nucleosomes, and inhibition of repressive epigenetic markers [8,13]. However, recent evidence indicates that a latency reversal agent will likely be clinically ineffective if it is incapable of inducing HIV-1 reactivation via T cell activation, a method through which positive controls reactivate viral reservoirs in latency reversal studies [8,14].

Similar to the episodic periods of quiescence, self-renewal, and differentiation that characterize CSCs, various subsets of $CD4^+$ memory T cells also display stem cell-like characteristics, including limited capacities for self-renewal and differentiation (Table 1). Central memory $CD4^+$ T cells (T_{CM}), which may be analogized to committed progenitors in stem cell lineages, have also been shown to reinforce HIV-1 latency by undergoing homeostatic proliferation without inducing T cell activation or latent HIV-1 reactivation [15]. Additionally, HIV-1 latency establishment and durability in recently discovered $CD4^+$ T memory stem cells (T_{SCM}), which display self-renewal and differentiation capabilities that more closely mirror undifferentiated CSCs, indicates that similar intracellular signaling mechanisms and cellular mediators likely characterize quiescence or latency in both CSCs and latent HIV-1 reservoirs and may be exploited to inhibit self-renewal and induce "activation", differentiation, and/or apoptosis in both cell types [16].

Table 1
Comparison of the similarities among Adult stem cells (ASCs), Cancer stem cells (CSCs), and T memory stem cells (TSCMs). Plus (+) sign indicates characteristic of each stem cell type.

	Adult stem cells (ASCs)	Cancer stem cells (CSCs)	T memory stem cells (TSCMs)
Self renewal	+	+	+
Differentiation	+	+	+
Multipotency	+	+	+
Quiescence	+	+	+

The hypothesis

We propose the novel hypothesis that because CSCs and latently-infected HIV-1 $CD4^+$ memory T cells exhibit several stem-cell like characteristics including self-renewal, differentiation, and quiescence/latency, AMPK activation, which is essential for T cell activation and differentiation of ESCs and ASCs, will also lead to CSC "activation", differentiation, and/or apoptosis as well as T cell activation-induced latent HIV-1 reactivation, facilitating viral cytopathic or cytolytic effects. Indeed, terminology adopted from HIV-1 cure research, the "shock and kill" approach, is equally applicable to methodologies designed to force CSC cell cycle re-entry and subsequent differentiation and/or apoptosis. Analogous to the ability of CSCs to self-renew and differentiate, giving rise to mixed cell lineages that include terminally-differentiated cells as well as cells with differing capacities for self-renewal, $CD4^+$ memory T cells also display a similar cellular hierarchy, with the recently discovered $CD4^+$ T_{SCM} cells exhibiting self-renewal and differentiation capacities similar to CSCs, giving rise to successively more differentiated T cell lineages that include $CD4^+$ T_{CM} cells, $CD4^+$ effector memory (T_{EM}) cells, and $CD4^+$ terminally-differentiated effector (T_{EFF}) cells. Recent evidence indicates that although T_{CM} cells are capable of limited self-renewal and differentiation and reinforce the latent reservoir via homeostatic proliferation, HIV-1 may preferentially establish a durable and long-lasting latency in T_{SCM} cells early during infection. AMPK activation has recently been shown to function as a metabolic block to the formation of iPSCs as well as promote mouse ESC differentiation into endoderm, as AMPK deletion inhibits ESC differentiation and exit from a pluripotent state. AMPK activation has also been shown to be critical in facilitating an effective immune response to bacterial and viral challenges and in the generation of cytotoxic $CD8^+$ memory T cells, a T cell subset that is essential for both cancer cell and pathogen elimination. As such, the activation of AMPK likely represents a central node for the application of a "shock and kill" approach to eliminate both CSCs and latent HIV-1 viral reservoirs. Moreover, compounds that induce or facilitate CSC differentiation and/or apoptosis and latent HIV-1 reactivation (e.g. bryostatin-1, JQ1, metformin, butyrate, etc.) likely do so via a common mechanism of AMPK activation.