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Reduced cancer mortality at high altitude: The role of glucose, lipids, iron and physical activity

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ABSTRACT

Residency at high altitude (HA) demands adaptation to challenging environmental conditions with hypobaric hypoxia being the most important one. Epidemiological and experimental data suggest that chronic exposure to HA reduces cancer mortality and lowers prevalence of metabolic disorders like diabetes and obesity implying that adaption to HA modifies a broad spectrum of physiological, metabolic and cellular programs with a generally beneficial outcome for humans. However, the complexity of multiple, potentially tumor-suppressive pathways at HA impedes the understanding of mechanisms leading to reduced cancer mortality. Many adaptive processes at HA are tightly interconnected and thus it cannot be ruled out that the entirety or at least some of the HA-related alterations act in concert to reduce cancer mortality. In this review we discuss tumor formation as a concept of competition between healthy and cancer cells with improved fitness – and therefore higher competitiveness – of healthy cells at high altitude. We discuss HA-related changes in glucose, lipid and iron metabolism that may have an impact on tumorigenesis. Additionally, we discuss two parameters with a strong impact on tumorigenesis, namely drug metabolism and physical activity, to underpin their potential contribution to HA-dependent reduced cancer mortality. Future studies are needed to unravel why cancer mortality is reduced at HA and how this knowledge might be used to prevent and to treat cancer patients.

1. Introduction

Humans living at moderate (above 1500 m) and high (above 2500 m) altitude (HA) are chronically exposed to hypobaric hypoxia and need to adapt to this environmental challenge. The altitude-dependent drop in barometric pressure and subsequent decrease of the ambient partial pressure causes hypoxemia and tissue hypoxia. When sojourners acclimatize, their bodies respond first with short-term adaptations (hours to days; e.g. increased basal ventilation [1], plasma volume reduction [2,3]) and later with long-term adaptations (weeks to months; e.g. increased erythropoiesis [4]) that are mainly driven by tissue hypoxia. The magnitude of response to HA is the key factor for physiological adaption or pathological mal-adaption, the latter resulting in hypoxia-related altitude illnesses [5–7]. The cellular response to hypoxia is driven by hypoxia inducible transcription factors (HIF) that are rapidly activated when intracellular oxygen levels decline [8-10]. Iron-dependent prolyl-hydroxylases (PHDs) regulate the stability of HIF-α subunits resulting in either protein degradation when oxygen is sufficiently available or stabilization when oxygen supply is low [11]. The detailed regulation of HIFs by oxygen availability and their down stream targets have been extensively reviewed [11–13]. During oxygen deficiency, hematopoiesis is driven by the renal hormone erythropoietin (Epo) that is oxygen-dependently regulated by HIF-2 [14] and promotes red blood cell production.

Epidemiological studies provide evidence that humans populating high altitude environments show reduced cancer mortality. Several possible explanations have been discussed in the past including elevated vitamin D synthesis due to higher background radiation [15]. However, the most adaptive processes at HA occur in response to reduced oxygen availability and this might be a much greater factor in cancer mortality. At the first glance, the observation of oxygen-dependent reduced cancer mortality at HA is counterintuitive because tumor hypoxia per se is rather a supportive factor for tumor growth and the development of aggressive phenotypes [16,17]. Both hypoxia-inducible factors 1 and 2 (HIF-1/2) have been reported to promote tumor growth and metastasis [18–20]. In contrast, some studies show

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that the loss of HIF-1α expression promotes kidney cancer [21] suggesting that at least in some tissues stabilized HIF is tumor suppressive. Recent studies analyzed evolutionary selected variants *EGLN1* (encoding for PHD2) and *EPAS1* (encoding for HIF-2α) genes in Tibetans and reported association of these variants with increased lung [22] and gastric [23] cancer risk. These HA-adapted variants of *EGLN1* with D4E and C127S polymorphisms increased PHD2 activity and promote HIF-α degradation [24,25] suggesting that HIF stabilization at HA might contribute to reduced incidence/mortality of at least some types of cancer. In this review we briefly summarize the results of epidemiological and animal studies and discuss mainly oxygen-based mechanisms that may account for reduced cancer mortality. It should be mentioned that "mortality" is a clinical relevant outcome but does not further explain at which steps during the course of cancer disease (incidence, progression, dissemination, response to therapy) exposure to HA has affected and altered.

2. Epidemiology

2.1. Human Studies

In 1974/75 an inverse relationship of HA and leukemia cancer mortality in humans was reported for the first time [26–28]. These studies were followed by additional studies within the last decades that considered potential cofounders (such as environment and socio-economic status) and confirmed these findings [29–35]. Although overall cancer mortality negatively correlates with HA [31], site-specific cancer seem to respond differently to HA. While lymphoma, breast [36], lung, cancers of tongue and mouth or larynx [29,35] display reduced mortality at HA, liver and cervix mortality showed no difference between low and high altitude. As expected, mortality from melanoma was increased due to the higher background radiation [37]. Very recently, it has been shown that highlanders display a reduced incidence of lung and breast cancer [38] supporting earlier observations that HA is indeed involved in prevention of tumorigenesis.

2.2. Animal Studies

Reduced cancer mortality at HA is not unique to humans but has been observed in mice exposed to very high altitude (4540 m) for a prolonged period of time after exposure to sub-lethal levels of x-rays resulting in reduced incidence of tumor formation [39]. Additionally, the incidence of spontaneous leukemia is reduced at HA [40] but spontaneously forming pulmonary tumors display a higher incidence at HA [41]. Back in the 1980s, studies in several rat and mouse tumor models demonstrated reduced primary tumor growth and metastatic spread as well as improved response to therapeutic treatment at HA [42–44]. A more recent study showed reduced tumor incidence not only in two spontaneously developing tumor mouse models, namely $p53^{-/-}$ and $APC^{Min/+}$, but also in a chemically induced skin cancer model in mice exposed to 10% normobaric oxygen [45] corresponding to an extreme altitude of approximately 5500–6000 m above sea level [12]. With their experimental setup, the latter authors prove that reduced oxygen levels protect from oncogenic events and tumorigenesis matching the epidemiological findings of Simeonov and Himmelstein [38].

3. Cancer and adaptation

Theoretically, cancer cells can be considered to be evolutionary selected cell lineages that have escaped control of replication and cell death and meet the traditional characteristics of minimal Darwinian populations, namely variation, selection and inheritance [46]. As a consequence, the evolutionary process of tumor formation, progression and metastasis depends on the nature of the niche that is populated by cancer cells and their ability to compete for resources with healthy cells within the same niche. Natural selection demands genotypes that differ in fitness to result in improved reproduction success. Although oncogenic events are commonly assumed to increase cellular fitness, DeGregori [47] suggests a model of adaptive oncogenesis, in which genetic variations rarely result in advantageous traits in healthy (and young) populations of (stem) cells, since they always display a high degree of fitness to maintain tissue integrity and this successfully competes against somatic cancer cell evolution [47]. Cell age and/or damaging insults reduce cellular fitness and change the adaptive landscape due to accumulation of mutations and alterations in the microenvironment, both promoting selection of adaptive oncogenesis events [47]. An example in relation to cancer at HA is melanoma that is increased due to increased radiation exposure [37] resulting in increased damage of epidermal cells and consequently the reduction in cell fitness. In the light of this hypothesis, we discuss below reduced cancer mortality and incidence at HA as a competitive mechanism between cancer and healthy cells. We suggest that HA increases fitness of healthy cells and/or modifies the tumor microenvironment resulting in adverse conditions for tumor cell development and expansion. Other diseases (e.g. stroke and cardiovascular diseases) display also a link between high altitude and reduced mortality [48] supporting our assumption. As a matter of fact, the metabolic syndrome, diabetes type 2 and obesity are cancer risk factors [49,50] and have a lower prevalence in humans populating elevated areas [51–53]. In the next sections, we consider cell biological and metabolic alterations at HA that might pose a bottleneck for emerging tumors in humans living at higher elevations.

3.1. Metabolic alterations

3.1.1. Glucose and glutamine metabolism

The competition for nutrition in a resource-restricted environment may result in different metabolic pathways being susceptible to alterations that might occur at HA. The most prominent metabolic reprogramming in tumor cells is the "Warburg effect" resulting in aerobic metabolism of glucose and increased lactate production – even when sufficient oxygen is available [54]. A recent review summarizing tumor metabolism and discussing metabolites that limit tumor progression as potential therapeutic targets suggested that neither ATP nor NADPH may limit tumor proliferation [54]. However, restoration of tricarboxylic acid (TCA) cycle metabolites and the synthesis of nucleotides may be a limiting factor in tumor progression due to the high demand for DNA synthesis in proliferating cells. Glucose and/or glutamine (depending on tumor type and microenvironment) refuel the TCA cycle and provide substrates for the nucleotide metabolism [55,56]. Consequently, both, glucose and glutamine may limit tumor progression when insufficiently supplied to cancer cells (e.g. when healthy cells increase their demand, or when less substrate is provided from blood). As expected, hyperglycemia correlates with an increased risk of tumorigenesis [57] and because highlanders have reduced plasma glucose and glutamine concentrations (at least in acute and prolonged exposure to HA [58,59]) this restriction possibly contributes to reduced cancer mortality [58,60]. Blood glucose levels are mainly controlled by the liver and partially by kidneys [61,62] and release of hepatic glucose is stimulated by glucagon, fatty acids and catecholamines but suppressed by insulin [61]. Accordingly, as Andean highlanders display higher glucagonemia and lower glycemia, their exposure to HA might reduce hepatic glucagon sensitivity resulting in reduced glucose release from the liver. In cancer cells, HIF-1 increases the expression levels of glucose transporter 1 and 3 (GLUT1/3) to facilitate glucose uptake [63]. However, adipocytes respond similarly to hypoxia with increased GLUT1/3 expression levels [64]. Furthermore, acclimatization to HA increases the uptake and metabolism of blood glucose by human skeletal and heart muscle [61], facilitated by a hypoxia-driven increase in HIF-1 as well as GLUT4 expression levels in human muscle cells [61,65].