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Abstract

Humans living at high altitude (HA) are exposed to chronic (hypobaric) hypoxia. Despite the permanent stress of hypoxic exposure, humans populating high altitude areas have reduced cancer mortality over a broad spectrum of cancer types. In fact, the majority of the physiological adaptive processes at HA occurring in response to hypoxia might be the driving force for reduced cancer mortality at HA. In this review, we summarize epidemiological and animal studies that compare cancer incidence and cancer mortality between high and low altitude or between hypoxia and normoxia, respectively. We discuss the potential role of oxygen-independent and oxygen-dependent mechanisms that might contribute to reduced cancer mortality at HA. Reactive oxygen species (ROS) and their detoxification as well as the hypoxia-inducible factors (HIFs) are especially promising targets and may be related to why cancer mortality is reduced at HA. Additionally, we briefly discuss two aspects with a proven impact on tumorigenesis, namely the immune system and tumor surveillance as well as HA induced metabolic changes. Further animal and clinical studies are clearly needed to explain why cancer mortality is reduced at HA and to decide if HA or hypoxia-based therapeutic approaches could be implemented for cancer treatment. However, exposure to HA activates multiple adaptive mechanisms (oxygen-independent and dependent) sharing common pathways as well as activating counteracting pathways, which complicate the identification of specific HA-induced mechanisms of tumor suppression.

1 Introduction

Living at high altitude (HA) and the associated hypobaric hypoxia (Burtscher 2014) requires considerable adaptation to a potentially inhospitable environment. However, even adapted highlanders are not completely protected from this physiological challenge and may develop altitude related diseases such as chronic mountain sickness. Notably other diseases like diabetes and obesity occur less frequently in highlanders. Surprisingly, it has been reported within the last decades that humans living at high altitude show either reduced cancer incidence or mortality. That suggests that HA exposure may have an impact on distinct cancer phases; namely initiation (incidence) or proliferation and metastasis (mortality). Here, we summarize the results of epidemiological and animal studies and discuss mechanisms that may account for a possible benefit of high altitude living in altering cancer incidence or mortality.

2 Human Studies

In 1974 and 1975, three studies reported an inverse relationship of HA and cancer mortality in humans (Burton 1975; Eckhoff and others 1974; Mason and Miller 1974). However, these early studies did not consider potential confounders such as industrialization, urbanization, economic status and ethnicity, which could cause false correlations between cancer and HA. In further published work over the next several decades, several studies that corrected for potential cofounders have confirmed these findings (Amsel and others 1982; Burton and Cornhill 1977; Hart 2010; 2011a; 2011b; Hart and Hyun 2012; Van Pelt 2003; Weinberg and others 1987). A recent study compared cancer mortality for Caucasians living at high and low altitude counties in the US (Hart 2011a) and showed a clear correlation between HA and reduced overall cancer mortality. However, types of cancer may respond differently to HA. Indeed, several reports that analyzed site-specific cancer mortality suggested that mortality from lymphoma, breast (Youk and others 2012), lung, tongue, mouth and larynx (Amsel and others 1982; Van Pelt 2003) is reduced whereas other cancers such as liver and cervix remain unaffected or are even increased (e.g. melanoma due to the higher

background radiation (Aceituno-Madera and others 2011; Boscoe and Schymura 2006); placental choriocarcinoma (Reshetnikova and others 1996)) (see also table 1). Additionally, carotid body tumor (paraganglioma) incidence is increased at high altitude (Arias-Stella and Valcarcel 1973; Astrom and others 2003). Although hypoxia causes chief cell hyperplasia (Arias-Stella and Valcarcel 1976), carotid body tumors have less malignant behavior than those tumors at low altitudes. and the ratio of female to male patients with these tumors increases from 2:1 at low altitude to 8.3:1 at HA (Rodriguez-Cuevas and others 1998).

In 2015, Simeonov and Himmelstein particularly analyzed the association of HA and cancer incidence and reported decreasing lung and breast (but not colorectal and prostate) cancer incidence with elevation (Simeonov and Himmelstein 2015) suggesting that HA protects cells of at least some tissues from undergoing malignant transformation. However, the Simeonov and Himmelstein study defined smokers (the biggest risk factor for lung cancer development) as individuals consuming more than 100 cigarettes in their lifetime without further differentiating between moderate and heavy smokers (Simeonov and Himmelstein 2015). The number of daily cigarettes clearly correlates with lung cancer risk (Law and others 1997) and if smoking habits (i.e. number of cigarettes per day) substantially differed between high and low altitude counties the results of this study could be biased. Nevertheless, the effect size of lung cancer incidence is possibly strong enough to statistically justify the observed relationship between lung cancer incidence and HA.

3 Animal Studies

In 1970 and 1974, Mori-Chavez et al. exposed mice to very high altitude (4,540 m) for a prolonged period of time after exposure to sub-lethal levels of x-rays and found a reduced overall incidence of neoplasms (Mori-Chavez and others 1970; 1974), especially thymic lymphoma and granulocytic leukemia, but an increased incidence of lung cancer compared to low altitude controls (Mori-Chavez and others 1970; 1974). However, the reduced life span of mice exposed to HA (Mori-Chavez and others 1970; 1974) might indirectly cause a reduced frequency of neoplasms because the mice could have died before a neoplasm developed. Similar to x-ray induced malignancies, the spontaneous onset of leukemia in C58 mice declines with increasing altitude (Mori-Chavez 1958) whereas spontaneous lung cancer

incidence increases (Mori-Chavez 1962). The difference in lung cancer incidence between human highlanders (reduced at HA) and mice (increased at HA) might be indeed related to cigarette consumption suggesting that smoking habits at HA should be considered. In addition to increased lung cancer incidence, metastasis in a model of intravenously injected ascites carcinoma cells increases at HA (Mori-Chavez and Salazar 1965). In contrast, it was shown in rat and mouse models that primary tumor growth rate as well as metastasis rate are reduced (Kulish 1987) and that the efficacy of chemotherapy is increased (Kulish 1985; Kulish and Galkina 1983) at HA, Recently, Sung et al. studied tumor incidence in two mouse models of spontaneous cancer, namely $p53^{-/-}$ and $APC^{Min/+}$, as well as in a chemically inducible skin carcinogenesis model. They observed delayed tumor formation in normobaric hypoxic mice (10% oxygen; equivalent to an extreme altitude of approximately 5,500 – 6,000 meters above sea level) (Sung and others 2011) under standardized laboratory conditions independent of other environmental factors (e.g. atmospheric pressure, radiation etc.). In the thymus of hypoxia-exposed mice reduced levels of oxidative DNA damage were observed. These data in rodents directly link oxygen concentration and tumor incidence giving strong support to the epidemiological data in humans. Another link of oxygen availability and tumor incidence has been reported in hypoxia-resistant naked mole rats that live under extreme hypoxic conditions (Schumacher and others 2015) and are able to sustain several minutes of total anoxia (Park and others 2017). They have been long thought to develop no tumors at all (Schumacher and others 2015), although some cancer cases have been reported recently (Delaney and others 2016; Piersigilli and Meyerholz 2016). Nevertheless, their very strong protection from cancer might be dependent on oxygen-related metabolic reprogramming (Park and others 2017), which will be briefly discussed below.

4 High Altitude Dependent Mechanisms of Cancer Incidence and Mortality Reduction

4.1 Oxygen independent environmental factors

The causes of reduced cancer incidence or mortality at HA are difficult to identify and might be quite tumor specific. HA positively correlates with ultraviolet-B (UV-B) exposure and negatively with oxygen levels and pollution, all of which have been discussed as causative or contributory. It has been hypothesized (Hayes 2010) that reduced cancer mortality at HA (e.g. lymphoma, breast, lung, etc. (Boscoe and Schymura 2006)) might be driven by UV-B dependent vitamin D production. The beneficial effects and the anti-carcinogenic properties of solar UV-B and increased vitamin D production have been nicely reviewed elsewhere (Bikle 2016). The vitamin D receptor is frequently (but not ubiquitously) expressed in tumor cells and the loss of its expression during tumor evolution is a poor prognostic factor (Bikle 2016; Narvaez and others 2014; Santagata and others 2014). Clinical trials suggest an inverse association of colorectal cancer incidence and vitamin D intake and/or serum levels (Bikle 2016). However, colorectal cancer incidence did not correlate with HA in a recent study (Simeonov and Himmelstein 2015). Evidence for and against vitamin D dependent protection from breast cancer has been reported (Bikle 2016) supported by a mild to moderate association of breast cancer incidence and HA (Simeonov and Himmelstein 2015). Finally, no effect of vitamin D as well as no association to HA has been shown in prostate cancer (Bikle 2016; Simeonov and Himmelstein 2015). Consequently, a protective role of elevated vitamin D levels against cancer mortality seems possible, but remains to be proven.

Apart from influences of vitamin D, other parameters vary with altitude, such as radon and airborne particulate matter. Particulate matter concentration generally declines with altitude and has been defined as a group 1 carcinogen by the International Agency for Research on Cancer (IARC 2013) to increase lung cancer incidence (Hamra 2014). However, the association of lung cancer incidence and high altitude seems to be independent of potentially carcinogenic variables such as particulate matter, radon, UV-B, and other oxygen independent factors as shown in a statistical model that estimated the odds if the replacement

of HA with other environmental factors (e.g. particulate) is superior (Simeonov and Himmelstein 2015).

Inextricably linked to living at high altitude is the mild hypocapnic respiratory alkalosis that arises from the ventilatory response and adaptation to hypoxia. The higher the resident altitude the greater is the hyperventilation and associated alkalosis. A considerable amount of cellular and animal work has shown that various means of imposing mild to moderate alkalotic conditions, either by base (bicarbonate) supplementation or lower ambient CO_2 lead to reduced carcinogenesis (Ibrahim-Hashim and others 2012), decreased development and spread of metastases (Azzarito and others 2016; Ibrahim Hashim and others 2011; Robey and Nesbit 2013), and greater efficacy of certain cancer drug therapies (Tavares-Valente and others 2013). Cancer cells are highly metabolic and hypoxia resistant, in part mediated by HIF induced changes in metabolism. These include a switch to a very high rate of oxidative and non-oxidative glycolysis. This well-recognized Warburg effect generates large amounts of CO_2 and lactic acid in supplying cancer cells with short carbon chain substrates for protein, lipid and nucleic acid synthesis. As part of this strategy, malignant cells must dispose of these acids by active transport into the extracellular fluid (ECF) by up-regulation of numerous membrane acid-base transporters, such as the monocarboxylate transporter (MCT-1) for lactate and the tumor-associated carbonic anhydrase (CA) isozymes, CA IX and XII (Swenson 2016). In addition to disposal of these acids to limit end-product metabolic inhibition, acidification of the ECF acts to reduce tumor surveillance and killing by host immune cells discussed below. Thus it can be postulated that the relative greater ECF alkalinity at high altitude may favorably suppress malignant cell initiation and spread, as was postulated by (Burton 1975) but without defining how this might occur.

4.2 Oxygen and Reactive Oxygen Species (ROS)

Simeonov and Himmelstein (2015) attributed their observation of reduced lung cancer incidence in humans to hypobaric hypoxia and even hypothesize that oxygen *per se* (due to the formation of reactive oxygen species ROS) is carcinogenic in lung tissue as the organ that experiences the highest levels of oxygen as the site of oxygen uptake. What is surprising about these human data is that other organ sites of cancer, which physiologically have lower

PO_2s than the lung owing to their position in the oxygen cascade from the environment to the periphery, are not protected.

Similarly, the authors of the aforementioned study of hypoxia-exposed mice with reduced cancer incidence hypothesized that physiological oxygen levels may be carcinogenic due to the formation of reactive oxygen species (ROS) resulting in fatal DNA damage (Sung and others 2011). To support their interpretation, they discuss the reported increased cancer incidence of premature infants that received ventilatory support with excessive oxygen (Sung and others 2011) suggesting that at least very high concentrations of oxygen in predisposed subjects may be carcinogenic. However, hyperbaric oxygen therapy is occasionally used in cancer therapies (e.g. breast cancer), and so far no evidence of oxygen-dependent increased risk of tumor recurrence or stimulation of tumor progression has been found (Moen and Stuhr 2012). In fact, Hatfield et al. showed that increased inspired oxygen (hyperoxia) decreases intratumoral hypoxia resulting in decreased immunosuppression and enhanced recruitment of anti-tumorigenic T-cells to the tumor microenvironment (Hatfield and others 2015). As a consequence, the survival of mice was prolonged and both, primary (lung) tumor and (breast) metastasis regressed with oxygen supplementation (Hatfield and others 2015). Importantly, serum ROS levels are even increased instead of reduced upon acute exposure to HA (Murray and Horscroft 2016; Sinha and others 2009) and the ROS levels of highlanders chronically exposed to ambient hypoxia may exceed those of lowlanders (Sinha and others 2009), although in this study the low- and highland subjects may have been of different ethnicity.

Clearly, ROS are involved in oxidative stress and DNA damage and thus may result in oncogenesis, but a balanced level of ROS is essential to mediate cell physiological responses (Sabharwal and Schumacker 2014). To promote their damaging potential ROS levels have to exceed and overcome cellular anti-oxidant scavenging systems, which involve superoxide dismutases, catalase, and glutathione peroxidase to name but a few. In fact, the oxidative defense system displays a higher level of activity in subjects populating HA regions (Sinha and others 2009), most likely in response to enhanced ROS formation. Therefore, it cannot be excluded that improved ROS detoxification instead of reduced oxygen-dependent ROS generation rate accounts for hypoxia-dependent reduced tumor incidence at HA.

4.3 Oxygen and The Hypoxia Inducible Factor (HIF) Pathway

With increasing altitude the barometric pressure decreases, resulting in reduced inspired oxygen partial pressure (pO_2). Consequently, alveolar oxygen partial pressure is reduced – approximately 50% at an altitude of 5800 meters (Peacock 1998). At sea level, the arterial oxygen partial pressure reaches almost alveolar levels during gas exchange. However, the reduced oxygen partial pressure at very high altitude is insufficient to fully oxygenate and equilibrate the blood with alveolar air during its passage through the pulmonary capillaries. Diffusion limitation and impaired gas exchange further increase the difference between blood oxygen partial pressure at sea level and at high altitude (Peacock 1998). At approximately 5800 m the arterial oxygen partial pressure nearly equals the mixed venous oxygen partial pressure at sea level. The difference between arterial and mixed venous pO_2 is much smaller at high altitude (35 to 21 mmHg), respectively when compared to sea level (100 to 40 mmHg) (Peacock 1998). Despite physiological compensations such as increased cardiac output, ventilation, hemoglobin, and angiogenesis via VEGF (Paralikar and Paralikar 2010), nonetheless there remains a degree of reduced oxygen availability to the tissues (Gassmann and Muckenthaler 2015). In fact increased cardiac output as a short-term physiological adaptation reduces the passage time of blood through the lung capillaries impairing oxygen uptake by erythrocytes. Consequently, tissue (including tumors) experience reduced oxygen levels at high altitude.

At the cellular level the tightly oxygen-regulated, heterodimeric hypoxia-inducible factors (HIFs) quickly and precisely respond to the oxygen availability and regulate a large number of cellular responses to hypoxia by up- and down-regulating the transcription of over 1000 genes involved in hypoxia tolerance (Ema and others 1997; Flamme and others 1997; Semenza and others 1991; Semenza and Wang 1992; Tian and others 1997). Prolyl-hydroxylases (PHDs) are oxygen-sensitive hydroxylases that regulate the stability of HIF-alpha subunits resulting in rapid protein degradation when oxygen is sufficiently available (Kaelin and Ratcliffe 2008). At the first glance, the observation of oxygen-dependent reduced cancer mortality (or incidence) at HA is surprising because tumor hypoxia *per se* is rather a supportive factor for tumor growth and the development of aggressive phenotypes in many cancers (Brown 2007; Vaupel and Mayer 2007). In combination with tumor-associated or

therapy-induced anemia, aggressive phenotypes develop even faster and HIF1 and 2 have been reported to promote tumor growth and metastasis (Liu and others 2015; Semenza 2010; Zhao and others 2015).

Although HIF1 and 2 regulate many similar genes, both transcription factors have been also shown to regulate distinct target genes and cellular pathways (Loboda and others 2010), which seems to be also reflected by their site-specific role in tumorigenesis. As an example, HIF1 critically contributes to breast cancer malignancy and HIF1 inhibition reduces breast cancer metastasis (Wong and others 2012). In contrast, HIF2 has been reported to play a critical role in clear cell renal cell carcinoma (Biswas and others 2010; Kondo and others 2003; Raval and others 2005) and might be a potential therapeutic target (Cho and Kaelin 2016). However, other groups have argued that HIF1 rather than HIF2 promotes renal carcinogenesis (Fu and others 2011; 2013; Xu and others 2010) emphasizing the complexity of the disease. It has been also reported that loss of HIF-1 expression may promote renal cell carcinoma proliferation (Shen and others 2011) suggesting that at least in some tissues stabilized HIF might be tumor suppressive. In fact, a study reported that evolutionary selected variants of HIF pathway genes – namely *EGLN1* (encoding for PHD2) and *EPAS1* (encoding for HIF-2 alpha) – in Tibetans have a role in this population's higher lung cancer risk (Lanikova and others 2016). High altitude-adapted variants of EGLN2 with D4E and C127S polymorphisms increase PHD2 activity leading to HIF-alpha degradation under hypoxic conditions (Lorenzo and others 2014; Simonson and others 2010). These data suggest, that the stabilization of HIF-1 and HIF-2 in hypobaric hypoxia at HA might contribute to reduced mortality in at least some types of cancer.

4.4 Tumor Metabolism and the Organism

Adaptations to acute and chronic HA result in hypoxia-driven metabolic changes including those that involve glucose and lipid metabolism. Obesity and type 2 diabetes mellitus are metabolic disorders associated with an increased cancer risk (Arnold and others 2016; Goday and others 2015), but are less prevalent in humans living at HA (Diaz-Gutierrez and others 2016; Woolcott and others 2014; Woolcott and others 2016). Highlanders have reduced plasma glucose concentrations (Augustin and others 2015) that might protect them from hyperglycemia-associated increased cancer risk (Duan and others 2014). Additionally,

lipids are essential for energy homeostasis, membrane assembly and regulation of cancer-associated signaling pathways (Chen 2011; Fritz and Fajas 2010; Hashmi and others 2015). Since high plasma lipid concentrations are associated with increased cancer risk (Allott and Hursting 2015; Gong and others 2014), reduced plasma fatty acid concentrations in highlanders (Woolcott and others 2015) as well as their lower cholesterol concentrations may contribute to the reduced cancer mortality at HA. A more detailed consideration of metabolic alterations in tumor cells as well in healthy tissue at HA and their influence on cancer mortality has been recently published (Thiersch and others 2017).

4.5 The Immune System and Tumor Surveillance

The many and variable responses of the neuro-immune system to acute and chronic hypoxia are predicted to have a possible impact on tumor incidence and mortality. Hypoxia has significant effects on infection risks and prevalence, both negative and positive (for review see (Mazzeo and Swenson 2014). In part, this is by modulation of the innate and acquired arms of the immune system, the most interesting leading to a much-reduced risk of tuberculosis. The immune system additionally can recognize neoantigens on malignantly transformed cells as foreign and act to repress tumor growth and metastatic spread. It is reasonable to ask whether the immune-modulating effects of hypoxia on microbial pathogens might also extend to the immunosurveillance of cancer. Dendritic cells and lymphocytes are critical elements in host defense against malignancy and the functions of both are altered with hypoxia. Although hypoxia in general may depress lymphocyte-mediated functions involved in cancer recognition, hypoxia and HIF-1 alpha stimulation of natural killer cell tumor surveillance (Groth and others 2011; Wang and Wu 2009) may be more important and underlie the epidemiological findings of reduced cancer at high altitude. Cancer immune-editing, i.e. the different three stages of tumor cell elimination equilibrium and escape (3E) (Swann and Smyth 2007), shows that the immune system is a double-edged sword during tumorigenesis. Initially eliminating malignant cells and keeping the myriad immune cells in equilibrium, the immune system actually supports tumor malignancy by chronic inflammation after cancer cells have escaped immunosurveillance. It might be possible that hypoxia enhances the efficacy of the immune system prior to tumor formation (improved elimination) and/or reduces chronic tumor inflammation after tumor formation.

5 Future Work and Conclusions

HA potentially impacts on both, cancer incidence and mortality. Patients with prolonged survival and reduced mortality, due treatments delaying the progression rather than curing the disease, are over-represented in prevalence analyses. That might also happen if HA reduces tumor malignancy and metastasis and increases patient survival. Thus, separating these different cancer phases can be complicated in epidemiological analyses.

In our opinion, there is currently little evidence that ambient oxygen (21%) at sea level *per se* is carcinogenic – at least in healthy subjects - as several oxygen detoxification pathways keep ROS formation tightly balanced. In patients and animals with genetic (or other health-related) predisposition, oxygen may contribute to cancer formation – when ROS are excessively produced or not sufficiently detoxified. The data on ROS levels in hypoxia exposed animals and in humans populating elevated areas are contradictory and more information particularly about ROS formation and detoxification in cancer patients at HA is required. In the light of the aforementioned publication by Lanikova and colleagues (Lanikova and others 2016), the HIF-pathway may be involved in HA-dependent reduced cancer incidence. Since the control of ROS formation is also regulated by HIFs, their interactions may offer more insight into differences in cancer biology HA. A better understanding of the role of hypoxia-mediated changes in metabolism as well as in immune system function in cancer surveillance may also be important in explaining the reduced incidence of many cancers and differences in tumorigenesis at HA.

In conclusion, exposure to HA has been shown to reduce cancer incidence as well as mortality and reduced oxygen levels may at least partially account for these effects. However, the mechanisms that protect from tumor initiation and ameliorate disease progression remain to be fully identified.

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