MELANOMA OCCURRENCE IN OUTDOOR ATHLETES: CDC25 PHOSPHATASES AS A PROMISING TARGET

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Review paper

Abstract
Melanoma represents one of the most aggressive skin tumors, characterized by a low responsiveness to conventional therapies. The most important risk factor for developing malignant melanoma is the exposure to UV rays, because of their genotoxic effect. Outdoor athletes are exposed to considerable solar UV rays and probably have a higher risk to develop skin cancer. Epidemiological studies showed that extreme UV exposure in winter and summer outdoor sports, was associated with an increased prevalence of precancerous skin lesions and melanoma and non-melanoma skin cancer. Currently, targeted therapy and immunotherapy are the new standard for melanoma treatment, even though melanoma has a high tendency to relapse, because of acquired drug resistance. Therefore, a great effort has been devoted to discover new molecules helpful in the treatment of this cancer, acting through the modulation of key pathways involved in drugs resistance. CDC25 phosphatases, key regulators of cell cycle and overexpressed in several tumors, represent promising target for anticancer treatment. Hence, the study of the effects of new CDC25 inhibitors in melanoma cells, could be helpful for finding other possible targets for melanoma treatment.

Key words: *Melanoma; outdoor athletes; CDC25 inhibitors.*

Introduction

Melanoma is an aggressive and deadly tumor with a high tendency to relapse and high metastasis rate (Uzdensky et al., 2013; Vanella et al., 2019). At the start of 21st century, while the incidence of many tumor types is decreasing, melanoma occurrence continues to increase. Although it represents only 5% of all skin cancers, it is responsible for about 75% of deaths in this disease. Survival of patients with advanced metastatic melanoma is very low,as it rapidly spreads due to infiltration of malignant cells into tissues, lymphatic and blood vessels (Uzdensky et al., 2013; Rastrelli et al., 2014). Melanoma is considered as a multi-factorial disease arising from an interaction between environmental factors and genetic predisposition (Avagliano et al., 2019; Lugović-Mihić et al., 2019; Ruocco et al., 2019; Avagliano et al., 2020). Ultraviolet radiations are the most important environmental risk factors as UV rays causes genetic changes in the skin, impairs immune function, increases the local production of growth factors, and induces the formation of DNA-damaging reactive oxygen species that affect keratinocytes and melanocytes. Development of cutaneous melanoma is primarily associated with intermittent but intense episodes of UV light exposure and sunburns, especially in childhood. In addition, the artificial UV exposure, through the use of indoor tanning beds, may play a role in the progress of this tumor (Rastrelli et al., 2014; Seidl-Philipp et al., 2019). Moreover, epidemiologic data suggest that people with a prolonged and intense UV rays exposure during work and outside activities, such as outdoor workers, military personal and athletes, have an increased risk to develop skin cancer (Harrison et al., 2009; Modenese et al., 2018).

Melanoma occurrence and outdoor sports

Physical exercise has been shown to be a safe intervention to improve physical functioning, fatigue, and quality of life in patients with cancer, and may also modify the tumor microenvironment. Observational studies suggest correlations between self-reported physical activity and reduced risk and recurrence across many cancer types; however, two tumors, such as melanoma and prostate cancer, have shown an association between physical activity and a higher risk of cancer. In particular, for melanomathe UV radiation (UVR) due to sun exposure during physical exercise has been established as the most important risk factor for melanoma occurrence (Warner et al., 2019). Outdoor athletes are exposed to solar UVR and probably are at higher risk for developing skin cancer. In addition to sun exposure, the immunosuppression induced by physical exercise may increase the risk for skin cancer in athletes (Moehrle et al., 2008). Some athletes are exposed to increased amounts of UV rays and are at increased risk of sunburn because of their training schedules and conditions. Summer sports are frequently conducted during peak UVR exposure

hours, with uniforms that do not provide adequate sun protection. In winter sports, direct radiation occurs from the sun, often at higher altitudes, and from reflection off the snow and ice, to exposed areas such as the face and hands (Harrison et al., 2009). Regarding to summer sports, surfing is one of the most popular outdoor aquatic activities in Australia. As a result, the expected risk of skin cancer in surfers, due to long periods of exposure to ultraviolet radiation, wearing less clothing and reflection from water, is of great concern. A study by Climstein et al. (2016) found alifetime prevalence for melanoma to be 1.4% within a surfing population. Mountaineering, tennis, and running are among the most popular outdoor activities. Several studies showing the appearance of skin melanomas in marathon runners and cyclists support the idea that these activities may increase the risk of skin cancer. The sport activity with the highest measured UV exposure is represented by the mountaineering (Serrano et al., 2011). In the mountain environment professional outdoor workers such as mountain guides as well as recreational alpinists encounter increased erythemogenic UV radiation due to the effects of altitude and reflection from snow and ice. Therefore, professional mountaineering was associated with an increased prevalence of precancerous skin lesions and skin cancer (Moehrle et al., 2003; Moehrle et al., 2008). Regarding to running, regular moderate exercise is considered to improve health, while high-intensity long-term exercise may have harmful effects. In a recent study, it has been raised the question of whether marathoners, and even more ultramarathoners, have an increased risk of developing skin cancer, in particular malignant melanoma.

Sun exposure, frequent sunburns, the development of new nevi and lentigines in sun exposed areas, the presence of atypical nevi and changing nevi are several risk factors that may put marathon runners at the condition of developing melanoma. Furthermore, immunosuppression due to prolonged endurance exercise may increase the risk of melanoma (Richtig et al., 2008). Tennis is a popular outdoor sport with extended play intervals and its players present a highly significant sun damage and future skin cancer diagnosis risk. Some studies have shown that median daily UVR exposure of tennis players can quickly exceed the levels that lead to extreme sunburn and sun damage. Most recently, Downs et al. (2019)have detailed how Olympic athletes participating in daytime sports events, such as tennis, are highly susceptible to damaging levels of solar UVR exposure (Igoe et al., 2019). Another popular outdoor activity is cycling, used for recreational, transportation and competitive purposes. While cardiovascular and other health benefits of cycling are well documented, it is likely that cyclists are potentially exposed to harmful doses of UV radiation while pursuing their activity. Case reports of melanoma among cyclists support that this activity may increase the risk of skin cancer (Kimlin et al., 2006).

DC25 phosphatases: a promising target for melanoma treatment

In the recent years, immunotherapy with immune checkpoint inhibitor antibodies, and targeted therapy, became the new standard for melanoma treatment (Ruocco et al., 2019), and these advances have substantially improved survival rates. In particular, BRAF and MEK inhibitors have been used in targeted therapy, and most responses to these remain transient, as a result of primary or acquired resistance. Therefore, to overcome this resistance, promising treatments are the targeted therapy combined with immunotherapy and sequencing approaches. Furthermore the combination of different drugs that simultaneously inhibit multiple pathways involved in the pathogenesis and progression of melanoma, could represent an additional therapeutic approach to overcome the therapy resistance (Kakadia et al., 2018; Vanella et al., 2019).

Promising targets for anticancer therapy are the cell division cycle 25 (CDC25) dual specific phosphatases, which hydrolyze both tyrosine and serine/threonine phosphoesters on these proteins. CDC25 phosphatases are key regulators of the cell cycle and mediators of the cell's response to DNA damage. In the mammalian cells, there are three forms: CDC25A, CDC25B and CDC25C. The principal function of these enzymes is to activate cyclin-dependent kinase (CDK) complexes, removing the inhibitory phosphates from tyrosine and threonine residues on CDKs (Boutros et al., 2006; Boutros et al., 2007; De Laurentiis et al., 2011). Accumulating evidence indicates that CDC25 phosphatases are associated to oncogenic transformation, and, in particular, CDC25A and CDC25B have been reported to be overexpressed in various human cancers, such as breast, ovarian, prostate, lung, colorectal, thyroid, gastric, pancreatic, neuroblastoma, non-Hodgkin lymphoma and melanoma. In most cases, overexpression of these phosphatases correlates with higher-grade, more aggressive tumors, and poor prognosis (Boutros et al., 2007; Kiyokawa et al., 2012).

The discovery of new CDC25 inhibitors is extremely significant for cancer therapy because of the critical roles that these phosphatases play in regulating cell-cycle progression and DNA damage-induced checkpoint arrest and recovery. Over the past few years, several synthetic and natural molecules with different structural features targeting CDC25 activity have been reported. The most studied CDC25 inhibitors belong to various chemical classes including phosphate bioisosteres, electrophilic entities, and quinonoids (Brezak et al., 2008; Brenner et al., 2014). The quinone-containing compounds, derived from vitamin K, are the most numerous and active CDC25 inhibitors (Contour-Galcera et al., 2007). Recently, new CDC25 inhibitors, NSC119915 and NSC28620 have been discovered. The first, a quinone compound, displays irreversible inhibition, while NSC28620, with non-quinonoid structure, displays reversible inhibition.

Both generate intracellular ROS, arrest cells in the G0/G1 and G2/M phases of the cell cycle, and significantly suppress the growth of various human cancer cell lines (Lavecchia et al., 2012).

To improve the inhibitory potency of NSC119915, more active analogs of this compound were obtained and characterized, and one of these, has been identified as the most promising inhibitor for its toxic action in melanoma cells.

In particular, it displays reversible CDC25 inhibition, causes a reduction of melanoma cell growth rate, arrests cells in G2/M phase of cell cycle, activates an apoptotic program, modulates the levels of some proteins involved in the control of apoptosis and survival pathways and increases the intracellular ROS levels (Gelzo et al. 2014; Capasso et al., 2015). It is important to note that the more active CDC25 inhibitors have a quinonoid structure with the quinone moietyinducing a non-specific side-toxic effects.To date, only a limited number of literature reports have described the identification of CDC25 inhibitors characterized by a non-quinonoid structure (George Rosenker et al., 2015; Zwergel et al., 2017).

To this aim a group of non-quinonoid derivatives of NSC28620 have been characterized and one of these, exerts a toxic effect in melanoma cells at low concentration and, interestingly, it did not show any toxic effect when it is tested on a non-tumorigenic fibroblasts cell line (Cerchia et al., 2019).

Conclusion

In this review, we report that the risk to develop skin cancer, such as melanoma, is greater in the athletes practicing outdoor sports. This is due to their increased UV radiation exposure and physical exercise-induced immunosuppression. Frequently, athletes seem to know little about the risk of sun exposure. Protective means, such as use of sunscreen, sun avoidance behaviors, and sun protecting clothes, are recommended in the community of outdoor sportsmen. Hence, further efforts to identify individuals with a high risk to develop melanoma and other skin cancer should be focused also on outdoor sportsmen (Moehrle et al., 2008; Harrison et al., 2009). Moreover, in recent years, the treatment of patients with melanoma has positively changed and several options are now available, especially for patients with the BRAF mutations. However, many questions still remain unanswered, regarding to drug resistance and combination therapy (Vanella et al., 2019). Indeed, other agents, that target the main pathways involved in the pathogenesis and progression of melanoma, are being actively investigated to overcome the BRAFinhibitors resistance. CDC25 phosphatases, key regulator of cell cycle progression, which are often deregulated in many tumors, including melanoma, could be considered as a possible oncotarget *in vivo*. Hence, the characterization of new CDC25 inhibitors, and the study of the effects in melanoma cells could be helpful for finding new and more effective agents for the treatment of melanoma.

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