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Review

Senescence modulation as a key process in the dual role of hyaluronan in cancer: the deforestation allegory

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Cancer is one of the leading causes of death worldwide and has been associated with ageing. Although there are numerous reports that have demonstrated the dual role of hyaluronic acid and senescence induction in cancer prevention and promotion, both players have been linked to ageing in opposite ways. Hyaluronan is recognized for its antiaging role, whereas senescence is associated with ageing. In this review we address these dual roles, showing their interrelation, hypothesizing that the downregulation of senescence mediated by HA would be a key factor in the ambivalent effects described. Likewise, the deforestation allegory aims to explain, through the use of a metaphor, the contradictory yet valid results found in the literature. Considering this background, we propose new strategies for improving tumor therapy. Understanding the biology of these complex diseases and the temporal implication of the different players in dissimilar contexts could bring us closer to the therapeutic improvements needed in the field of oncology.

Key words: hyaluronan; senescence; cancer; ageing.

Introduction

Cancer is one of the leading causes of death worldwide. Although patient survival has improved, it is still a challenge to find new therapeutic alternatives and molecular markers for an early diagnosis and to predict malignancy as well as response to therapy. For this reason, there are numerous reports that study the molecules and molecular mechanisms involved in both the progression and prevention of tumor pathologies.

Likewise, cancer is a disease associated with ageing (Hoeijmakers 2009). Interestingly, hyaluronic acid (HA) levels decline throughout life (Fedarko et al. 1992; Itakura et al. 2009; Simpson et al. 2009; Temple-Wong et al. 2016), whereas the antiaging effect of HA is highly recognized (Stern and Maibach 2008; Lee et al. 2019). Moreover, the accumulation of senescent cells throughout life has been demonstrated and have been associated with age-related pathologies (Campisi & d'Adda di Fagagna 2007; Childs et al. 2014; van Deursen 2014).

In this context, both HA and the induction of senescence seem to be key players due to their dual effect on tumor progression. Why mention is made of a dual effect? Because depending on multiple factors, both of them can act as anti- or pro-tumor modulators (Lujambio 2016; Bohaumilitzky et al. 2017; Liu et al. 2019). The literature is vast with regard to the effect of HA on malignancy progression (Sironen et al. 2011; Provenzano and Hingorani 2013; Vigetti et al. 2014; Chanmee et al. 2016; Morera et al. 2017; Heldin et al. 2018; Theocharis et al. 2019). However, HA is a key player in the protection against cancer development in naked mole-rats (NMR; Tian et al. 2013; Seluanov et al. 2018; Takasugi et al. 2020). Likewise, senescence is a known mechanism of tumor suppression; however, its chronic induction leads to an inflammatory state associated with tumor progression (Childs et al. 2014).

We have previously described that HA is able to avoid the induction of senescence in human leukemic and glioblastoma cell lines (Lompardía et al. 2013; Pibuel et al. 2021a; Díaz et al. 2021). Similarly, the NMR exhibits high levels of HA without accumulation of senescent cells (Tian et al. 2013; Bohaumilitzky et al. 2017). In concordance with the previously mentioned data, it has been reported that the silencing of HAS (enzymes responsible for HA synthesis) induced senescence in fibroblasts (Li et al. 2016).

This briefly introduced background supports the hypothesis that the capability of HA to avoid senescence induction would have an impact on ageing, as well as on cancer development and progression. Therefore, the aim of this review was to analyze the relationship between HA and senescence with respect to cancer progression and ageing. Finally, we suggest potential therapeutic implications, as well as the allegory of deforestation. Through this metaphor, we attempt to explain how, depending on the context, HA can prevent or promote tumor development, just as forests can counteract fire initiation in a specific context but act as fuel in a different one.

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Hyaluronan: dual role in cancer

HA is the main glycosaminoglycan (GAG) of the extracellular matrix (ECM; Toole 2004). It is made up of repeating disaccharide units of *N*-acetyl glucosamine and D-glucuronic acid. Depending on the disaccharide repetition number, it is classified into oligomeric HA (oHA), low molecular mass HA (LMM-HA), high molecular mass HA (HMM-HA), or very high molecular mass HA (vHMM-HA), each of which have different functions (Liu et al. 2019; Tavianatou et al. 2019). HA is synthesized by hyaluronic acid synthases (HAS) and degraded by hyaluronidases (HYALs; Hascall et al. 2014; Karousou et al. 2017). The balance between its synthesis and degradation together with receptor-mediated internalization are the 3 factors that mainly determine its levels (Vigetti et al. 2014).

The physiological functions of this GAG are copious (Csoka and Stern 2013; Dicker et al. 2014). In addition to its structural and support roles, HA is able to bind several receptors such as CD44, RHAMM, Lyve-1, HARE, TLR-2 and 4, triggering different signaling pathways. In this way, HA is a key factor for the maintenance of hematopoietic and neural stem cells pools (Khaldoyanidi et al. 2014; Su et al. 2018). Furthermore, it favors tissue repair (Aya and Stern 2014; Frenkel 2014), enhances cell proliferation and migration (Solis et al. 2012) and participates in leukocyte trafficking (Jackson 2009; Jackson 2019), among others.

Interestingly, alterations in HA quantity and quality have been reported in both cancer and ageing (Toole 2009; Misra et al. 2015; Theocharis et al. 2019). Indeed an increase in HA levels compared with normal tissue has been described in numerous types of tumors, which have been associated with a worse prognosis (Auvinen et al. 2013; Tammi et al. 2008; Provenzano and Hingorani 2013; Caon et al. 2020; Pibuel et al. 2021b). In this context, malignant cells take advantage of the physiological role of HA in pursuit of tumor progression. For instance, the protection exerted by HA on stem cells by the activation of efflux pumps capable of expelling genotoxic compounds is used by tumor cells to extrude chemotherapeutic agents (Bourguignon et al. 2008; Lompardía et al. 2013). Likewise, its effects on cell proliferation and migration, which are important in tissue repair, are used by tumor cells in pursuit of their survival and disease progression (Mascaro et al. 2017; Klarić et al. 2019; Pibuel et al. 2020). Its anti-inflammatory and regulatory effects are used to contribute to the immunosuppressive microenvironment that favors the evasion of the antitumor immune response (Termeer et al. 2003; Cordo Russo et al. 2012). Similarly to what occurs in the physiological context, in malignancies the effects of HA are mediated by its interaction with membrane receptors (mainly CD44 and RHAMM) and the consequent activation of signaling pathways such as PI3K/Akt and MAPK in cancer cells (Toole 2009).

In contrast, it was described that HMM-HA shows antitumor effects on colon carcinoma and melanoma cells (Mueller et al. 2010; Takabe et al. 2015) and that it is a key player in cancer resistance in NMR (Tian et al. 2013). In addition, Tian et al. described that as a result of knocking down HAS2 or overexpressing HYAL2, NMR cells become susceptible to malignant transformation (Tian et al. 2013). It is worth noting that recent studies showed that the molecular mass of HA from the NMR would be on average 2.5 MDa (being HMM-HA) and not vHMM-HA (Del Marmol et al. 2021). Del Marmol et al. (2021) demonstrated that NMR have larger amounts and higher molecular weight of HA in serum and several tissues tested than guinea pigs (*Cavia porcellus*) and mice (*Mus musculus*). Still, HA (HMM or vHMM) would be a key player in preventing cancer development and extending the lifespan of NMR (Tian et al. 2013; Faulkes et al. 2015; Bohaumilitzky et al. 2017; Seluanov et al. 2018; Gorbunova et al. 2020). Therefore, the dual role of HA in preventing or promoting cancer would depend on its quality and quantity, as well as on the physiological or pathophysiological context studied (Bohaumilitzky et al. 2017). As is known, cancer is a disease associated with ageing and throughout life a decrease in HA levels has been described (Meyer and Stern 1994; Simpson et al. 2009). Thus, HA showed antiaging qualities both due to its filling effect and regenerative capacity (Lee et al. 2019). Taking into account this background, HA could prevent cancer development, whereas, with ageing, tumor initiation would be promoted by decreasing its levels. Once cancer is established, HA is increased in the tumor microenvironment and would act as a stimulating factor for malignancy progression.

Senescence: implication in cancer and ageing

Senescence is characterized by the irreversible arrest of the cell cycle. It is essential for homeostasis, being considered one of the most important mechanisms of tumor suppression (Childs et al. 2014; Salama et al. 2014).

Senescence can be induced by different stressors (telomere shortening, over-activation of oncogenes, chemotherapy, and oxidative stress) that determine the type of senescence triggered (replicative, oncogene-induced, chemotherapy-induced, or premature senescence). This complex stress response can also be induced by external stimuli (nonautonomous senescence), being senescent cells capable of triggering senescence in neighboring cells (Pérez-Mancera et al. 2014).

The senescent phenotype is characterized by the increase in cell cycle inhibitors, senescence-associated β-galactosidase activity, presence of senescence-associated heterochromatin foci, mitochondrial dysfunction, among others (Hernandez-Segura et al. 2018). Although senescent cells lose their replicative capacity, their metabolism remains very active and they are able to interact with the microenvironment through the synthesis and release of factors due to the senescence-associated secretory phenotype (SASP; Lujambio 2016). The conformation of the SASP depends on the type of senescence and the stimulus that triggered it, being widely varied (Tchkonia et al. 2013). Physiologically, one of the main functions of the SASP is to activate the immune system (IS) to kill the transformed or damaged cells. In this context, senescence is an acute process in which such cells are eliminated (Childs et al. 2014). However, throughout life there is an accumulation of senescent cells (chronic senescence) due to failure in their elimination mechanisms, which leads to a chronic inflammatory process responsible to a great degree for age-related diseases such as cancer (Childs et al. 2014). Remarkably, the quality of the SASP seems to be crucial in the modulation of such processes, since it can present both antitumor or pro-tumor features (Lecot et al. 2016).

The evidence described supports the dual role of senescence in both preventing and promoting cancer depending

on the specific context. The acute induction of senescence, with the consequent elimination of the transformed cells, is crucial for accurate tumor suppression. However, failures in the clearance of senescent cells lead to their accumulation, which is associated with a chronic inflammatory process and ageing. This situation generates a propitious environment for the development of diseases such as cancer.

Interplay between hyaluronan and senescence

There are few reports that describe a direct relationship between HA and senescence, most of which are cited by Bohaumilitzky et al. in an interesting and pioneering review that raises the dual role of HA and senescence (Bohaumilitzky et al. 2017). Moreover, we demonstrated that the inhibition of HA synthesis leads to senescence induction in human leukemic cell lines, whereas the addition of exogenous HA avoids senescence induction (Lompardía et al. 2013). Likewise, we showed that imatinib decreases HA production and induces senescence; whereas the addition of this GAG abrogates imatinib-induced senescence in human CML cells (Lompardía et al. 2019). In agreement with the previously mentioned, Alessio et al. reported that HA treatment delays replicative senescence of mesenchymal stem cells (Alessio et al. 2018). Furthermore, it was reported that the synthesis of HA is downregulated in senescent mesenchymal stem cells (Jung et al. 2011). Likewise, Li et al. demonstrated that HAS-2 deletion induces fibroblast senescence in pulmonary fibrosis (Li et al. 2016). Likewise, it was described that miR-23a-3p inhibits HAS-2 expression, inducing senescence, which would be involved in skin ageing (Röck et al. 2014). Moreover, we recently demonstrated that HA prevents senescence induction in human glioblastoma and acute leukemia cells (Pibuel et al. 2021a; Díaz et al. 2021).

Other reports indirectly seem to show a relationship between HA and senescence. For instance, it was described that HA exerts a protective effect on oxidative DNA damage (Zhao et al. 2008; Gorbunova et al. 2020), one of the most recognized stimuli for senescence induction. Furthermore, reactive oxygen species are capable of degrading HA, as well as inducing senescence (Ziegler et al. 2015; Liu et al. 2019). Similarly, UV radiation is able to induce senescence and skin ageing (Gragnani et al. 2014), whereas UV-B increases HYAL activity in keratinocytes (Kurdykowski et al. 2011; Bourguignon and Bikle 2015). Finally, it was shown that senescent cells alter the extracellular matrix (Mavrogonatou et al. 2019), whereas, as previously mentioned, NMR have large amounts of HMM-HA/vHMM-HA, not showing accumulation of senescent cells (Bohaumilitzky et al. 2017; Tian et al. 2013; Del Marmol et al. 2021).

In light of this background, an inverse relationship between HA levels and induction of senescence could be established. Therefore, we hypothesize that high levels of HA, such as those observed in the early stages of life, would prevent DNA damage, induction of senescence and, finally, tumor initiation. Conversely, in old age when HA levels decrease, DNA damage could occur, consequently leading to induction of senescence. The lower activity of the IS observed in ageing could favor accumulation of senescent cells. Thus, chronic senescence would generate a microenvironment of chronic inflammation due to the SASP, which would promote cancer initiation. Once the tumor process is established, the malignant cells, as well as the tumor-associated cells could synthetize high amounts of HA, generating a propitious microenvironment for its pro-survival properties and avoiding senescence induction. Thereby, the dual role of HA and the induction of senescence related to the initiation and progression of cancer could be explained (Fig. 1). In accordance with this hypothesis, the results of Mikami et al. show that the systemic inhibition of HA synthesis favors liver carcinogenesis (Mikami et al. 2018). However, in a cancer context, there are high levels of HA and the treatment with 4-methylumbelliferone (4MU) results in a marked antitumor effect in accordance with the hypothesis raised (Piccioni et al. 2012; Lompardía et al. 2013; Pibuel et al. 2020; Karalis et al. 2018; Lokeshwar et al. 2010).

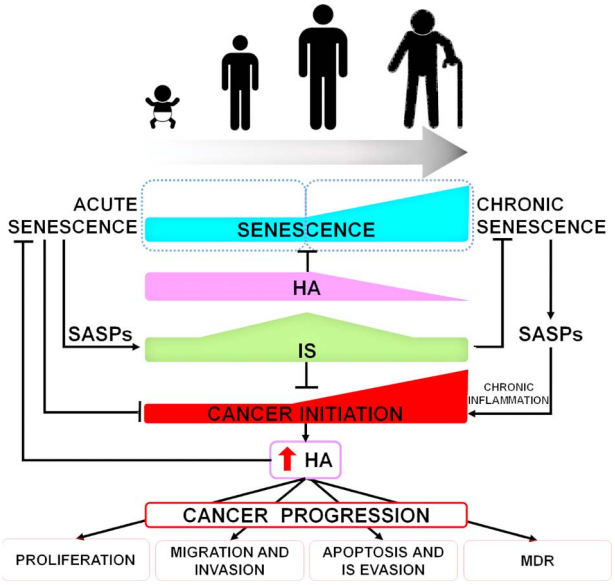

Fig. 1. Hypothesis about the relationship between HA and senescence. Under physiological conditions, HA protects cells from genomic damage, thus preventing the induction of senescence. However, in the face of cellular stress, this process is triggered, and through the release of SASPs can activate the IS favoring the elimination of senescent cells (acute senescence). Thus, the development of cancer would be avoided. However, throughout life the levels of HA and the competence of the IS drop, which would promote the induction and the accumulation of senescent cells (chronic senescence). Thus, the state of chronic inflammation would favor ageing and related diseases such as cancer. In this pathological context, HA enhances disease progression by promoting cell proliferation, migration, invasion, multidrug resistance (MDR) and, by evasion of apoptosis, senescence and IS.

Therapy implications

Considering the role of HA and senescence in ageing and cancer progression, the modulation of such players would be relevant for an accurate therapeutic approach.

In this way, a reduction of HA levels would be needed to improve cancer therapy. One promising alternative is the inhibition of HA synthesis using 4MU. This coumarin derivative shows substantial antitumor effects in several cancer models (Nagy et al. 2015; Lompardía et al. 2019; Pibuel et al. 2021a; Kudo et al. 2017; Yates et al. 2015; Lokeshwar et al. 2010; Yoshida et al. 2016; Piccioni et al. 2012; Urakawa et al. 2012; Díaz et al. 2021; Pibuel et al. 2020; Vitale et al. 2021). It is worth noting that 4MU is a safe drug and its use in humans, as a choleretic agent, is approved in Asia and Europe (Nagy et al. 2015). Therefore, the use of 4MU in cancer therapy implies a repurposing of this drug. Another approach

to reducing HA levels is the use of HYALs, showing interesting results with advanced clinical trials in pancreatic cancer (McAtee et al. 2014; Doherty et al. 2018). In order to mitigate HA effects, the use of oHA is a valid option. These small molecules are not able to cross-link the HA receptors, and the literature is vast regarding their antitumor effects (Alaniz et al. 2006; Cordo Russo et al. 2008; Slomiany et al. 2009; Lompardía et al. 2013; Lompardía et al. 2016).

Moreover, CD44 and RHAMM are associated with therapy resistance and a worse prognosis in several cancer types, being both studied as targets for therapy (Tzankov et al. 2011; Mooney et al. 2016; Zhou et al. 2017; Liu et al. 2019; Carvalho et al. 2021). Taking into account the overexpression of CD44 and RHAMM in numerous cancer types (Sironen et al. 2011; Tzankov et al. 2011; Schwertfeger et al. 2015; Ferrer et al. 2018; Shalini et al. 2018), HA drug delivery nanotechnology systems are being studied for cancer therapy (Shah et al. 2015; Han et al. 2016). Moreover, considering the particular antitumor features of vHMM-HA (Tian et al. 2013; Faulkes et al. 2015; Bohaumilitzky et al. 2017; Kulaberoglu et al. 2019), it is also being studied as a new and promising strategy to be used in nanotechnology to target tumor cells and improve the patient outcomes (Gorbunova et al. 2020).

On the other hand, senolytic compounds are able to induce death in senescent cells (Davan-Wetton et al. 2021). Considering the role of senescent cell accumulation in ageing and the undesirable effects of chemotherapy, senolytic drugs could represent an interesting therapeutic alternative (Jeon et al. 2017; Scudellari 2017; Zhu et al. 2017). In this respect, it was described that senolytics are able to alter the extracellular matrix, decreasing fibrosis that is associated with ageing-related diseases (Harvey et al. 2016; Lehmann et al. 2017; Hu et al. 2020). In addition, numerous chemotherapeutic agents induce senescence as part of their antitumor mechanism of action (Gewirtz 2014; Villodre et al. 2017), and our reports indicate that the inhibition of HA synthesis, as well as the mitigation of its effects mediated by HA oligomers induce senescence in leukemia cells (Lompardía et al 2016; Lompardía et al 2017). Although senescence is a tumor suppression mechanism capable of promoting the removal of transformed cells mediated by the IS, it is also known that SASP can promote cancer progression, and some undesirable effects of chemotherapeutic drugs were attributed to senescent cells (Baar et al. 2017; Campisi & d'Adda di Fagagna 2007; Demaria et al. 2017). Likewise, the immunoregulatory features of the tumor microenvironment could avoid the clearance of senescent cells, leading to their accumulation. Thereby, the use of senolytic drugs after the use of chemotherapeutic agents or radiotherapy would be an interesting and novel therapeutic strategy in oncology (Scudellari 2017; Wang et al. 2022). Chemotherapy or radiotherapy kill some cancer cells and induce senescence in others since the latter require a greater stressful stimulus for death. The cells that are resistant to cancer therapy can be impacted by the SASP, consequently these factors could induce non-cell autonomous senescence in therapy resistant cells. Thus, the use of senolytic drugs would kill those senescent cells, abrogating their accumulation and improving cancer therapy.

Deforestation allegory

In view of all the reports cited, as well as the hypothesis suggested previously (Fig. 1), the deforestation allegory is proposed:

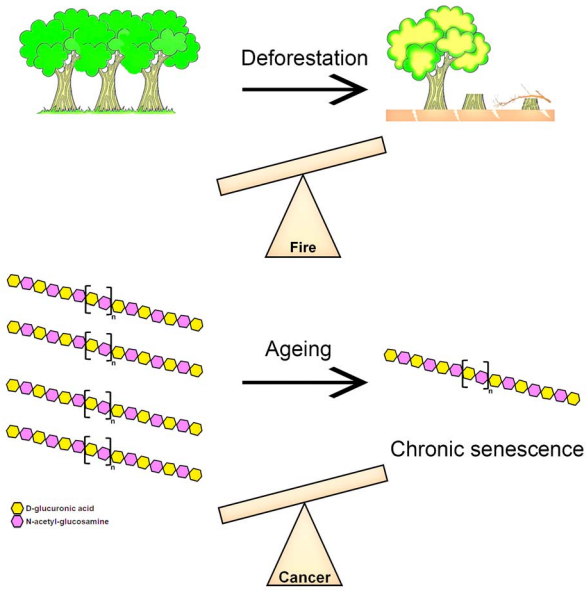

Fig. 2. Deforestation allegory I. The forest is necessary to avoid fire initiation, and so is HA to abrogate chronic senescence, ageing and cancer.

On the one hand, let's think of a forest, a young, dense forest full of green trees favoring a moist soil, which makes it difficult to start a fire, and, on the other hand, a less dense cleared forest, with a greater amount of light that passes through that causes the ground to become drier with remains of felled trees and stumps, thus increasing the probability of a spark causing a fire (Fig. 2, upper panel). Therefore, to avoid this process, it is important to promote dense afforestation. However, in another context such as in the presence of fire, dense forestation represents a greater threat and greater difficulty to control the fire than a deforested area (Fig. 3, upper panel). In this sense, considering HA as the trees in our forest, the decrease in its levels due to ageing (deforestation), in addition to the lower activity of the IS, leads to senescence, favoring cancer (fire) initiation. Therefore, the quality and adequate levels of the GAG would avoid the induction of chronic senescence and age-related diseases such as cancer (Fig. 2, lower panel). However, in a cancer context, high levels of HA increase cell proliferation and migration, and could prevent the induction of senescence, thus promoting disease (Fig. 3, lower panel).

Conclusion

In this brief review, we propose a viable explanation for the dual role of HA with respect to cancer initiation and progression. In this way, we try to clarify the opposite but valid results with regard to the pro- and antitumor effects of HA and its relationship with senescence modulation. Although this is a hypothesis and may not be entirely correct, it provides a feasible description of the ambivalent effect of HA and senescence on cancer progression, considering the physiological and pathological context, as well as its chronological analysis. Based on the hypothesis suggested, different potential therapeutic approaches were analyzed, such as the potential uses of 4MU, vHMM-HA and senolytic drugs to improve cancer therapy. Finally, the deforestation allegory also tries to explain the relationship between hyaluronan and senescence

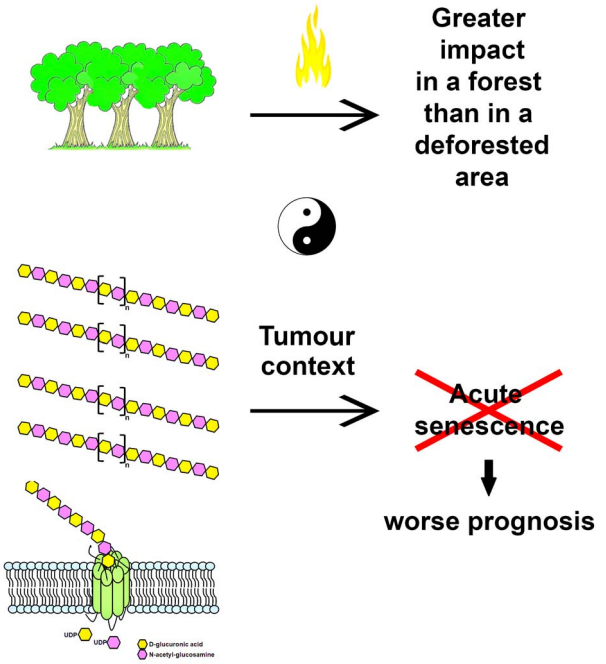

Fig. 3. Deforestation allegory II. In a different context, that same forest can serve as fuel making it difficult to control a fire. Similarly, in a pathological context, high levels of HA promote the progression of cancer, avoiding the induction of senescence and enhancing the proliferation and migration of malignant cells, which leads to therapeutic complications and a worse prognosis.

in regard to cancer and ageing, through a metaphor of macromolecular life.

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