Medical Hypotheses 84 (2015) 227–230

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Cancer stem cells and mesenchymal stem cells in the hypoxic tumor niche: Two different targets for one only drug ☆

Francesca Bonafè, Carlo Guarnieri, Claudio Muscari *

Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

ARTICLE INFO

Article history:
Received 27 July 2014
Accepted 7 January 2015

ABSTRACT

Putative cancer stem cells (CSCs) reside in a hypoxic microenvironment where mesenchymal stem cells (MSCs) are also present. In this niche MSCs seem to promote the generation of CSCs and sustain tumor progression. Therefore, it may assume clinical relevance to produce a drug which kills not only CSCs but also MSCs. We hypothesized that bifunctional nanoparticles, loaded with a HIF-1α inhibitor and conjugated with an aptamer targeting a common receptor of CSCs and MSCs, may fulfill this strategy. The nanoparticle should ensure that: (1) the conveyed drug is less susceptible to degradation, (2) the common receptor of CSCs and MSCs is recognized by a superselective aptamer, and (3) receptor-mediated internalization is the main process to enter target cells. Small RNA or DNA aptamers represent an advantage over antibodies because do not cause immune reactions, are better internalized into the target cell, are more resistant to degradation, their cost of production are lower, and the purity of the oligonucleotide ligand is extremely elevated. Concerning the drugs to be delivered, we suggest to employ those exerting an anti-HIF-1α activity because they should be harmful for hypoxic CSCs and MCSs in their tumor niche but provide very limited toxicity, or even none, to well-oxygenated normal cells. Corresponding experimental approaches to perform pre-clinical studies and verify this hypothesis are also addressed.

Introduction

Several experimental evidence suggest that tumors are generated from a few cells with stem cell characteristics, named cancer stem cells (CSCs), tumor initiating cells, or tumor propagating cells [1]. To prevent the progression and propagation of the neoplasia via metastasis diffusion, it has been proposed to destroy not only the bulk tumor but also CSCs since they are more resistant to chemo- and radiation-therapy [1].

The microenvironment where CSCs reside (niche) differs from that of the bulk tumor and is constituted by extracellular matrix (ECM) factors interacting with a heterogeneous cell population which is inadequately vascularized [1,2]. In this niche, which has been identified in both primary tumor and areas of metastasis, mesenchymal stem cells (MSCs) are often present and play an important role because produce several paracrine factors which are necessary for the formation and progression of CSCs. Moreover, MSCs generate other cell types, such as cancer-associated fibroblasts (CAFs) and tumor-associated myofibroblasts, which sustain CSC activities [1–3].

MSCs migrate from the bone marrow (bone-marrow stromal cells) and/or the vessel wall (pericytes) to the tumor niche due to the presence of chemoattractant growth factors and cytokines, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and stromal cell-derived factor 1α (SDF-1α), which are produced by cancer cells [4]. In particular, under hypoxic conditions cancer cells upregulate the expression of interleukin 6 (IL-6) which promotes the migration of MSCs through signal transducer and activator of transcription 3 (STAT3) and mitogen activated protein kinase (MAPK) pathways [5].

The putative transition of bulk tumor cells to CSCs could be also fostered by MSCs. Li et al. have described an integrated mechanism in which the cancer cell-mediated release of interleukin 1 (IL-1) induces MSCs to produce at first PGE_2 and then many cytokines, e.g. IL-6, interleukin 8 (IL-8), and growth-related oncogene-α (GROα), which are responsible for the generation of new CSCs [6]. Another property of MSCs which is exploited for tumor growth is their immunosuppressive action which further attenuates the natural defense of the body attempting to destroy malignant cells [7]. MSCs help tumor to grow because they improve cancer cell metabolism [8], stimulate angiogenesis [9], and generate, at least

☆ *Source of support in the form of Grants:* Fondazione del Monte di Bologna e Ravenna, Italy.

* Corresponding author at: Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Via Irnerio 48, 40126 Bologna, Italy. Tel./fax: +39 0512091245.

E-mail addresses: f.bonafe@unibo.it (F. Bonafè), carlo.guarnieri@unibo.it (C. Guarnieri), claudio.muscari@unibo.it (C. Muscari).

http://dx.doi.org/10.1016/j.mehy.2015.01.001
0306-9877/

in part, other supporting cells living in the tumor niche, e.g. 20% of CAFs [10].

More relevantly, it has been described that MSCs might be necessary for cancer propagation. Karnoub et al. demonstrated the tumor niche can stimulate MSCs to produce chemokine (C–C motif) ligand 5 (CCL5) which, in turn, increases cancer cell mobility, invasiveness, and metastatization [11]. Moreover, MSCs seem to promote the endothelial-to-mesenchymal transition (EMT) of cancer cells, thus transforming the primary tumor in migrating metastasis [12].

Although under certain conditions MSCs can act also as a tumor suppressor, by reducing cell survival through release of tumor necrosis factor (TNF), TNF-related apoptosis inducing ligand (TRAIL), and p38 MAPK [4], most MSC-dependent effects reported in the literature support the notion that they promote tumor cell renewing, growth, and malignant progression.

Therefore, it is conceivable that therapies aimed at eliminating only CSCs are not definitive without killing MSCs. As for CSCs, MSCs have been demonstrated to be very resistant to hypoxic conditions in which they even gain some important benefits, including the overexpression of prosurvival genes and receptors for cell migration and homing [13]. The most effective adaptation of tissue hypoxia involves the activation of members of the family of hypoxia inducible factors (HIFs) [14]. In the hypoxic tumor cells the activity of HIF-1α increases significantly and seems to play a relevant role in the formation of CSCs and their evolution toward malignancy [15]. Interestingly, HIF activity can be increased also in normoxia in the presence of growth factors and cytokines which can upregulate HIF expression and overcome the constitutive inhibiting effect due to its degradation through oxygen-mediated proteasome processing [16].

MSCs and CSCs overexpress some common surface markers such as CD44, the most investigated receptor of hyaluronic acid (HA) [17]. Relevant effects generated by the interactions between HA and CD44 have been reported in both MSCs [18–21] and CSCs [22]. So far, several studies to evaluate the anti-tumor effects of antibodies targeting CD44 and other markers of CSCs have been performed [23]; however, these treatments show several limitations especially due to the presence of CD44 in non-tumor cells, although at lower surface density, which causes side effects [24].

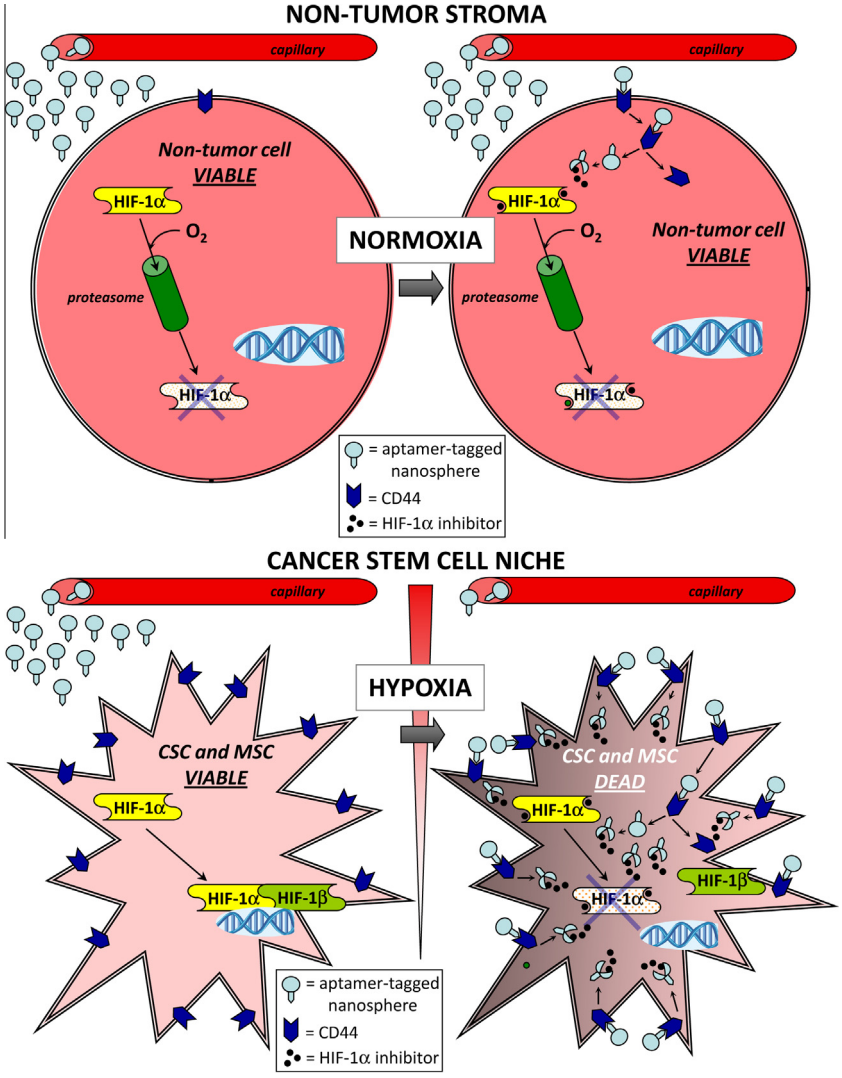

Fig. 1. Different tropism of aptamer-tagged nanospheres toward CD44 expressed by normoxic cells and hypoxic CSCs and MSCs. The superficial receptor CD44 is normally expressed in well-oxygenated non-tumor cells (upper panel), while it is overexpressed in CSCs and MSCs which reside in the hypoxic tumor niche (lower panel). Aptamer-tagged nanospheres addressed toward CD44 are preferentially attracted by CSCs and MSCs, due to their higher density of CD44. As a consequence, a more consistent amount of HIF-1α inhibitor molecules are delivered in CSCs and MSCs which are destined to die without the protection exerted by HIF-1α. On the contrary, normoxic non-tumor cells are not affected by the drug because HIF-1α is not necessary for their survival and then it is degraded in the proteasome due to the presence of normal oxygen tension.