Cytokine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review article

Anti-metastatic functions of type 1 interferons: Foundation for the adjuvant therapy of cancer

Angélica Ortiz, Serge Y. Fuchs

Department of Biomedical Sciences, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form 19 January 2016
Accepted 20 January 2016
Available online xxxx

Keywords:
Interferon
Cancer metastasis
Invasion
Colonization

ABSTRACT

The anti-tumorigenic effects that type 1 interferons (IFN1) elicited in the *in vitro* studies prompted consideration of IFN1 as a potent candidate for clinical treatment. Though not all patients responded to IFN1, clinical trials have shown that patients with high risk melanoma, a highly refractory solid malignancy, benefit greatly from intermediate IFN1 treatment in regards to relapse-free and distant-metastasis-free survival. The mechanisms by which IFN1 treatment at early stages of disease suppress tumor recurrence or metastatic incidence are not fully understood. Intracellular IFN1 signaling is known to affect cell differentiation, proliferation, and apoptosis. Moreover, recent studies have revealed specific IFN1-regulated genes that may contribute to IFN1-mediated suppression of cancer progression and metastasis. In concert, expression of these different IFN1 stimulated genes may impede numerous mechanisms that mediate metastatic process. Though, IFN1 treatment is still utilized as part of standard care for metastatic melanoma (alone or in combination with other therapies), cancers find the ways to develop insensitivity to IFN1 treatment allowing for unconstrained disease progression. To determine how and when IFN1 treatment would be most efficacious during disease progression, we must understand how IFN1 signaling affects different metastasis steps. Here, we specifically focus on the anti-metastatic role of endogenous IFN1 and parameters that may help to use pharmaceutical IFN1 in the adjuvant treatment to prevent cancer recurrence and metastatic disease.

Contents

1. Introduction

Cancer metastasis contributes to approximately 90% of cancer-related mortality [1,2]. Metastatic cancer cells (MCCs) possess molecular traits different than the tumor cells of the primary lesion, thus altering and often diminishing responses of these cells to therapeutic modalities designed to target primary tumor cells [2–4]. Severity of metastatic dissemination contributes to poor

Abbreviations: MCC, metastatic cancer cells; IFN, interferon; IFNAR1, type 1 interferon receptor subunit 1; IFNAR2, type 1 interferon receptor subunit 2; JAK, janus kinase; ISG, interferon stimulated gene; EMT, epithelial-to-mesenchymal transition; MET, mesenchymal-to-epithelial transition; E-Cad, epithelial cadherin; N-Cad, neuronal cadherin; AJ, adherens junction; ECM, extracellular matrix; VEGF, vascular endothelial growth factor.

E-mail addresses: anortiz@vet.upenn.edu (A. Ortiz), syfuchs@vet.upenn.edu (S.Y. Fuchs)

http://dx.doi.org/10.1016/j.cyto.2016.01.010
1043-4666/

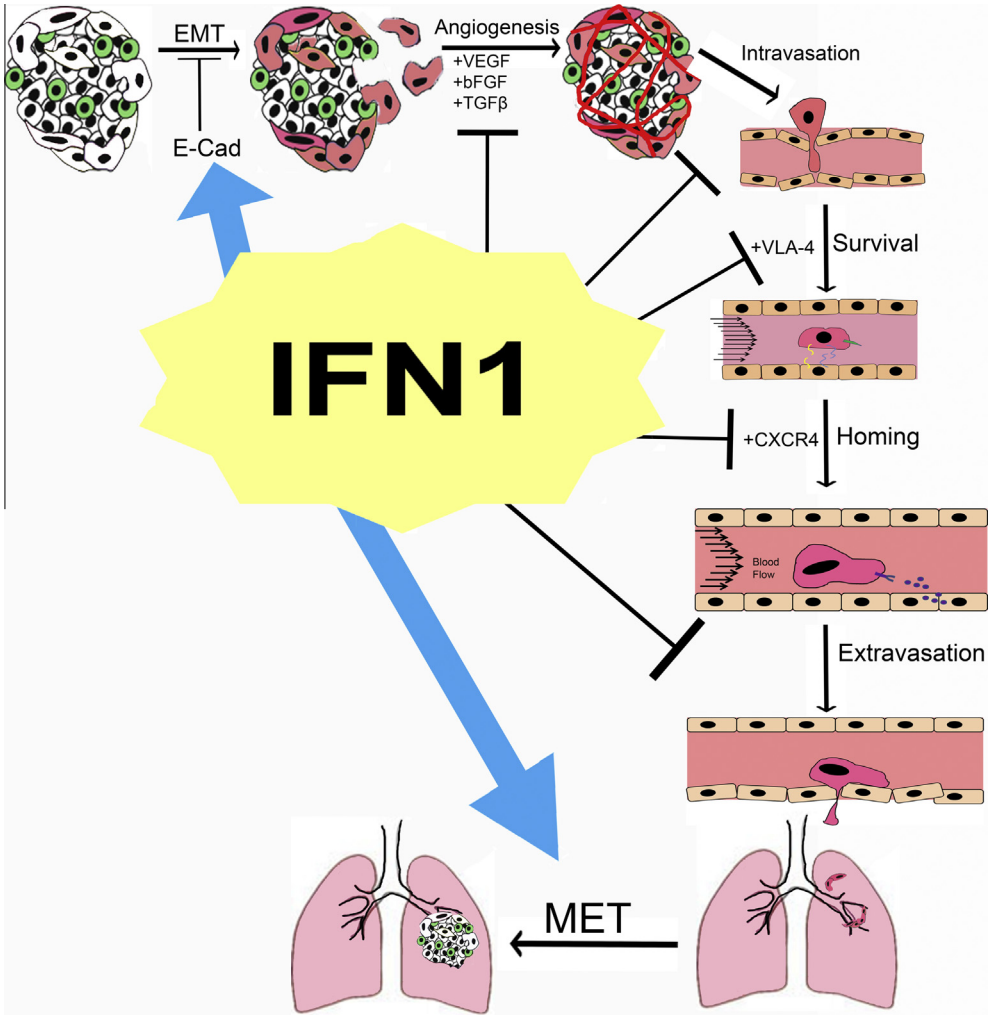

Fig. 1. Elements of metastatic processes and their regulators, whose activities are modulated by IFN1 are depicted.

patient survival and quality of life [5,6]. The process of metastasis can be described as an "obstacle course" (Fig. 1) in which MCCs must overcome numerous and substantial hurdles (imposed by stromal cells in proximal and distal tissues) to enter and travel within lymph or blood vessels, survive the hostile environment within circulation, home to and arrive at metastasis-permissive tissues, and, finally, colonize a secondary site [4]. At the early stages of metastatic process, specific alterations in cellular adhesion molecules enable MCCs to interact with different cell types and extracellular matrix (ECM) molecules [7–9]. Furthermore, aberrant expression of cell adhesion molecules on MCCs alter intracellular signaling and cytoskeleton structure eliciting changes in cell morphology and increased cell migration/invasion [7,8].

Once MCCs utilize these changes to escape the confines of the primary tumor, they engage with endothelial cells and gain entrance into the circulatory system. MCCs that survive circulation then follow exact and complex homing signals to arrive at specific distal tissues, which are defined by expression of MCC-trapping molecules induced during the development of primary tumors. Cells that survive in the new metastatic site can remain dormant or rapidly proliferate to form metastatic lesions.

MCCs rely on intrinsic cellular and environmental factors to aid in the completion of this process [7,10,11]. Importance of understanding the mechanisms that contribute to suppressing MCCs from completing each step of the metastatic process cannot be overestimated. Advances in this area are likely to identify novel prognostic markers and molecular regulators as targets, which could potentially lead to therapies that extend cancer patients survival.

Anti-viral cytokines that belong to the superfamily of type 1 interferons (IFN1), are able to modulate cell growth, cell differentiation, and promote tumor immune surveillance [12,13]. These cellular functions are elicited when IFN1s bind to a cell surface receptor comprised of two subunits (IFNAR1 and IFNAR2). Interaction of IFN1 with the receptor leads to activation of receptor associated Janus kinases (JAKs) JAK1 and TYK2. Activated JAKs then phosphorylate IFNAR2 to recruit STAT1 and STAT2 Subsequent phosphorylation and dimerization of STAT1/2 and recruitment of IRF9 protein completes the assembly of the ISGF3 transcription factor that translocates to the nucleus, interacts with IFN-stimulated response elements and transactivates the expression of the interferon stimulated genes (ISGs) [14].

Cancer cells engineered to overexpress IFN1 exhibited an impaired metastatic potential [15,16]. Moreover, treatment with recombinant IFN1 also suppressed metastasis in mouse models [17,18]. Conversely, tumors grown in IFNAR1-null mice were shown to rapidly progress to development of metastases [19]. These studies demonstrated that IFN1 possess potent anti-metastatic properties. Furthermore, it was suggested that administration of pharmacologic IFN1 could be beneficial for patient treatment and resulted in FDA approval for the use of IFN1 in the treatment of hairy cell leukemia (1985), AIDS-related Kaposi's

Please cite this article in press as: A. Ortiz, S.Y. Fuchs, Anti-metastatic functions of type 1 interferons: Foundation for the adjuvant therapy of cancer, Cytokine (2016), http://dx.doi.org/10.1016/j.cyto.2016.01.010