Journal of
Clinical and Experimental Pharmacology

Botti et al., Clin Exp Pharmacol 2012, 2:3
DOI: 10.4172/2161-1459.1000e118

Editorial Open Access

Extracellular Matrix Molecules as Targets for Melanoma Therapy

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Abstract

Malignant melanoma, between human diseases, represents a best model to study tumor progression process. In fact, during its evolution, a series of events takes place involving several molecular mechanisms associated to both melanocytes transformation and to the surrounding microenvironment, with a prevalent involvement of Extracellular Matrix (ECM).

A large series of mechanisms correlated to the activity of these molecules have been studied to establish specific interfering system for target therapies in several human cancers. We suggest that the combination of specific ECM target therapies and immune-therapy, making more efficient the therapeutic approaches for malignant melanoma disease.

Editorial

The incidence of melanoma is gradually growing around the world, with particular increase among young individuals. The out-of-control cell growth and the loss of cellular homeostasis play a key role in the genesis and progression of the tumor. At junction level these mechanisms control the proliferation, differentiation and apoptosis of melanocytes. In particular, interactions between transformed cells and transformed cell with extracellular matrix are crucial for melanoma progression. Molecules of the extracellular matrix in tumor micro-environment are responsible for tumor progression. Therefore, in order to establish specific target therapies, it is extremely important to set up molecular models which inhibit their activity.

Several studies have proved, for various tumor typologies, the possibility either to inhibit or interfere with the function of these molecules, both in vitro and in vivo. The inhibition can take place at gene transcription level, using specific siRNA, as well as at protein level using specific antibodies against ECM proteins [1-7].

Silencing, employing specific siRNA, causes a reduction in cell proliferation, colony formation and invasiveness of tumor cells in vitro as demonstrated by Dong et al. [8] and Shen et al. [9] on metallo proteinases investigations. Besides in vitro studies carried out on cell models of melanoma have shown that the down-regulation by siRNA technique of MMP13 strongly enhanced pigmentation of melanocytes as well as a decreasing in cell proliferation [10].

MMP-2 silencing, through adenovirus-mediated and siRNA techniques in spinal metastatic melanoma model, significantly inhibits tumor growth and results in a complete retention of neurological function in animals [11].

Several molecules have been considered capable of inhibiting MMPs catalytic activity, especially pseudopeptides and non-peptidic molecules, which selectively bind themselves to zinc-bing site of these proteins. Batimostat, barimostat, AG3344 and bay-219566 are the most used molecules at present [12].

Many integrin-inhibitors have also been set up. They have a strong capacity of inhibiting the progression of neoplastic cells as shown by studies on animal models. In particular, Cyclic RGD peptides have been synthetized, which selectively inhibit alpha v integrins [13,14]. Synthetic peptides against alpha5beta1 and alphavbeta3 integrins are now days employed in pre-clinical studies [15-17]. "Disintegrins" represent another category of integrin inhibitors. They are small non-enzymatic proteins with the capacity of interacting with many cell types, including melanoma cells. Salmosin, Jararhagin, Eristostatin, Contortrostatin and Obtustatin are the most studied and used "disintegrins" [18-22].

Anti-integrin antibodies have also been obtained (targeting alpha vs. integrins in particular): in mice model, Vitaxin and CNT095 strongly inhibit the growth of melanoma tumors [23].

The employment of RNA interference (siRNA), blocking Osteopontin (OPN) expression in melanoma cells, reduces cells number and invasiveness [24], whereas in other tumors, the employment of siRNA against OPN transcript causes a consistent suppression of tumorigenicity in vitro [25]. Beside, blocking of OPN expression can down-regulate other ECM molecules, specifically some metallo proteinases [26].

In recent years, several molecules have been identified as inhibitors of OPN, in particular Agelastatin A, an alkaloid with high anti-tumor efficacy [27]. Humanized monoclonal antibodies blocking OPN have been lately targeted: ASK 8007, is very efficacious in patients with rheumatoid arthritis [28] and anti-human OPN antibody 1A12 is used in breast cancer treatment [29].

Regarding SPARC (Osteonectin) silencing, it has been shown that anti-sense expression vector in melanoma cells is capable of reducing the invasive and adhesive capacity of tumor cells [30]. Moreover, siRNA blocking SPARC expression in cell and animals models of melanoma, inhibits cell growth with G (1) arrest induction [31]. In uveal melanoma too, OPN silencing is capable of reducing tumor cells proliferation [32].

Small peptides have been recently synthesized. Their molecular structure is very simple, capable of binding different SPARC protein domains, blocking angiogenesis and inhibiting tumor growth as shown in animal models [33,34].

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Received November 21, 2012; **Accepted** November 23, 2012; **Published** November 26, 2012

Citation: Botti G, Cerrone M, Anniciello A, De Cecio R, Ascierto P, et al. (2012) Extracellular Matrix Molecules as Targets for Melanoma Therapy. Clin Exp Pharmacol 2:e118. doi:10.4172/2161-1459.1000e118

The effects of both siRNA [35] and monoclonal antibodies against different domains of Tenascin C protein has also been investigated [36].

Finally, CCN3 protein expression is in reverse correlation to neoplastic progression of melanoma. Many experiments on both induction and silencing of CCN3 have been carried out and the results have shown a subsequent alteration of adhesion capacity to laminin and vitronectin [37].

It is then feasible to assume that the improvement and progression of therapeutic approaches for melanoma could be achieved by the integration of specific therapies against ECM molecules combined with immunotherapy.

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