MDA-9/SYNTENIN AS A POTENTIAL DRUG TARGET IN HEPATOCELLULAR CARCINOMA

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MDA-9/Syntenin is a member of the family of PDZ domain-containing scaffold proteins displaying different biologic functions, including intracellular adapter through binding to syndecans, development and neural function, cytoskeleton rearrangement, intracellular trafficking and an emerging role also in the regulation of exosome biology (1-4). Overexpression of MDA-9/Syntenin occurs in multiple human cancer cell lines including melanoma, breast and gastric cancer, glioma and urothelial cell carcinoma; in particular MDA-9/Syntenin seems to be a marker of higher grade of tumor and of invasiveness and metastasis (5, 6). The relationship between MDA-9/Syntenin and NF-κB activation was identified in melanoma cells where MDA-9/Syntenin/c-Src complexes functionally cooperate with NF-κB to promote anchorage-independent growth, motility and invasion (7). In the same cancer model, Swadesh K. Das et al. have shown an inverse relationship between MDA-9/Syntenin and RKIP since MDA-9 transcriptionally downregulated RKIP and conversely ectopic RKIP expression suppressed MDA-9-mediated signaling (2).

We have analyzed the presence of a regulation loop like that between MDA-9/Syntenin - NF-κB - RKIP in hepatocellular carcinoma, already highlighted in triple negative cancer cells (8).

We have examined basal expression of MDA-9/Syntenin in three HCC cell lines (HA22T/VGH, Hep3B and HepG2). Western blot analysis has demonstrated that MDA-9/Syntenin expression levels were higher in HA22T/VGH, the cell line characterized by higher proliferative and invasive capacities than HepG2 and Hep3B cells. Moreover, it is interesting to note that in the same cell lines, there was an inverse relationship between MDA-9/Syntenin and RKIP expression levels, and a positive correlation between MDA-9/Syntenin expression and NF-κB activation levels.

By silencing with a siRNA anti-MDA-9/Syntenin we have observed in all cell lines a very strong increase of RKIP at mRNA level but not of RKIP protein, suggesting intervention of post-transcriptional regulation mechanisms like proteasomal degradation, already supposed in this cancer type by us and others (9, 10).

Interestingly, inhibition of MDA-9/Syntenin expression induced NF-κB downregulation and contemporary a reduction of invasion ability in all the three HCC cell lines.

Moreover, we have evaluated expression of numerous factors after silencing with siRNA anti-MDA-9/Syntenin both at mRNA and protein levels, in particular NF-κB targets and markers of invasiveness and metastasis (E-cadherin, vimentin, MMP-2).

Given that Sp1 is activated by syntenin in SCLC cells (11), we have examined also Sp1 activation by siRNA anti-MDA-9/Syntenin, but the result of Sp1 activation assay excluded this theory in HCC.

Finally, we have investigated if MDA-9/Syntenin downregulation sensitizes HCC cell lines to cell growth inhibition by NF-κB inhibitors (DHMEQ and Curcumin), proteasome inhibitor (MG132), or conventional antitumor drugs (Doxorubicin and Cisplatin).

In conclusion our preliminary results on HCC models confirmed the key role of MDA-9/Syntenin in cancer biology, in particular regard to invasiveness capacity, and might suggest new therapeutic strategies.

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