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MicroRNAs and metastases

The neuroblastoma link

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MicroRNAs (miRNAs) are small noncoding RNAs of approximately 22 nucleotides in length that regulate gene expression post-transcriptionally. These small RNAs are fundamental regulators of several cellular processes, such as differentiation, development, apoptosis, proliferation, cell cycle regulation and metabolism, through the binding to 3' untranslated regions, coding sequence or 5' untranslated regions of target messenger RNAs (mRNAs), preventing their translation or causing their degradation.[1] A modest change in only one miRNA will affect multiple mRNA targets; consequently, the deregulation of miRNAs has important consequences to the cellular homeostatic stability, and aberrant miRNAs expression patterns have been described in several types of cancer.[2] Recently, miRNAs have been implicated in the metastatic process of several tumors such as human breast and colorectal cancers[3] and, as reported this issue of *Cancer Biology & Therapy* by Guo et al. in neuroblastoma.[4] These are extracranial solid tumors, arising from neural crest cells, that are most common in infants and children; metastasis, the main cause of death, is present at the time of diagnosis in approximately 60% of patients.[5] Metastatic disease may cause bone pain, bone marrow suppression and weight loss, but some patients do not present symptoms.[6] Therefore, the study by Guo et al. is important for the identification of specific miRNAs responsible for metastasis not only to better understand the molecular behavior of theses tumors but also to identify markers of early diagnosis/prognosis, and in the future, possible new therapeutic targets.

Using a heterotopic transplant mouse model of neuroblastoma and a microRNA microarray analysis approach, Guo et al. identified 54 miRNAs differentially expressed between primary and metastatic neuroblastoma tumors.[4] Three of the top ten downregulated miRNAs in this study, namely miR-7, miR-338-3p and the let-7 family, have an anti-metastatic role in other tumors types.[7] Specifically, in breast cancer, Reddy et al. described that endogenous miR-7 expression is positively regulated by the homeodomain transcription factor HoxD10, a gene that has been linked with the invasive and metastatic potential in human breast cancer cells. In this breast cancer cell line, the authors showed that miR-7 introduction suppresses motility, invasiveness, anchorage independence and tumorigenesis.[8] Regarding miR-338-3p, it has been suggested that this microRNA contributes to the formation of basolateral polarity in epithelial cells, which can be important for metastasis prevention.[9] Concerning the let-7 family, several studies demonstrate that it can inhibit tumorigenesis and metastasis as it targets important oncogenes such as RAS, MYC and HMGA2. Interestingly, MYC and let-7 are involved in a feedback loop since MYC can be a target of let-7 and at the same time can control its expression. In breast tumor cells, Dangi-Garimella et al. demonstrate that RKIP represses metastasis, in part, through a signalling cascade that involves the inhibition of MAPK, MYC and LIN28, leading

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to the induction of let-7 and the consequent downregulation of its targets.[10]

In the present reported study, Guo et al. also identified several miRNAs whose association with metastases was not previously described. In futures studies, it will be important to further analyse those miRNAs with the purpose of understanding their functional role in metastisation. In addition to the identification of miRNAs involved in the neuroblastoma metastatic process, and using computer-aided algorithms, Guo et al. suggest potential mRNA targets that can be regulated by those miRNAs. Interestingly, some of those targets have been described as deregulated in neuroblastoma.[4] For example, according to Guo et al. miR-29-a/b is overexpressed in metastatic neuroblastoma and one of the predicted targets of this microRNA is CASP8. The absence of this apoptosis-mediated protein has been implicated in neuroblastoma metastasis in vivo. In chick embryos, Stupack et al. detected lung and bone marrow neuroblastoma metastases mostly in embryos bearing tumors deficient in CASP8 when compared to CAPS8-positive tumors. Furthermore, reconstitution of CASP8 expression significantly suppressed metastasis.[11] The authors propose that unligated or antagonised integrins on the neuroblastoma cell surface activate a CASP8-dependent checkpoint and block cell invasion into an inappropriate microenvironment.[11] This mechanism is inactive in the absence of CASP8.[11,12] Interestingly, integrins are also predicted to be a target of miR-29a/b, which is overexpressed in metastatic versus primary neuroblastoma.[4] In addition to CASP8 deletion and methylation,[12] it is tempting to speculate that another mechanism by which CASP8 is downregulated in metastatic neuroblastoma is through miR-29a/b overexpression. However, it is imperative to validate this hypothesis through functional studies.

It will be important in future studies to functionally validate the interference between the other miRNAs that were differently expressed (primary versus metastatic NB) in the Guo et al. study and the predicted targets. In humans, neuroblastoma can metastasize to bone, bone marrow, lung, liver and/or non-contigous lymph nodes.[13] It will be also interesting to analyse differences at the microRNA level between the different metastatic sites.

In conclusion, the identification of differentially expressed microRNA in the metastasis of neuroblastoma is an important step towards the understanding of the metastatic process in this disease.

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