

Highly skewed distribution of miRNAs and proteins between colorectal cancer cells and their exosomes following Cetuximab treatment: biomolecular, genetic and translational implications

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ABSTRACT:

It has been convincingly proposed that exchange of molecules via exosomes is a means of intercellular communication in eukaryotes, especially within the tumour microenvironment. However, there are no data on the alterations of exosomal molecular cargo caused by cues as pharmacological anticancer treatments. To approach this issue, we determined the abundance of 754 miRNAs and 741 cancer-related proteins in exosomes secreted by Caco-2 (Cetuximab-responsive) and HCT-116 (Cetuximab-resistant) colorectal cancer cells before and after Cetuximab treatment; these profiles were then compared with those from whole source cells. Cetuximab significantly altered the molecular cargo of exosomes from Caco-2, as we detected: (1) increased abundance of miRNAs and proteins activating cell proliferation and proinflammatory processes; (2) a decrease of miRNAs and proteins related to immune suppression. These changes did not overlap with those in source cells, suggesting a Cetuximab-linked distribution bias. Molecular changes of a minor extent were also detected in exosomes from HCT-116. Transfection of exosomes from Cetuximab-treated Caco-2 into HCT-116 significantly increased HCT-116 viability; conversely, Caco-2 transfected with exosomes from treated HCT-116 did not show viability alterations. This suggests that the molecular phenotype of source cells is important for determining both the exosomal cargo as the biological effects of transferred exosomes. Gene Ontology analysis of networks, comprising targets of differentially expressed (DE) exosomal miRNAs and proteins, demonstrates a significant involvement of biological processes related to proliferation control, inflammation, immune response and apoptosis. Our data contribute to extend our knowledge on molecular mechanisms of intercellular communication in eukaryotes, especially in the context of oncological processes. Their translation to clinical settings is likely to add new weapons to the existing therapeutic repertoires against cancer.