Extracellular vesicles and their microRNA cargo serve as biomarkers and communicators in liquid biopsies in liver disease

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Liquid biopsies (serum or plasma) are of great interest in the diagnosis and prognostication of liver diseases. Extracellular vesicles (EVs), that contain nucleic acids including microRNAs and proteins are produced by most cell types in the liver, are being exploited in biomarker discovery. We have shown that different types of liver injury (alcoholic, drug-induced or inflammation-related) result in increased levels of circulating EVs and these EVs are enriched in miR-122 indicating hepatocyte injury or miR-155 indicating liver inflammation. We found significantly increased number of circulating EVs in mice with alcoholic liver disease (ALD). Exosomes represented most of the EVs (~80%). MicroRNA array of EVs revealed a significant increase of 7 inflammatory miRs (miR-192, -122, -30a) in alcohol-fed mice compared to controls and of those miRNAs showed excellent diagnostic value by ROC analyses. In patients with acute alcoholic hepatitis, we found a significant increase in the number of circulating EVs compared to controls with an increase in miR-192 and miR-30a in their cargo. Mass spectrometric analysis of circulating EVs in mice revealed a distinct signature of proteins involved in inflammatory responses, cellular development, and cellular movement between ALD EVs and control EVs. We also identified uniquely important proteins in ALD EVs that were not present in control EVs. Finally, we found that ALD EVs injected intravenously into alcohol naive mice were taken up by hepatocytes and MØs in the recipients' livers. The biological activity of ALD EVs in recipient mice was indicated by increased numbers of inflammatory (M1) Kupffer cells and infiltrating macrophages, while the percentage of anti-inflammatory (M2) macrophages was decreased. We identified heat shock protein 90 in ALD EVs as the mediator of ALD-EV - induced macrophage activation. These results indicate a specific miRNA and protein signature of ALD EVs and demonstrate a functional role of circulating EVs in ALD.

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