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602.MYELOID ONCOGENESIS: BASIC

Biological Role of Extracellular Vesicles in Myeloid Neoplasms: A Systematic Review of the Current Literature

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Background and aim: Extracellular vesicles (EVs) are lipid-bilayer membrane vesicles secreted by a variety of cells that carry bioactive molecules like proteins, lipids and nucleic acids. They are of increasing interest as they play an important biological role in cancer by a multitude of cell-extrinsic and cell-intrinsic mechanisms. However, the investigations of their biology in myeloid malignancies has not been systematically reviewed so far. Therefore, the aim of this review was to summarize the currently published literature in the field and provide an overview of their potential clinical applications.
Method: We performed a systematic literature research with defined search strings in the *Embase*, *Medline* and *PubMed Central* databases and used a standardized data-extraction form to collect all relevant information.
Results: 63 of 1529 studies met the inclusion/exclusion criteria and could be assigned to seven main investigational categories (*A*). They comprised studies on their effect on i) prothrombotic activity (n=13), ii) tumor-microenvironment (n=14), iii) malignant transformation (n=5), iv) tumor progression (n=4), v) chemotherapy-resistance (n=5) as well as their use as vi) biomarkers (n=14) and vii) pharmacotherapeutic carriers (n=3) (*B*). The most relevant biological mechanism is the transfer of microRNA (miRNA) by EVs from different clonal and non-clonal cells, which target the microenvironment, vascular system, as well as immune cells. All mechanisms identified in our review were assigned to one of the seven main categories and the most relevant are summarized in *C:* i) Prothrombotic activity: Leukaemic cells shed prothrombotic EVs containing tissue-factor (TF) and anionic phosphatidylserine (PS), which facilitate the recruitment of coagulation factors and a pro-coagulant state (*Zannoni, 2019*). Reduction of EVs from platelets and leucocytes after chemotherapy attenuates this pro-coagulant state (*Van Aalderen, 2011*). ii) Tumor microenvironment: EVs derived from MDS cells can disrupt the osteolineage differentiation of bone marrow mesenchymal stromal cells (BM-MSCs) and impair hematopoiesis (*Hayashi, 2022*). iii) Malignant transformation: EVs containing BCR-ABL1 mRNA are integrated into BM-MSCs, which induce BCR-ABL1 expression and secretion of TGF-β1 leading to enhanced proliferation of BM-MSCs (*Fu, 2017*). iv) Tumor progression: EVs derived from leukemic cells promote tumor progression by reducing apoptosis and tumor immune-surveillance. v) Chemotherapy resistance: AML-cells expel PEGylated liposomal doxorubicin (PLD) through EVs thus increasing their resistance (*Hekmatirad, 2021*). vi) Disease biomarkers: AML patients at diagnosis have a higher number of EVs carrying the myeloblast markers CD34, CD117, CD33 and HLA-DR than AML patients in remission or healthy controls (*Tzoran, 2015*). Based on differential abundancy and the content of proteins, lipids and nucleid acids EVs may be suitable as biomarkers for diagnosis, prognosis, and disease monitoring. vii) Pharmacotherapeutic role: Cytotoxic T-lymphocytes are more effective in killing the parental leukaemic cells after being exposed to their cell-derived EVs. The mechanism is related to leukemia antigen presentation on EVs to dendritic cells (DCs) using ICAM1 and Hsp70 (*Shen C, 2011*). Finally, EVs can be used as carriers for bioactive compounds and may expand their potential use for cell-type specific delivery of drugs.
Conclusions: EVs open the window for the future investigation of novel pathophysiological mechanisms that will improve our understanding of their role in the biology of myeloid malignancies, Moreover, they hold promise as potential biomarkers and drug carriers for cell-type specific treatment

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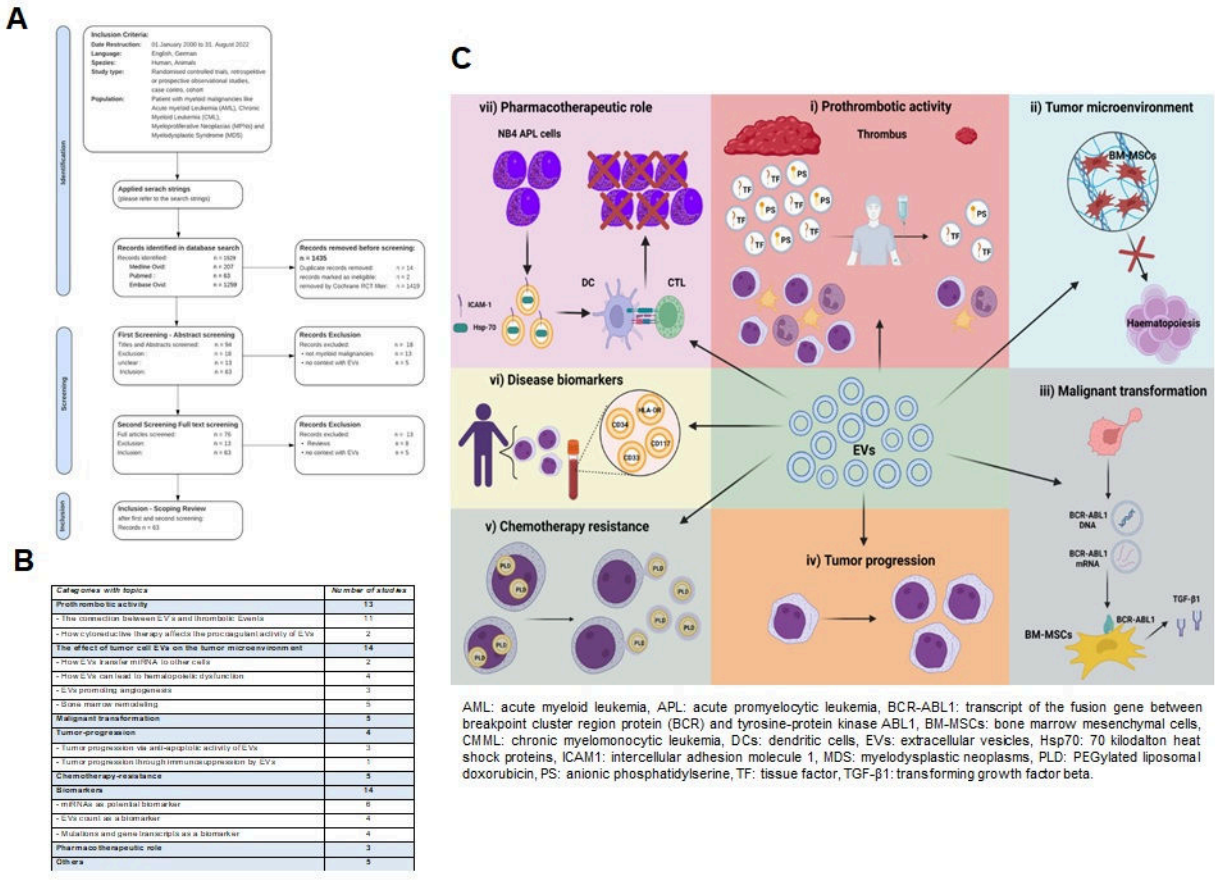

Figure 1

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