mgr Agata Braniewska

Zbadanie pobierania hemoglobiny przez makrofagi i jej przekazywania komórkom nowotworowym

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: dr hab. n. med. Tomasz Rygiel

Zakład Immunologii

Wydział Lekarski

Warszawski Uniwersytet Medyczny

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Agata Braniewska

Tomasz Rygiel

Streszczenie w języku angielskim

Investigation of Hb uptake by macrophages and its transfer to cancer cells.

Hemoglobin (Hb) belongs to the group of iron-binding proteins and is involved in the transport of oxygen and carbon dioxide. Hb performs its physiological function inside erythrocytes, whereas free Hb shows prooxidative and proinflammatory properties. Therefore, to prevent negative consequences of free Hb, a specific detoxification system exists in the body: extracellular Hb is bound by serum protein haptoglobin and taken up by CD163 receptor on macrophages, where Hb is degraded to amino acids, carbon monoxide, iron, and bilirubin. This constitutes a fundamental manner of Hb processing in macrophages. Our group has observed that Hb can be transferred from macrophages to other cells, including cancer cells.

This study aimed to verify uptake of Hb by macrophages, as well as to characterize the new phenomenon of Hb transfer and to investigate the molecular mechanism of Hb transfer. Most of the experiment was carried out using macrophages differentiated from monocytic cell line THP-1 and cancer cell lines MDA-MB 231 and SKOV3, as well as human macrophages differentiated from blood monocytes, murine macrophages differentiated from bone marrow cells and cell line RAW 264.7

Obtained results indicate that among peripheral blood mononuclear cells only monocytes took up Hb. All tested macrophages - human and murine, primary cells and cell lines – took up Hb. Results suggest that macrophages can uptake Hb independently of haptoglobin and CD163 receptor.

Transfer of Hb from macrophages to cancer cells was verified using flow cytometry, confocal microscopy, and fluorescence correlation spectroscopy. All examined macrophages were able to transfer Hb to cancer cells. Transfer of Hb grew with time. Results of experiments indicate that transfer of Hb is protein-unique since other protein – bovine serum albumin - which is taken up by macrophages, is not transferred to cancer cells. Hb transfer is not restricted to cancer cells as Hb was transferred between macrophages.

In this study we excluded the engagement of tunneling nanotubes in Hb transfer. We showed that secretion mechanism is involved in Hb transfer as Hb was transferred through culture medium. Finally, we proofed the release of Hb by macrophages in extracellular vesicles and then its uptake by cancer cells.

Due to the presence of iron in the Hb molecule, the process of Hb secretion by macrophages can be considered as an element of iron recycling. Alternatively, the release of Hb from macrophages loaded with this protein seems to protect the cell from ferroptosis, an iron-dependent cell death. The mechanism of Hb transfer from macrophages to cancer cells can be used in cellular anti-cancer therapy, in which the drug will be linked to Hb, loaded into macrophages,

and then administered to the patient. In a potential therapy, macrophages will migrate to the tumor site and will deliver the Hb-conjugated drug to the cancer cells.

To conclude, this study describes a new phenomenon of Hb transfer from macrophages to cancer cells through extracellular vesicles. The observation of this so far unknown process prompts the continuation of research on Hb metabolism.