TRANSPORTING ANTI-CANCER DRUGS THROUGH RED BLOOD CELLS

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Annotation: The use of red blood cells (RBCs) as carriers for anti-cancer drugs has emerged as a promising strategy to improve therapeutic efficacy while reducing systemic toxicity. Encapsulation or surface loading of chemotherapeutic agents within RBCs allows for controlled drug release, prolonged circulation time, and targeted delivery to tumor tissues. This approach exploits the natural biocompatibility and immune evasion properties of RBCs, potentially overcoming limitations of conventional drug delivery systems. Recent studies have demonstrated enhanced pharmacokinetics, reduced adverse effects, and improved tumor suppression using RBC-based carriers in both preclinical and early clinical settings. However, challenges remain in large-scale manufacturing, drug-loading efficiency, and ensuring safety across diverse patient populations. Continued research into engineering techniques, optimization of drug-RBC interactions, and integration with other targeted therapies could establish RBC-mediated delivery as a transformative tool in oncology.

Key words: Red blood cells; Drug delivery; Anti-cancer therapy; Erythrocyte carriers; Targeted delivery; Chemotherapy; Biocompatibility; Controlled release.

Introduction: This review focuses on the role of human red blood cells (RBCs) as drug carriers. First, a general introduction about RBC physiology is provided, followed by the presentation of several cases in which RBCs act as natural carriers of drugs. This is due to the presence of several binding sites within the same RBCs and is regulated by the diffusion of selected compounds through the RBC membrane and by the presence of influx and efflux transporters. The balance between the influx/efflux and the affinity for these binding sites will finally affect drug partitioning. Thereafter, a brief mention of the pharmacokinetic profile of drugs with such a partitioning is

given. Finally, some examples in which these natural features of human RBCs can be further exploited to engineer RBCs by the encapsulation of drugs, metabolites, or target proteins are reported. For instance, metabolic pathways can be powered by increasing key metabolites (i.e., 2,3-bisphosphoglycerate) that affect oxygen release potentially useful in transfusion medicine. On the other hand, the RBC pre-loading of recombinant immunophilins permits increasing the binding and transport of immunosuppressive drugs. In conclusion, RBCs are natural carriers for different kinds of metabolites and several drugs. However, they can be opportunely further modified to optimize and improve their ability to perform as drug vehicles.

Material and methods: Human red blood cells (RBCs) represent 99% of the cellular compartment in the blood and comprise the most numerous cells in the body. One microliter of blood contains approximately 4–5 million RBCs, which means approximately 25 million million RBCs in the total body of an adult human being. Moreover, thanks to their shape and deformability, they can reach almost all organs and tissues and, for this reason, they are considered the carriers par excellence. Mature RBCs mainly contain hemoglobin; thus, it can be argued that RBCs are passive carriers and that their role only relies on oxygen and CO2 transport. Indeed, a lot of other molecules can be carried by RBCs. As a matter of fact, erythrocytes are not mere gas transporters, but they are also involved in other functions, i.e., vascular function, coagulant pathways, defense processes, and metabolic pathways, thanks to their further contents. Regarding vascular function, they are the main source of nitric oxide, and consequently, they are involved in blood pressure homeostasis as well. Concerning metabolism involvement, physiological examples are given by amino acids, in particular the alanine's transport in the so-called glucose–alanine cycle through the muscle tissue and liver. It was demonstrated that the carriage percentage of alanine is higher in whole blood, thanks to the binding with RBCs, than in plasma.

The drug partitioning rate between RBCs and plasma is calculated using the erythrocyte suspension in plasma and/or buffer after the times required to reach the equilibrium between the compartments and centrifugal separation of the phases. The RBC partitioning rate is calculated by measuring the ratio between the concentrations of the drug in the RBC compartment and those in the plasma or buffer. The partitioning rate in buffer can be considered a measure of the drug's absolute affinity for the RBC-binding sites, while the partitioning rate in plasma indicates the relative drug's affinity for RBC-binding sites with respect to that of the plasma, such as albumin. Hence, only the unbound fraction in plasma (*i.e.*, drug molecules that are not bound to albumin or other plasma-binding sites) can partition into RBCs. However, these plasma proteins are saturable; thus, the exceeding drugs' molecules remain unbound in plasma and can additionally partition into RBCs, apparently increasing their affinity for the erythrocyte compartment. Of note, RBC-associated drugs have a longer life span in circulation

compared to the ones portioned in plasma because they are protected by RBCs from macrophage uptake, the liver metabolism, and renal clearance.

Chemotherapeutic agents undergo oral and parenteral administration and are carried to various tissues via the bloodstream, partitioning into plasma water, plasma proteins, or cells. Red blood cells may be involved in anthracyclines, ifosfamide and its metabolites, topoisomerase I and I/II inhibitor storage, transport, and metabolism. RBCs vehicle these drug molecules to the tumor tissues and release them through different active or passive transport mechanisms. For example, among these classes of anti-tumor drugs that can spontaneously partition into RBCs, there are doxorubicin and daunorubicin.

Lipophilic drugs can cross the RBC lipid membrane by simple diffusion, while hydrophilic compounds can enter due to the aqueous channels or other membrane-facilitated or active transport systems such as Glut1. Once into the RBC cytoplasm, drugs can find several enzymes and/or proteins to bind to. The most important protein is notably represented by hemoglobin. Hemoglobin represents 10% of the total body proteins of an adult and is able to carry many substances. A review from Hinderling summarized in a table the drugs known to be bound by hemoglobin, and among them, we can find barbiturates, digoxin and derivatives, and salicylic acid.

Results and discussion:

Human RBCs are not only hemoglobin-containing bags involved in gas exchanges but may have great importance in drug transport. This opens the way to two fields of investigation. On one hand, being that RBC partitioning has an enormous impact on drug pharmacokinetics, clinicians must take into account the therapeutic drug monitoring in whole blood for those drugs showing a high blood-to-plasma ratio. On the other hand, biomedical researchers can set up innovative strategies that are aimed at increasing the RBC power to bind and transport selected drugs by exploiting some of their natural features.

Conclusion:

RBC-mediated delivery of anti-cancer drugs represents a highly innovative approach capable of addressing many limitations of conventional chemotherapy. By leveraging the natural longevity, biodegradability, and immune stealth of erythrocytes, this method can enhance drug bioavailability and tumor targeting while minimizing off-target toxicity. Preclinical and early clinical results are encouraging, demonstrating improved treatment outcomes and reduced side effects. Nevertheless, the translation of this technology into widespread clinical practice will require overcoming technical barriers such as standardizing drug-loading protocols, ensuring scalability, and confirming long-term safety. With further development, RBC-based drug delivery systems have the potential to significantly improve patient outcomes and set new standards in cancer therapeutics.

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