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The manipulation of natural killer cells to target tumor sites using magnetic nanoparticles

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ABSTRACT

The present work demonstrates that Cy5.5 conjugated Fe_3O_4/SiO_2 core/shell nanoparticles could allow us to control movement of human natural killer cells (NK-92MI) by an external magnetic field. Required concentration of the nanoparticles for the cell manipulation is as low as ~20 μg Fe/mL. However, the relative ratio of the nanoparticles loaded NK-92MI cells infiltrated into the target tumor site is enhanced by 17-fold by applying magnetic field and their killing activity is still maintained as same as the NK-92MI cells without the nanoparticles. This approach allows us to open alternative clinical treatment with reduced toxicity of the nanoparticles and enhanced infiltration of immunology to the target site.

1. Introduction

A variety of solid nanoparticles, such as metals, metal oxides and semiconductors nanoparticles, possess unique chemical and physical properties and have been widely utilized for biomedical applications, such as molecular imaging probes and nanomedicine [1–5]. However, many problems including chemical toxicity, biodegradability, and excretive clearance still remain to be solved before their clinical translation [6–8]. According to H. S. Choi et. al., for example, CdSe quantum dots with a hydrodynamic diameter above 5.5 nm cannot perfectly be eliminated by renal filtration, which leads to their prolonged retention time in the blood circulation [6]. Therefore, numerous nanoparticles with few tens nm in size maybeeasily accumulate in the non-targeted organs such as liver, spleen, kidneys, and lung, although we could well design the surface of the nanoparticles for specific targeting through various biomodification procedures [9–11]. This fact plus the potential toxic degradation components of the nanoparticles seriously limits the ability to advance nanoparticles to clinical applications [6–8]. Compared to nanoparticles, cells used for therapy like immunological cells have minimum cytotoxicity problems [12]. Especially, natural killer (NK) cells are well known a type of lymphocyte and play a central role in the tumor elimination from our body. However, it is often difficult to control the trafficking of these cells to target sites. The reason for this is not clear but may involved direct immune evasion strategies employed by cancer cells [13]. Nevertheless, clinical studies have demonstrated that increased tumor infiltration by NK cells correlate with improved prognosis and suggest that enhancement of NK cell infiltration could be a useful anti-tumor strategy [14]. The cell sorting method based on magnetic nanoparticles could be a promising alternative approach to resolve two main problems associated with the nanoparticles and cell based therapy. Because required concentration of the nanoparticles to control the cell could be very low and the cells incorporated with magnetic nanoparticles could then be isolated and attracted under the external magnetic field [15–19]. Whereas this technique has been used to not only enrich and detect circulating tumor cells in the blood stream but also delivery stem cells in injury site, its use for magnetic guided in-vivo delivery of immunological cells has been rarely reported so far. [17,18,20]

In this study, we demonstrate that magnetic iron oxide (Fe_3O_4) nanoparticles can control the movement of human natural killer (NK-92MI) cells using an external magnetic field. NK cells comprise

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