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Living immune cells as drug carriers in cancer therapy

Although there has been great progress in cancer therapy in the past decades, a continuous increase in new cases and cancer deaths could not be prevented. According to the World Health Organization, the global burden of cancer doubled in the last third of the 20th century and continues to rise mainly because of population aging and growth (1). Moreover, the developing world progressively adopts cancer-causing behaviors, particularly smoking, which additionally affects the cancer rates (2).

Many serious courses of cancer are due to the low effectiveness of existing treatments. However, limited efficacy is not the only drawback of existing therapies. In addition, many standard treatments (chemo- and radiation therapies) lack specificity and are therefore accompanied by severe adverse effects. Hence, alternative more effective treatment modalities are required which allow selective targeting of tumors in order to reduce undesirable side effects.

At present, immunotherapies involving autologous cytotoxic T lymphocytes (T cells) are among the most promising new cancer therapy approaches. Today, the combination of preparative lymphodepletion, TIL (tumor-infiltrating lymphocytes) infusion and interleukin-2 administration represents the most effective treatment for patients with metastatic melanoma who no longer respond to other therapies. Besides, retargeting strategies involving virally transduced, chimeric antigen receptor (CAR) expressing or bispecific antibody (bsAb) redirected T lymphocytes have shown promising clinical outcome including complete, durable regressions (3, 4).

Given the curative potential of T cell therapies, it is not surprising that T lymphocytes also have been explored in the context of cell-mediated drug delivery. Using T lymphocytes and other defense cells as transport vehicles for anti-cancer therapeutics offers several advantages: Unlike artificial drug carriers, immune cells actively move towards sites of inflammation, injury and cancer. This intrinsic homing ability allows efficient enrichment of immune cell-delivered therapeutics at the target site. Furthermore, some defense cells including T lymphocytes possess a natural cytotoxic activity that can additionally be exploited to fight malignancies, as specified above. However, the development of cell-based drug delivery systems for cancer therapy also includes great challenges: At first, living carrier cells must be efficiently protected against their toxic drug payload. Furthermore, controlled release and action of delivered pharmaceuticals at the target site should be achieved (5).

The research team of Anja Philippi at the Korea Institute of Science and Technology (KIST) Europe develops novel cancer immunotherapies which exploit on the one hand the intrinsic killing function of redirected cytotoxic T lymphocytes. In addition, the cells will be used as targeted delivery system for anti-cancer drugs. To preserve T cell viability and functions, two different strategies have been explored until now.

The first approach was jointly developed by KIST Europe, Claus-Michael Lehr from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) and Gerhard Wenz from Saarland University. It aims to encapsulate toxic chemotherapeutic agents in nanoparticles in order to protect loaded lymphocytes from the drug effect. In particular, newly prepared maleate-based polyesters have been used as encapsulation material. Furthermore, gold shell nanoparticles have been tested (unpublished results).

To enable long-term survival of loaded T cells and specific activation of the drug at the target site, the team of Anja Philippi focuses now on stimulus-sensitive anti-cancer drugs. In a proof-of-concept study, T cells were incubated with a novel polymer-photosensitizer complex which was developed by Marc Schneider (Philipps University Marburg) (6). T cell viability and cytotoxic function were not impaired if upon loading the cells were kept in the dark. In co-cultivation experiments the light-inducible drug was transferred from loaded T lymphocytes to carcinoma cells and induced cancer cell death if co-cultures were illuminated. Furthermore, a combined T cell-drug effect on target cells was observed (unpublished results).

Thus, stimulus-sensitive pharmaceuticals such as photosensitizers provide an attractive solution for preventing premature death of carrier cells which has been a major drawback of cell-based transport of anti-cancer drugs until now. The novel concept opens up new

perspectives in the field of cell-mediated drug delivery, but also T cell therapies could benefit from the findings described. Furthermore, the selectivity and efficacy of photodynamic therapy (PDT) could be enhanced by using cytotoxic T lymphocytes as transport vehicles for photosensitizing agents.

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Anja Philippi studied Biology at the University of Saarland (Saarbrücken, Germany). She conducted her doctoral thesis at the Biochemistry Center of the University of Heidelberg, Germany and the Biochemistry department of the University of Regensburg, Germany where she graduated in 2007. In May 2008, Dr. Philippi joined the Korea Institute of Science and Technology (KIST) Europe in Saarbrücken. After an initial phase as postdoctoral fellow, she became team leader of the Cellular Immunotherapy team in April 2010. Her research interests include cancer immunotherapies, cell-mediated drug delivery, nano-drug carriers, stimulus-sensitive drugs and the tumor microenvironment including tumor-associated macrophages.

André-René Blaudszun studied Biochemistry at the Ruhr-University Bochum, Germany. In 2007 he graduated and joined the Korea Institute of Science and Technology (KIST) Europe as a research assistant. Since 2010 he is enrolled as a PhD student at Saarland University in Saarbruecken, Germany. As a member of the Cellular Immunotherapy Team at KIST Europe and in cooperation with the Department of Biopharmaceutics and Pharmaceutical Technology at Saarland University his PhD work focuses on T lymphocyte-mediated drug delivery.