Molecular Biology

Name of the Student

Name of the University

Author Note

News

Leukemia is a type of bone marrow/blood cancer. It is a fatal disease that affects haematopoiesis along with immune defence mechanism of body. Chemotherapeutic approach is often problematic because the drugs used for the treatment of leukemia is often toxic to the other healthy growing cells like the stem cells and thereby affecting the normal haematopoiesis mechanism. Hence targeted delivery of the cytotoxic drugs towards the human malignant blood cells causing leukemia is considered as one of the promising approach for success treatment of leukemia (Vick and Mahadevan 2016). This is because, the targeted drug delivery model will specifically target the faulty malignant cells of leukemia via side-passing the normal proliferating haematopoietic stem cells and thereby helping to reduce the limit of cyto-toxicity (Vick and Mahadevan 2016).

The discovery conducted by Yasinska et al. (2018), aims to analyse the efficacy of citrate-stabilised gold nano-particles (AuNPs) in conjugation with T-cell immunoglobulin and mucin domain 3 as a medium for drug delivery. The importance of this approach is AUNPs have anti-inflammatory properties and are unable to affect the cells in their own. Thus this targeted drug delivery model will help to kill the leukemic cells selectively while reducing overall toxicity on other healthy proliferating cells (Yasinska et al. 2018).

Yasinska et al. 2018 used gold nano-particle over the human leukemia cell-line. The binding of the cytotoxic drugs was monitored via the expression of the actin molecules (cell surface molecules) through phosphorylation of the mTOR pathway in Western blot analysis. Cell surface expression of Tim-3 protein (marker protein) was analysed via FACS (fluorescence activated cell sorter). They coupled anti-Tim antibody with gold nano-particle via employing glutathione (GSH) as a linker. Avogardo constant was taken into consideration in order to calculate the amount of bounded antibody (1 mole of anti-Tim-3-ScAb contained 6.023x 1023 antibodies). Following the antibody mobilization, the unbounded surface of the

gold nano-particle was covered with rapamycin (cytotoxic) molecules conjugated with GSH ester. The success of the conjugate generation was then verified via near-UV and far-UV spectrophotometry. The structure which is responsible for the conjugate formation was found to be beta-plated sheet of the protein structure on the basis of far-UV and SRCD spectrum. Thus they concluded that the single chain antibody-GSH is attached with the gold nanoparticles via co-valent bonding while retaining beta-strand configuration. They further tested the stability of the nano-conjugates via incubating the materials at an increasing pH and temperature levels and showed that both anti-Tim antibody and rapamycin are coupled with the gold nano particles via GSH that contains cysteine amino acids. It has been previously reported that numerous antibody molecules can be successfully immobilised over one nano-particles and hence they used 1:1 ration in order to ensure that there were adequate space on the surface of gold nano-particles to be covered by rapamycin. They used anti-Tim-3 to conjugate with the gold nano-particles because human myeloid leukemia cell line express Tim-3 molecules which acts as the trafficker and a receptor for galectine-9. Galectine-9 is a protein that protects leukemic cells from host defence. Via employing FACS they found that undifferentiated leukemic human cell line have less surface bound tim-3 and galectin-9 in comparison to differentiated cell lines. Thus based on the results of the Western blot then found that successful inhibition of the mTOR-dependent phosphorylation of eIF4E-BP in human leukemic cell line is dependent on the amount of the expression of Tim-3 on the cell surface. Anti-Tim-3 molecules which are coupled with the gold nano-particles reacted with human leukemic cell line and thereby performing endocytosis. GSH then undergoes lysis via membrane bound enzymes releasing rapamycin inside the target cells. Significance of GSH cleaving is, only free rapamycin is capable of inhibiting mTOR activity inside the leukemic cells and cleaving of GSH sets rapamycin free. Their study also elucidated that the in order to gain a comprehensive abrogation of mTOR activity in the THP-1 cells, the

concentration of free rapamycin has be 10 micro-meter in concentration. The summarised version of the results showed that targeted nano-carrier enables the delivery of toxic drugs inside the leukemic cells with high level of eficacy under the action of Tim-3 expression. However, they also concluded that successful delivery of the cytoxic drugs inside the leukemic cells is dependent on the expression of the target protein (Tim-3). Further studies are required to be undertaken via employing in-vivo and ex-vivo system in order to test the efficacy of these findings (Yasinska et al. 2018).

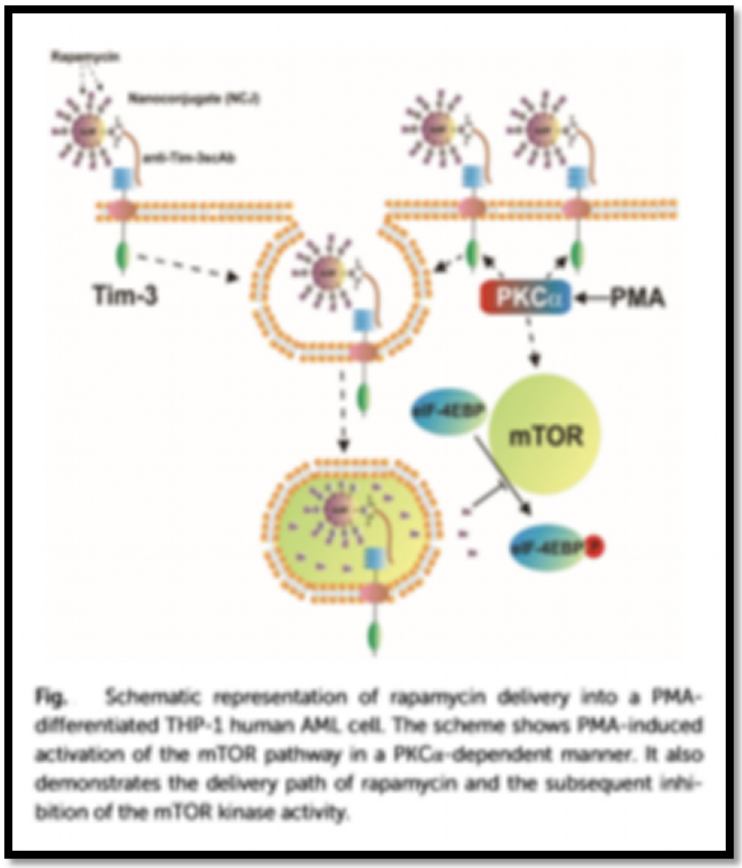

Fig. Schematic representation of rapamycin delivery into a PMA-differentiated THP-1 human AML cell. The scheme shows PMA-induced activation of the mTOR pathway in a PKCα-dependent manner. It also demonstrates the delivery path of rapamycin and the subsequent inhibition of the mTOR kinase activity.

(Source: Yasinska et al. 2018)

Views

The discovery conducted by Yasinska et al. 2018 is immensely effective in the domain of cancer therapy because, it provides an unique exposures towards the effective

framing to targeted drug delivery to the leukemic cells via nano-particles. According to von Roemeling et al. (2017), nano-medicine offers unique advantage towards treating human cancers. The human body possesses specific innate responses towards the nano-particles (NPs). This nano-response when combined with unique pathophysiological signatures under the tumor micro-environment can severely restrict the utility of nanomedicine under oncological settings. Furthermore, the study conducted by Yasinska et al. 2018 showed an actual image of advancement in the domain of cancer immune-therapies, proper understanding of the nano-immune interactions and development of immune-smart cancer nanomedicine, which can subsequent advantage of body's immune functions. According to von Roemeling et al. (2017) a better understanding of acquired biological processes that guide the fate of nano-medicine is an integral pillar towards the development of effective individuals' framework for curing cancer patients. The study conducted by Yasinska et al. 2018 is relevant in this domain and thus proving to be effective in the parameter of science and technology. The study also uncovered the opportunities in the domain of cancer nano-medicine that capitalize the increasing understanding of the tumour biology, the cell-surface receptors of the cancer molecules and their interactions with the nano-paticles and thereby helping to develop effective nano-therapeutic approaches for cancer patients. This is extremely significant in the domain of science and technology because the study gave a detailed insight about the stimulus-triggered drug release, while facilitating delivery of the drug to the intracellular sites via targeting cell surface molecule (Shi et al. 2017).

References

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