What's up in nanomedicine?

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The publications, discussed here are selected exemplarily among many other excellent publications. This also applies to the mentioned conferences or events. We very much appreciate your feedback on the column, suggestions for topics to be argued about, or other related information. As was already stated the purpose of this column is to present novel and/or significant developments within the multidisciplinary field of nanomedicine or significant developments in other scientific areas.

Publications digest

Ultrasound and nano/microbubbles for molecule delivery

Lymph nodes are important in responses of the immune system, antigen collection and in case of a solid tumor, the tumor cells are capable of migrating into the lymphatics of the primary tumor's environment. Therefore, the lymphatic system can be considered as the delivery route for therapeutic molecules, vaccines and diagnostic reagents. Sentinel lymph nodes are likely involved in the spread of tumor cells and therefore the status of these nodes are seen as an independent additional factor in the prognosis in disease (1). Diagnostic techniques such as ultrasound, magnetic resonance imaging and histological confirmation (biopsy) are used to investigate a possible metastasis to the sentinel lymph nodes (2–4). In the case of head and neck cancer, where a metastasis is confirmed, the removal of the sentinel lymph node is the primary option to increase the survival rate of the patient (5). Often this is not without side effects such as nerve injuries or fibrosis of the scar. Animal models to investigate lymph node metastasis are limited and therefore treatment methods are not fully explored yet. In earlier work done by this group, animal models (mice; MXH10/Mo/lpr) were developed with lymph node sizes similar to those found in humans (10 mm in mice 2.5–3 months age) (6, 7). When tumor cells are injected into the subiliac lymph nodes, metastasis in the proper axillary lymph can be introduced (7). In their current work, Kato et al. used their mice model to develop a new lymphatic delivery method (8). Liposomes were generated by the reverse phase evaporation method (1,2 distearoyl-sn-glycero-phosphatidylcholine and 1,2 distearoyl-sn-glycero-3-phasphatidylehtanolamine-methoxy-polyethylene glycol [ratio 94:6 mol/mol]). The nano/microbubbles were generated from the liposomes by sonication and in the presence of C_3F_8 gas. The main diameter provided was 199±84.4 nm, and about 0.01% had diameters that exceed a few micrometers. Approximately 80% of these bubbles contained liquid alone and 20% contained both liquid and gas. The fluorophore used in this investigation was TOTO-3. A solution containing the nano/microbubbles and fluorophores was injected into a subiliac lymph node and delivered to the proper axillary lymph node through the lymphatic vessels, which was confirmed by applying a contrast enhanced high frequency ultrasound imaging system. After exposure to destructive ultrasound, the fluorophores were taken up by the lymphocytes. This new method paves the way towards new clinical treatments of lymph node metastasis.

Targeting mitochondria in cancer cells

Mitochondria are important membrane bound eukaryotic organelles involved in tasks like the supply of energy, signaling, the cell cycle, growth and cell death (9). When cells are exposed to ionizing radiation, the mitochondria exhibit an increased oxidative stress, an adjusted function and may even induce cell death (10, 11). Thus, the enhancement of mitochondria by ionizing radiation, leading to apoptosis may offer possibilities to cancer treatment. Gold nanoparticles have been used as a radio-sensitizing agent for a variety of radiation sources (MV-kV photon spectra)

in a wide variety of cell lines [e.g. (12–14)]. Many tumors have an enhanced permeability and poor lymphatic drainage that enables the accumulation of gold nanoparticles in the tumors' microenvironment as presented by Upreti et al. (15), while in another study an uptake of 19:1 (tumor vs normal tissue) has been reported (16). The nanoparticles enter the cell via endocytosis and remain mainly in lysosomes, however, this depends on both size and coating properties of the nanoparticles (17, 18). Other investigations present the uptake of nanorods in lung carcinoma cells (19) and presence on or near the outer membrane of mitochondria (20). Thus, if enough gold nanoparticles are present in or near the mitochondria of cancer cells, the local dose enhancement arising from these particles may be investigated. Dose enhancement has been studied by others using Monte Carlo methods, however, not for mitochondria as presented by Kirby and Ghasroddashti (21). The investigators used the code developed by Salvat et al. (22). First, simple distributions were generated of localized dose enhancement around gold nanoparticles after the irradiation by individual monoenergetic photons. This was followed by the generation of models of mitochondria with gold nanoparticles attached to their outer membrane, which were than "exposed" to X-ray spectra from 6 MV to 90 kVp. As an example, the work of Karakatas et al (20) was used, who showed in their publication a mitochondrion covered with 565 gold nanoparticles (13 nm diameter). From the calculations it was concluded that the dose enhancement ratios [1] were the highest in the kilovolt range, [2] depend on the dimensions of the mitochondrion, [3] the number of gold nanoparticles, and [4] the thickness of the gold nanoparticle coating. The presented work suggests further investigation of the role of the mitochondrium in cellular response to radiation and a novel possibility for radiation therapy where the mitochondria are the target.

Bone regeneration in periodontitis

Periodontitis is a disease caused by bacteria that form biofilms, which induce a chronic inflammation resulting in the destruction of the supporting tissues of the teeth and osteoclast mediated bone resorption (23). Leukocytes are important for, e.g. killing of bacteria, secretion of inflammation cytokines, activation of osteoclasts (24). However, in susceptible individuals the inflammation might be unable to resolve which will result in a chronic inflammation in the periodontium and may lead to bone loss (25). At present there is urgent need for new therapeutics in regeneration due to our actual incapability to control the inflammation during regeneration (26).

Microparticles, which are shed by cell membranes, can be used to generate nano-proresolving medicines. The incorporation of proresolving lipid mediators enables the targeting of specific tissues as was shown by an investigation of Dalli et al. (27). Here an increased survival in animal models of sepsis is found. Lipoxin A_4 is such a lipid mediator.

In earlier investigations done by part of the authors of the work highlighted here, it is found that in rabbit periodontitis, the agonists of resolution of inflammation prevent periodontal bone loss and in addition, in case of existing periodontitis the regeneration of the periodontal bone occurs. Agonists include lipoxins and resolvins. In addition, it was found that lipoxins have direct anabolic actions on bone, which is in agreement with the increased actions that were observed in bone regeneration. The topical application of lipoxin stable analogs showed a dramatic reduction of the leukocyte infiltration, inflammation and bone loss (28).

Van Dyke et al. (26) generated nano-proresolving medicines containing the stable lipoxin analog benzo-lipoxin A_4. The nanomedicine was clinically evaluated in a large animal model of inflammation induced bone loss (Hanford miniature pig). Even though the number of animals used was not enough to generalize, the results are robust, valid and show evidence for a new regeneration mechanism of bone lost to inflammatory disease (e.g. periodontitis). The generated nano-proresolving medicine is transferred to the serum membrane receptors of bone cells and as well to the leukocytes regulating their responses to stimulate the formation of bone. While the bone is remodeled, the biofilm environment is controlled as a result of the cellular events, which are initiated by benzo-lipoxin A_4. This further results in an up regulation of the endogenous proresolving lipid mediators and direct actions on the bone cells which influences osteogenesis. The result is a significant regeneration of the connective tissue and bone and a recovery of the periodontal organ.

Upcoming events

Oxford University (United Kingdom), each year organizes a summer school that focuses on applications of nanotechnology. This year a Nanomedicine Summer School 2015 will be held from June 29th to the 3rd of July lead by key scientists from the field. Topics included are: nanomedicine diagnostics, nanopharmaceuticals, nanobiosensors, nanotechnologies for regenerative medicine and tissue engineering. This course is an introduction to

nanomedicine and interesting for scientists, health professionals and regulators. For more details see: https://www.conted.ox.ac.uk/ courses/details.php?id=J990-22

The 4th International Symposium on Sensor Science (I3S 2015) will be held from 13th to 15th of July in Basel (Switzerland). Part of this event overlaps with the nanomedicine field and presents the latest developments and exciting aspects in sensor sciences. Topics include: sensor applications for medicine, environmental monitoring, etc., sensor devices and sensor arrays/nanosensors and neurosensors. For the current keynote and invited speakers, see: http://sciforum.net/conference/ I3S2015/page/schedule and for more information see: http://sciforum.net/ conference/I3S2015.

The IEEEE conference on Nanotechnology 2015 will be held from 27th to 30th July in Rome (Italy). This conference is an excellent place to exchange knowledge and ideas, interactions and inspiration in a wide variety of branches in nanoscience and nanotechnology (e.g. nanobiology, nanofluidics, nanomaterials and 2D materials, nanomedicine and multiscale modeling and simulation). The event includes, track sessions, workshops, plenary and invited talks, exhibition of hardware, software and equipment. See also: http://www.ieeenano15.org.

Finally, I hope to meet you at the CLINAM summit from June 28th until July 1st at the Swiss Trade Fair congress Center (www.clinam.org).

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