Merging cold plasmas and biomaterials for osteosarcoma therapy

Cristina Canal[1,2,3*]

[1] Biomaterials, Biomechanics and Tissue Engineering Group, Department of Materials Science and Engineering, Universitat Politècnica de Catalunya (UPC), Av. Eduard Maristany 14, 08019 Barcelona, Spain; * cristina.canal@upc.edu
[2] Barcelona Research Center in Multiscale Science and Engineering, UPC, Barcelona, Spain
[3] Research Centre for Biomedical Engineering (CREB), UPC, Barcelona, Spain

Biomaterials are employed for tissue and organs regeneration or functional repair, including delivery of therapeutics. In bone regeneration and repair, incorporation of drugs to biomaterials has been investigated as a means of providing additional functionalities to the material, and plasma processes contributed to bone biomaterials ie. through polymerisation processes to modulate the drug release[1].

With the evolution of plasma devices, great advances have been made in therapies based in cold atmospheric plasmas (CAP)[2,3]. Production of reactive oxygen and nitrogen species (RONS) in liquids (water, saline solutions, cell culture media) resulting from treatment by cold atmospheric plasmas (CAP) has been focus of interest in the last years[4]. Plasma chemistry leads to the generation of an abundance of reactive species (RONS) such as H_2O_2, NO_2^-, NO_3^-, O_3^-, $ONOO^-$, etc.[2,4,5] which are suspected to play a key role in selective cancer cell death without damaging surrounding healthy tissues. Such effects of plasmas in liquids open the door for minimally invasive therapies that we aim at investigating for osteosarcoma, and expand from liquids to biomaterials which allow a sustained release of the plasma-generated RONS to the diseased site. In fact, the development of efficient vehicles which allow local confinement and delivery of RONS to the diseased site is a fundamental requirement. In this sense, biocompatible polymers with ability to form 3D networks can be an alternative to deliver the plasma-generated RONS locally. We will discuss the use of different hydrogels[6,7] for plasma treatment and their outcomes, as compared to Plasma Conditioned Liquids (PCM)[8,9]; in general, their physic-chemical properties remain unchanged by the plasma treatment. Their capacity to generate RONS during plasma jet treatment is highly dependent on the chemistry of the polymer solution, but often several-fold higher concentrations can be obtained than in a typical isotonic saline solution. The hydrogels show capacity for sustained release of the RONS. The biological effects of the treated hydrogels in osteosarcoma are discussed with regard to the different reactive species generated in the PAM (ie. $[H_2O_2]$, $[NO_2^-]$, short-lived RONS).

Lastly, we will discuss on the implications of using 3D models to evaluate the effects of PCM, by comparing both mouse OS tumour sections in organotypic culture[10], as well as in a tumor model generated from a composite scaffold.

Acknowledgement. This project has received funding from ERC under the European Union's Horizon 2020 research and innovation programme (grant agreement No714793).

References

1. K. Khurana et al. Plasma polymerized bioceramics for drug delivery: Do surface changes alter biological behaviour? Eur. Polymer Journal 107, 25 (2018).
2. M. Keidar, Plasma for cancer treatment, Plasma Sources Sci. Technol. 24 (2015) 33001.
3. P.J. Bruggeman, et al., Plasma-liquid interactions: A review and roadmap, Plasma Sources Sci. Technol. (2016). doi:10.1088/0963-0252/25/5/053002.
4. D. Graves, *Plasma Process*, 11, 1120 (2014)
5. A. Khlyustova et al., Important parameters in plasma jets for the production of RONS in liquids for plasma medicine: A brief review, Front. Chem. Sci. Eng. (2019).
6. C. Labay et al. Production of reactive species in alginate hydrogels for cold atmospheric plasma-based therapies, Sci. Rep. 9, 16160 (2019).
7. I. Hamouda, et al. Investigating the atmospheric pressure plasma jet modification of a photo-crosslinkable hydrogel Polymer, 192, 122308 (2020).
8. C. Canal et al., Plasma-induced selectivity in bone cancer cells death, Free Radic. Biol. Med. (2017).
9. J. Tornin, et al. Pyruvate Plays a Main Role in the Antitumoral Selectivity of Cold Atmospheric Plasma in Osteosarcoma Sci Reports 9, Article number: 10681 (2019).
10. M. Mateu-Sanz et al. Cold Plasma-Treated Ringer's Saline: A Weapon to Target Osteosarcoma, Cancers, 12(1), 227 (2020).