Doctoral Dissertation
Doctoral Program in Bioengineering and Medical-Surgical Sciences (36th Cycle)

Bi-functional scaffold for bone regeneration after osteosarcoma resection

By

Ilaria Corvaglia

Abstract

Osteosarcomas are highly aggressive tumours characterized by low incidence but often associated with delayed diagnosis and treatments leading to high mortality. Clinical eradication of the tumour is the most common choice for bone cancer treatment, that causes large-sized bone defects. To address the difficulties in spontaneous healing of such large defects, artificial substitutes can be conceived to fill the void and at the same time to support tissue regeneration.

In this context, the main goal of my PhD research work was the development of a multifunctional device able to support bone regrowth after osteosarcoma surgical resection and to avoid at the same time tumour relapse thanks to the sustained release of chemotherapeutic drugs. The developed device will be composed of two parts: a 3D composite cylindrical sponge and a core-shell hollow cylinder in which the sponge will be placed.

To achieve this, the first objective of the work was the synthesis of magnesium substituted nano-hydroxyapatite particles aiming to mimic the composition of natural bone tissue. The synthesis aimed to produce particles with dimension similar to bone apatite crystals, with comparable crystallinity and composition. Magnesium ions, introduced at different molar contents, were added because of their well-known properties in promotion of bone regeneration, positively affecting both osteoblast differentiation and osteogenic potential.

The second objective of the work was the development of a composite sponge composed of gellan gum enriched with the synthesised nano-hydroxyapatite particles. At first different processing parameters have been tested to evaluate their respective influence on the sponges' morphological and structural properties. Then, once determined the most promising processing conditions, the composite sponge was created by following two routes. The first route is a one-step approach in which the inorganic phase was dispersed in the crosslinking solution; the second one is a two-step process in which the inorganic phase was dispersed in distilled water and added to the gellan gum solution, followed by the dropwise addition of the crosslinking solution. The two methods were compared, and a comprehensive characterization of the composite sponges performed. Finally, a preliminary biological assessment to evaluate the composite sponge biocompatibility has been performed using healthy human osteoblasts.

The third objective of the work was the development of a hollow core-shell electrospun cylinder able to release drugs in a controlled manner. To achieve this, the first step was the optimization of both core and shell solutions and then the core-shell electrospinning was tested with the most promising solutions. Then, once evaluated the effective core-shell morphology of the fibres, the chemotherapeutic drug was introduced in the core solution and its release from the core-shell fibres was evaluated. Lastly, a preliminary biological evaluation on human osteosarcoma cells was performed to confirm the cytotoxicity of the electrospun membranes loaded with the chemotherapeutic compound.

Finally, the last objective of my PhD work was the combination of the two parts to assemble the multifunctional bicomponent scaffold. The bicomponent scaffold was preliminary characterized in terms of magnesium ions and drug release, swelling properties and *in vitro* degradation kinetics.