Nanostructured glyco-ECM mimetics: glycosylated tools for modeling lung cancer stem cell niche.

Giulia Bertolini
IRCCS National Cancer Institute

In lung cancer CD133+ cells represent the subset of cancer stem cells (CSCs) able to sustain tumor growth and metastatic dissemination. Similarly to normal stem cells, CSCs reside in specialized niches composed of both stromal cells and extracellular matrix proteins (ECM), mostly constituted of collagen that represents a pivotal regulator of adhesion, survival and proliferation of tumor cells. The relevance of collagen glycosylation, a fundamental post-translational modification controlling several biological processes, in regulating tumor cell phenotype remains largely unexplored.

To investigate the bioactive effects of differential ECM glycosylation on lung cancer cells, we prepared collagen based ECM mimetics functionalized with different sugar epitopes (glucose, galactose). We demonstrate that culturing of tumor cells on nanostructured glyco-ECM mimetics determines a selection of CSCs and triggers their expansion/generation. The functional relevance of $CD133^{+}$ CSCs increase was validated *in vivo*, proving an augmented tumorigenic and metastatic potential.

Mechanistically, we show that inhibition of the collagen-binding integrin β1 in tumor cells prevents CSCs enrichment, indicating that binding of integrin β1 to glyco-ECM epitopes subtends CSCs expansion/generation. Accordingly high expression of integrin β1 in its active form is associated with an increased proficiency of tumor cells to sense glycol-ECM signalling and to acquire stemness features.

By the exploitation of nanostructured glyco-ECM mimetics we provide evidence suggesting that collagen glycosylation could play an essential role in the creation of a niche favorable for the generation and selection/survival of lung CSCs. Interfering with this cross talk may represent an innovative therapeutic strategy for lung cancer treatment.