1. Record Nr. TD18002444

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Titolo	INDUCED PLURIPOTENT STEM CELLS: AN INNOVATIVE TOOL TO DISSECT OVARIAN CANCER PATHOGENESIS [Tesi di dottorato]
Editore	Università degli Studi di Milano, 2016-03-18
Lingua di pubblicazione	Inglese
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	diritti: info:eu-repo/semantics/openAccess In relazione con info:eu-repo/semantics/altIdentifier/hdl/2434/366384
Sommario	Ovarian cancer (OC) has one of the highest death-to-incidence ratios among all tumor types, which points to the need for novel therapeutic and prognostic strategies. Indeed, the absence of relevant tumor cell lines that can recapitulate disease histopathology highlights an acute need for new model systems to study this pathology. In particular, it is still unclear whether the most common and aggressive form of this disease, high grade serous ovarian cancer (HGSOC), could arise from in the ovarian surface epithelium (OSE), as initially thought, or might be arising from the fimbrial epithelium. Here I addressed these issues in two complementary ways based on induced pluripotent stem cells: i) the modeling of Ovarian Cancer by somatic cell reprogramming to pluripotency of tumor cells; ii) the molecular characterization of HGSOC and its putative cells of origin. Somatic cell reprogramming, by erasing tumor-associated epigenetic marks while preserving the underlying genetic mutations, would allow for the first time the precise dissection of genetic and epigenetic contribution to this disease, through the differentiation of OC-iPSC into disease-relevant cell types. I demonstrated the feasibility of OC reprogramming through a non-integrative platform, showing that OC-derived iPSC are closely similar to human ESC, and proving their tumoral origin by whole

	exome sequencing. Moreover, I showed that independent iPSC clones derived from the same tumor upon trilineage differentiation in vivo show differential tumorigenic potential. For a more precise dissection of this phenotype, I set up a differentiation protocol that allows differentiation of pluripotent cells into mesodermal progenitors, that are precursors of both fimbria and OSE. To isolate a pure population of these cells, I resorted to CRISPR/Cas9 to integrate a selection cassette in the MIXL1 locus. By this approach, I was able to show correct gene targeting at the intended site, allowing also for selection of mesodermal progenitors upon differentiation of normal iPSC. The same approach translated to OC-derived iPSC would allow to study the effects of genetic mutations deprived of tumor-associated epigenetic marks during differentiation, both at the stage of mesodermal progenitors and in cells directed towards the female reproductive epithelium in vivo. The second approach relies on the identification of specific molecular features of fimbria and ovarian surface epithelium, the two putative cells of origin of HGSOC. On this side, I offer a first glimpse on molecular features of HGSOC cancer and normal gynecological tissues. I could show that specific DNA methylation signatures of fimbrial epithelial cells and ovarian surface epithelium cells are partially retained in tumor samples and stratify HGSOC samples according to the putative cell of origin of this tumor. Moreover, I show for the first time a description of histone modifications in primary HGSOC, concentrating on marks of activation/repression sitting on promoter regions (H3K4me3 and H3K27me3, respectively) and marks that characterize active/closed-poised enhancers (H3K4me1, H3K27ac and H3K27me3).
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