1. Record Nr. TD21001680

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Titolo	LSD1-DIRECTED THERAPY HINDERS GLIOBLASTOMA BY DEREGULATING ATF4-DEPENDENT INTEGRATED STRESS RESPONSE [Tesi di dottorato]
Editore	Università degli Studi di Milano, 2020-12-11
Lingua di pubblicazione	Inglese
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	diritti: info:eu-repo/semantics/embargoedAccess In relazione con info:eu-repo/semantics/altIdentifier/hdl/2434/789247
Sommario	Glioblastoma (GBM) is a devastating tumor, whose heterogeneity, poor blood-brain barrier penetration and hierarchical organization obstacle the amelioration of the standard of care. A therapeutic breakthrough may be represented by the eradication of GBM tumor initiating cells (TICs), responsible of its growth and relapse. By exploiting patient-derived TICs and orthotopic xenograft models, I have demonstrated that Lysine-specific histone demethylase 1 (LSD1) is a druggable target in GBM TICs and that a novel, specific LSD1 inhibitor (LSD1i) is brain penetrant and well tolerated. LSD1i impairs growth, viability, stem-like traits and tumorigenic potential of GBM TICs and this phenotype is mirrored by LSD1 genetic targeting. My data point to LSD1 as a novel positive regulator of the activating transcription factor 4 (ATF4), the hub of the Integrated Stress Response (ISR), an adaptive pathway activated in response to nutrient shortage and accumulation of unfolded proteins, stressful conditions to which GBM is often subject. LSD1 targeting sensitizes GBM TICs to stress, triggering a maladaptive response eventually culminating in cell death. Finally, I show that LSD1 and ATF4 may cooperate to regulate the expression of ISR mediators and that LSD1i may deregulate this process by displacing the ATF4 trans-activator

	CBP from the LSD1-protein complex, thus shedding light on the importance of LSD1 scaffolding functions in GBM TICs. Overall, LSD1-directed therapy is likely a promising strategy to hinder GBM, and its effectiveness independently of GBM TIC heterogeneous molecular landscape places a strong rationale toward the rapid clinical translation of this approach for GBM treatment.
Localizzazioni e accesso	http://memoria.depositolegale.it/*/http://hdl.handle.net/2434/789247