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Sommario	Acute myeloid leukaemia (AML) is the most frequent leukaemia in adults, and still represents a disease with an unmet medical need, with 50-60% of patients relapsing within 3 years after diagnosis. AMLs are characterised by a high degree of intra-tumour heterogeneity, both at the biological and the genetic level, which is critical for tumour maintenance and response to treatments. Biologically, AMLs are organised hierarchically, with rare stem-like cells (leukaemia stem cells, LSCs) endowed with the unique properties of self-renewal and differentiation. Genetically, AMLs harbour patient-specific combinations of different driver mutations, which are organised within individual cases in sub-clones with distinct growth properties. We hypothesized that tumour maintenance and relapse in AMLs are driven by the selective expansion of quiescent sub-clones within the LSC population, which serve as the genomic and functional reservoir of the tumour. The experimental strategy we employed to test this hypothesis is based on the xenotransplantation of human leukaemias, the implementation of an in vivo clonal tracking approach, the functional isolation of leukaemic subpopulations with diverse proliferation histories and whole-exome sequencing (WES) of bulk and isolated leukaemic subpopulations. Our aims were to assess the proliferative

	hierarchy of LSCs and to examine their intrinsic genetic heterogeneity. We identified two functional LSC classes, quiescent and cycling, that are in equilibrium in the tumour and largely share the same clonal architecture. We further observed that genetic leukaemic clones appear to consist of a high number of individual LSCs, the majority of which exhaust upon serial transplantation. Finally, by genetic analyses of isolated leukaemic subsets, we were able to detect a specific enrichment for rare mutations in the quiescent compartment of two patient xenografts. Our data indicate that tumour evolution is sustained by the quiescent LSC pool and suggest that their highly proliferating counterpart has a finite lifespan. We expect that the results of our studies will provide new insights into the mechanisms of disease progression and treatment response in AML, and potentially reveal novel therapeutic approaches.
Localizzazioni e accesso	http://memoria.depositolegale.it/*/http://hdl.handle.net/2434/471776