Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell and Molecular Medicine
幹細胞分子医学分野

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Stem cells have the remarkable capacity to both self-renew and give rise to many types of more specialized cells in the body, which explains their great therapeutic potential in regenerative medicine. But that's not the only reason stem cells have become such a hotbed of scientific inquiry. These cellular transformers also offer an invaluable research tool for probing the disease mechanisms that underpin cancer, aging and a host of other health problems. Our major interest is to elucidate the mechanisms of self-renewal and multi-lineage differentiation of hematopoietic stem cells (HSCs). We are also interested in how the deregulated HSC functions are associated with aging of our body and the development of age-related hematological malignancies. We approach these issues mainly from the view point of epigenetics.

1. Chromatin accessibility in stem cells unveils progressive transcriptional alterations in myelodysplastic syndrome

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Myelodysplastic syndrome (MDS) originates from hematopoietic stem cell (HSC) clones with acquired gene mutations. However, the molecular characteristics of MDS stem cells remain poorly understood. Here, we show that the chromatin accessibility profiles of MDS stem cells more accurately reflect disease status than those of progenitor cells and reveal the process of stem cell alterations during disease progression. Characterization of differentially accessible regions (DARs) showed that MDS stem cells acquire progenitor-like chromatin accessibility during disease progression, leading to disruption of the normal stem-progenitor hierarchy. Profiling of transcriptional factor-binding motifs at DARs further uncovered precocious activation of myeloid transcriptional networks in MDS stem cells, with a concurrent loss of HSC-associated regulatory programs. In particular, increased chromatin accessibility at CEBP target sites represented the myeloid reprogramming status of MDS stem cells. Newly developed "progenitor scores" based on chromatin accessibility stratified disease status and correlated well with prognosis. These findings indicate that chromatin landscapes of MDS stem cells define their cell-autonomous behavior and contribute to disease progression.

2. Identification of a CD138-negative therapy-resistant subpopulation in multiple myeloma with vulnerability to splicing factor inhibition

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The molecular basis of therapy resistance in multiple myeloma (MM) remains poorly understood. Here, we performed single-cell RNA sequencing coupled with VDJ-targeted sequencing of highly purified primary MM cells from patient bone marrow. This approach uncovered cellular heterogeneity and phenotypic plasticity of MM cells across a spectrum of CD138 expression, accompanied by drastic epigenetic alterations. Notably, therapy-resistant subpopulations were identified within a minor fraction of $CD138^-$ MM cells, which were shown via CRISPR/Cas9 screening to be vulnerable to splicing pathway inhibition. Consistently, this fraction of $CD138^-$ MM cells showed increased differential splicing associated with overexpression of SR protein family splicing factors. Among these splicing factors, RNA-binding protein 39 (RBM39) was overexpressed in therapy-resistant cells and involved in aberrant splicing. Both genetic and pharmacological RBM39 inhibition exhibited a significant lethal effect on MM cells. Collectively, our findings identify distinct therapy-resistant MM subpopulations and highlight targeting the splicing pathway as a promising therapeutic strategy.

3. Tracking *Clusterin* expression in hematopoietic stem cells reveals their heterogeneous composition across the lifespan

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Hematopoietic stem cells (HSCs) exhibit significant age-related phenotypic and functional alterations. Although single-cell technologies have elucidated age-related compositional changes, prospective identification of aging-associated HSC subsets has remained challenging. In this study, utilizing *Clusterin* (*Clu*)-GFP reporter mice, we demonstrated that *Clu* expression faithfully marks age-associated myeloid/platelet-biased HSCs throughout life. *Clu*-GFP expression clearly segregates a novel age-associated HSC subset that overlaps with but is distinct from those previously identified using antibodies against aging maker proteins or reporter systems of aged HSC signature genes. *Clu*-positive (Clu^+) HSCs emerge as a minor population in the fetus and progressively expand with age. Clu^+ HSCs display not only an increased propensity for myeloid/platelet-biased differentiation but also a unique behaviour in the BM, favouring self-renewal over differentiation into downstream progenitors. In contrast, *Clu*-negative (Clu^-) HSCs exhibit lineage-balanced differentiation, which predominates in the HSC pool during development but becomes underrepresented as aging progresses. Both subsets maintain long-term self-renewal capabilities even in aged mice but contribute differently to hematopoiesis. The predominant expansion of Clu^+ HSCs largely drives the age-related changes observed in the HSC pool. Conversely, Clu^- HSCs preserve youthful functionality and molecular characteristics into old age. Consequently, progressive changes in the balance between Clu^+ and Clu^- HSC subsets account for HSC aging. Our findings establish *Clu* as a novel marker for identifying aging-associated changes in HSCs and provide a new approach that enables lifelong tracking of the HSC aging process.

Publications

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