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Researchers propose novel theory for mammalian stem cell regulation

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Linheng Li, Ph.D., Investigator, together with Hans Clevers, M.D., Ph.D., Director of the Hubrecht Institute in Utrecht, Netherlands, co-authored a prospective review published today by the journal *Science* that proposes a model of mammalian adult stem cell regulation that may explain how the coexistence of two disparate stem cell states regulates both stem cell maintenance and simultaneously supports rapid tissue regeneration.

Adult stem cells are crucial for physiological tissue renewal and regeneration following injury. Current models assume the existence of a single quiescent (resting) population of stem cells residing in a single niche of a given tissue.

The Linheng Li Lab and others have previously reported that primitive blood-forming stem cells can be further separated into quiescent (reserved) and active (primed) sub-populations. Emerging evidence indicates that quiescent and active stem cell sub-populations also co-exist in several tissues — including hair follicle, intestine, bone marrow, and potentially in the neural system — in separate yet adjacent microenvironments. In the review, Dr. Li proposes that quiescent and active stem cell populations have separate but cooperative functional roles.

"Both quiescent and active stem cells co-exist in separate 'zones' in the same tissue," explained Dr. Li. "Active stem cells are the 'primed' sub-population that account for the generation of corresponding tissues,

whereas quiescent stem cells function as a 'back-up' or 'reserved' sub-population, which can be activated in response to the loss of active stem cells or to tissue damage."

The new model would explain how the balance can be regulated between stem cell maintenance and simultaneous support of rapid tissue regeneration, not only at the individual cell level but also at the stem cell population level. The advantage of maintaining 'zoned' sub-populations of stem cells is to increase longevity of stem cells within organisms that have long life spans and large bodies.

The existence of two sub-populations of adult stem cells offers another advantage in the rapidly regenerating tissues in mammals by reducing the risk for mutations that cause tumors.

Intriguingly, cancers may utilize this same mechanism to maintain co-existing active-quiescent pools of stem cell sub-populations that support fast tumor growth (by active stem cells) while preserving the root of malignancy (by quiescent stem cells). This may explain the basis of drug resistance to cancer treatment.

"If this hypothesis is true, the critical question will be how to target quiescent drug-resistant cancer stem cells," said Dr. Li. "We will test this model in cancers in an effort to determine how to activate quiescent (drug-resistant) cancer stem cells for further targeting."

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