Inhibiting CDK6 prevents leukemic relapse

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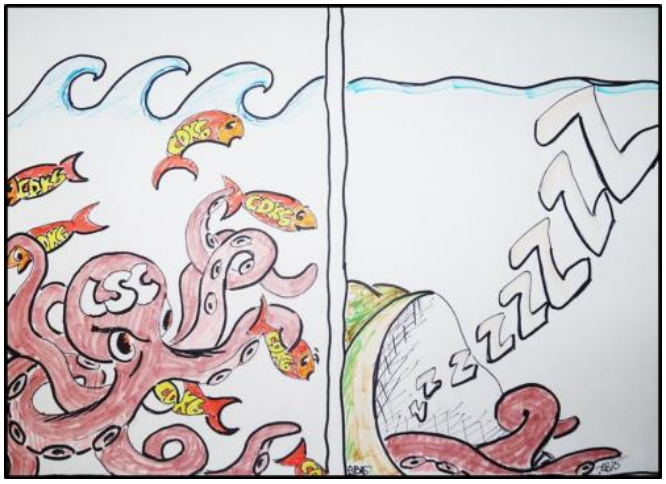

CDK6 is needed for leukemic stem cell activation (left). When CDK6 is absent, the LSC remains in a quiescent state and leukemia formation is prohibited (right). Credit: Angelika Berger/Vetmeduni Vienna

Despite enormous progress in cancer therapy, many patients still relapse because their treatment addresses the symptoms of the disease rather than the cause, the so-called stem cells. Work in the group of Veronika Sexl at the University of Veterinary Medicine, Vienna has given a tantalizing clue to a solution. In the current issue of *Blood*, the scientists report that the cell-cycle kinase CDK6 is required for activation of the stem cells responsible for causing leukemia.

Hematopoietic stem cells (HSCs) are normally inactive, i.e. quiescent. When new blood cells are needed, for example to replace blood that has been lost, HSCs start to multiply and develop into mature blood cells. If the process is initiated at an inappropriate time, hematopoietic diseases such as leukemia may result and leukemic stem cells may develop. These represent a major challenge to leukemia therapy: they are quiescent and thus protected from elimination by the immune system and from treatment such as chemotherapy. Leukemic stem cells frequently cause relapse in cancer patients, often years or even decades after an apparently successful treatment.

Working with stem cells isolated from mice, Ruth Scheicher and colleagues at the University of Veterinary Medicine, Vienna have investigated possible differences between leukemic stem cells and the healthy stem cells in the body. They looked in particular at the function of the CDK6 protein, which is known to be involved in controlling the cell cycle. Surprisingly, CDK6 was also found to regulate the activation of hematopoietic and leukemic stem cells, which it does by inhibiting the transcription factor Egr1. Upon loss of CDK6, Egr1 becomes active and prevents stem cells from dividing. In a further twist to the tale, the mechanism operates only when hematopoietic stem cells are stressed, e.g. in leukemia, and not in the normal physiological situation.

Scheicher is quick to note the significance of her finding: "CDK6 is absolutely necessary for leukemic stem cells to induce disease but plays no part in normal hematopoiesis. We thus have a novel opportunity to target leukemia at its origin. Inhibiting CDK6 should attack leukemic stem cells while leaving healthy HSCs unaffected."

More information: 'CDK6 as a key regulator of hematopoietic and leukemic stem cell activation' by Scheicher R, Hoelbl-Kovacic A, Bellutti F, Tigan AS, Prchal-Murphy M, Heller G, Schneckenleithner C, Salazar-Roa M, Zöchbauer-Müller S, Zuber J, Malumbres M, Kollmann K and Sexl V. *Blood*. www.bloodjournal.org/content/125/1/90.long

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