An ancient player that works on making proteins in our cells also helps stop bleeding

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*Background*

Platelets are one of the blood cells that have a critical role in stopping bleeding at times of injury. Low platelet counts occur in various conditions including genetic mutations, blood diseases, and adverse effects of cancer therapies. Patients with low platelet counts are at risk for life-threatening internal bleeding.

We found that an enzyme known to play a fundamental role in protein synthesis also has a previously unknown function in the regulation of platelet production. It is one member of a group of 20 enzymes (catalysts of reactions in the cell) that play an important role in making proteins. In addition to their basic role in protein synthesis, these enzymes gained additional functions as they evolved over the eons. For example, YRS, a member of this enzyme group, gained an extra segment during evolution (at the stage of fungi and insects), which it retained ever since. This extra piece is not required for its activity in protein synthesis.

The mystery was solved in 1991 when Schimmel and Wakasugi showed that human YRS can be activated in a way that unmasks new activities that involve this added segment. Interestingly, unlike the other 19 members of the enzyme group, YRS is abundant in platelets. Because platelets normally do not synthesize many proteins compared to other types of cells, we set out to search for its role in platelet biology.

We first studied how YRS influences platelet generation. To mimic a platelet-based human disease condition, mice were treated to give a condition of low platelet count. Then, they were treated with an activated form of YRS (YRSACT). This treatment enhanced platelet production and accelerated the recovery of their platelet count. In another line of investigation, mice were treated by irradiation to recapitulate the situation with cancer patients going through radiation therapy. As expected, platelet count was decreased after irradiation. Here again, YRSACT treatment mitigated the platelet decrease and accelerated recovery.

*How does a protein which normally works on protein synthesis help generate platelets?*

YRSACT targets a specific population of blood cells to induce production and release of factors that enhance expansion of platelet precursor cells in the bone marrow. Interestingly, we observed a unique population of these platelet precursor cells that were induced only when treated with YRSACT. The unique precursor cells induced by YRSACT are similar, although perhaps not identical, to those previously reported to be activated by inflammation from viral infection.

*Does YRS works on platelet production as a full-time job or part-time job?*

We speculate that YRSACT works continuously on platelet generation but also more prominently under conditions of stress. When the platelet count is decreased and there is an obvious need for rapid replenishment to prevent bleeding, YRSACT works more as a part of an emergency response. For example, platelet counts are often decreased by viral infections. In such situations, YRS released from cells may be activated for the purpose of rapid platelet replenishment.

*How does it help future medicine?*

Thrombopoietin (TPO) plays a major role in platelet generation. Agents that mimic the action of TPO have been used as therapeutics to increase platelet numbers. However, the clinical application is limited because, in certain patients, there is a serious risk of adverse effects. In addition, there are also patients who do not respond to TPO. Interestingly, our results suggest the mechanism of action of YRSACT is independent of TPO, in both mouse and human systems. This suggests that YRSACT has the potential to provide a new therapeutic option for patients suffering from low platelet counts. Also, as part of the possible therapeutic applications, we were able to show that, by differentiation of stem (primordial or precursor) cells from an afflicted patient, YRSACT successfully increased platelet precursor cells in culture in the laboratory. This suggests that YRSACT can be used to stimulate production of patients’ platelets outside the body, and then have these platelets re-introduced into the patient.

Finally, because YRS is a natural protein, its therapeutic application is expected to provide a safe treatment options with low risk of causing immune reactions and adverse effects. Indeed, in our work, no evidence of toxicity was seen in our studies in animals.