A new plasminogen receptor

Dudley K. Strickland  UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Efficient activation of the fibrinolytic pathway occurs when plasminogen and its activators are sequestered on the cell surface. Identification of receptors responsible for localizing plasminogen to the cell surface has been elusive. Using a proteomics approach, Andronicos and colleagues have identified a novel 17-kDa transmembrane receptor, termed Plg-R<sub>K</sub><sub>T</sub>, that binds plasminogen with high affinity and promotes its activation.<sup>1</sup>

Plasminogen is a zymogen that, when activated, is the major enzyme responsible for degrading fibrin<sup>2</sup> and is therefore critical for maintaining vascular patency. In addition, the plasminogen system facilitates monocyte migration<sup>3</sup> by promoting matrix degradation. It also functions in modulating the inflammatory response to bacterial pathogens.<sup>4</sup> Plasminogen has long been known to associate with cells via lysine binding sites located within its kringle domains, where it is more readily activated by its physiological activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), and is protected from inhibition by its primary inhibitor, α<sub>2</sub>-antiplasmin.<sup>5,6</sup>

The identification of molecules that sequester plasminogen on the cell surface has proven to be a fruitful yet challenging area of research as a number of cell-associated plasminogen-binding proteins have been identified. Several of these molecules contain carboxy-terminal lysine residues, a requirement for binding to the lysine binding sites on plasminogen. However, most candidate molecules, such as enolase-1,<sup>7</sup> have established intracellular functions, and thus it is not apparent how their cell-surface localization might be regulated. An attractive candidate for sequestering plasminogen to the cell surface is annexin II, a member of a family of phospholipid-binding peripheral membrane proteins that binds both plasminogen and tPA, and mediates the plasminogen-dependent invasion of matrix by monocytes.<sup>3</sup>

To identify a transmembrane cell-surface protein with a carboxy-terminal lysine residue that could function as a plasminogen receptor, Andronicos et al first identified a myeloid precursor cell line (Hoxa9-ER4) that was unable to bind plasminogen but could bind plasminogen after differentiation into monocytes.<sup>1</sup> To identify the molecule involved, the investigators first tagged the cell-surface proteins with biotin. Then they isolated the cell membranes and subjected the extracted proteins to affinity chromatography on plasminogen-Sepharose. The proteins eluted from this affinity step were then bound to immobilized avidin to capture the cell-surface proteins tagged with biotin. After elution and digestion of these proteins with trypsin, the digest was subjected to multidimensional chromatography and tandem mass spectrometry.

This procedure identified a single 147-amino acid protein, termed Plg-R<sub>K</sub><sub>T</sub> (plasminogen receptor with a C-terminal lysine) that is predicted to contain 2 transmembrane helices with a C-terminal lysine residue on the ectodomain. Studies demonstrated that the expression Plg-R<sub>K</sub><sub>T</sub> is induced when Hoxa9-ER4 cells are differentiated along the monocytic pathway. Plasminogen as well as tPA, which also contains lysine binding sites in its kringle domains, were shown to specifically bind to a carboxy-terminal peptide representing the C-terminal region of Plg-R<sub>K</sub><sub>T</sub> with a very high affinity. In M-CSF–differentiated Hoxa9-ER4 cells, Plg-R<sub>K</sub><sub>T</sub> colocalizes with the urokinase receptor (uPAR), a cell-
Targeting telomerase: T-cell friendly fire

Rodrigo T. Calado  National Institutes of Health

In this issue of Blood, Ugel and colleagues provide evidence that, in murine models, telomerase is an efficient target for adoptive cell therapy against a variety of cancer cells, but also can elicit an autoimmune response against B cells.1

Telomerase is a reverse transcriptase enzyme that elongates and maintains telomeres, the very ends of linear chromosomes. As DNA polymerase is unable to fully replicate the extremities of the linear DNA molecule during mitosis, telomeres become a little shorter after every cell division, eventually becoming too short to allow cell division and thus provoking cell senescence and apoptosis. Telomerase prevents telomere erosion and consequent cell senescence in highly proliferative cells.

The vast majority of cancers (> 90%) express telomerase to maintain their telomeres and their ability to proliferative indefinitely, making telomerase a good target candidate in treatment of cancer: it is present in many different types of cancers and is essential for unlimited proliferative capacity of most cancers. Different strategies to hit telomerase have been developed: telomerase inhibitors, telomere-disrupting agents, and telomerase vaccines.2 There are several clinical trials currently evaluating these approaches, but the results are not yet known. Ugel and colleagues used a different approach to target telomerase. They developed an adoptive cell therapy by expanding high-avidity T cells reactive against telomerase epitopes that, when injected back into transgenic mice, were able to hamper adenocarcinoma progression. The results also were impressive against human cancer. Using the mouse model, T cells specific against human telomerase abrogated tumor growth of several human cancer cell lines.

Because the use of adoptive cell therapy has been effective in the clinic only for patients with melanoma, these results are promising and suggest that using the right targets, adoptive cell therapy may go far beyond melanoma.

However, the injection of T cells reactive against telomerase induced a severe depletion of B cells in peripheral blood, lymph nodes, and spleen. B-cell lymphopenia happened because telomerase expression is not specific to cancer cells. Normal tissues also express telomerase, especially cells with high proliferative requirements. B cells express telomerase and hence are potential targets for transferred reactive T cells. These findings raise important issues on the use of telomerase as a target for the immune therapy of cancer. In humans, telomerase is expressed by T and B cells, as well as by hematopoietic stem and progenitor cells, which could be targeted by transferred T cells reactive against telomerase, inducing clinically relevant cytopenias. Deficient telomerase due to genetic mutations are associated with bone marrow failure syndromes, such as aplastic anemia and dyskeratosis congenita. It is not surprising that using telomerase as the target epitope may eventually cause destruction of lymphocytes or even hematopoietic progenitors in the bone marrow. In fact, a major toxic effect of telomerase inhibitors in current clinical trials appears to be hematologic. Taken together, the results available so far suggest that targeting telomerase may further suppress hematopoiesis, deepening myelosuppression caused by chemotherapy. The findings by Ugel and colleagues suggest that the use of telomerase as a target for adoptive cell therapy against cancer has to be conducted with caution and hematologic toxicity has to be monitored carefully.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


A new plasminogen receptor

Dudley K. Strickland