maximal utility. In this regard, it is noteworthy that the administration of gal-1 successfully removed autoreactive T cells from a model of experimental multiple sclerosis.[5]

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

REFERENCES

1. Werlen G, Hausmann B, Naeher D, Palmer E. Signaling life and death in the thymus: timing is everything. Science. 2003;299:1859-1863.

2. Leishman AJ, Gapin L, Capone M, et al. Precursors of functional MHC class I- or class II-restricted CD8alphaalpha(+) T cells are positively selected in the thymus by agonist self-peptides. Immunity. 2002;16:355-364.

3. Hernandez JD, Baum LG. Ah, sweet mystery of death! Galectins and control of cell fate. Glycobiology. 2002;12: 127R-136R.

4. Camby I, Le Mercier M, Lefranc F, Kiss R. Galectin-1: a small protein with major functions. Glycobiology. 2006; 16:137R-157R.

5. Offner H, Celnik B, Bringman TS, et al. Recombinant human beta-galactoside binding lectin suppresses clinical and histological signs of experimental autoimmune encephalomyelitis. J. Neuroimmunol. 1990;28:177-184.

● ● ● ● **HEMOSTASIS**

Comment on Stepanova et al, page 100

Urokinase: the identity crisis continues

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Although urokinase-type plasminogen activator (uPA) was first identified due to its role in fibrinolysis, new studies increasingly uncover novel mechanisms by which uPA may regulate cell physiology. In this issue of *Blood*, Stepanova and colleagues demonstrate that binding of single-chain uPA to nucleolin facilitates nuclear translocation of uPA and promotes expression of smooth muscle α–actin (α–SMA).

In many multidomain proteases, exosites regulate protease activity by facilitating zymogen activation, controlling reaction with inhibitors, and localizing the protease with substrates. However, in some proteases, the enzyme active site may be regulatory, and the principal function may be something other than peptide-bond hydrolysis. uPA was first identified as 1 of 2 major mammalian plasminogen activators. The function of uPA in fibrinolysis is supported by the observation that simultaneous deletion of the genes for uPA and tissue-type plasminogen activator (tPA) in mice causes more severe thrombosis than tPA deletion alone.[1]

The activity of uPA is intimately linked with that of its primary cell-surface receptor, uPAR. uPA-binding to uPAR, which requires the N-terminal EGF-like domain in uPA, mobilizes a cascade of cell-surface proteases that may support cell migration and tissue remodeling. Furthermore, uPA-binding to uPAR triggers cell signaling to factors such as ERK/MAP kinase and Akt.[2] Regulation of cell signaling downstream of uPAR has been implicated in cell migration, cell survival, gene transcription, and processes integral to cancer progression, such as epithelial-mesenchymal transition.[3] The low-density lipoprotein receptor–related protein (LRP-1) functions as a second uPA receptor, albeit with lower affinity. The principal function of LRP-1 in regulating uPA probably involves endocytosis and catabolism; however, LRP-1 also controls cell signaling in response to uPA-Serpin complexes.[4]

The interaction of single-chain uPA with nucleolin, as described by Stepanova and colleagues, represents a novel pathway by which uPA may regulate cell physiology. Their biochemical and imaging studies provide compelling evidence that nucleolin shuttles intact single-chain uPA to the nucleus. Nuclear translocation of uPA appears to be necessary for regulating the expression of α-SMA, a marker of myofibroblasts implicated in processes such as pulmonary fibrosis and atherosclerosis.[5] Thus, in a manner reminiscent of thrombin, the interaction of uPA with cells may involve a menu of receptors and pathways. Based on K_D values, one might argue that binding of uPA to uPAR should be favored; however, biochemistry occurring at the cell surface is not an equilibrium system, and many high-affinity interactions are dominated by slow off-rate constants.

How might the pathway selected by uPA be regulated? The authors show that mild acidification decreases the binding affinity of uPA for uPAR almost 10-fold while increasing the binding affinity for nucleolin. They argue that this shift may favor uPA association with nucleolin in endosomes. Although this is plausible, one must also consider the extracellular tumor microenvironment and its propensity for acidification.[6] Finally, the fact that 2-chain uPA does not localize to the nucleus emphasizes the importance of understanding various regions in the structure of uPA that are cleaved by plasmin, converting single-chain uPA into 2-chain uPA, high-molecular-weight uPA into low-molecular-weight uPA, and deleting the EGF-like domain.[7] These reactions may play a pivotal role in controlling how uPA affects cell physiology.

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

REFERENCES

1. Carmeliet P, Schoonjans L, Ream B, et al. Physiologic consequences of loss of plasminogen activator gene function in mice. Nature. 1994;368:419-424.

2. Blasi F, Carmeliet P. uPAR: a versatile signaling orchestrator. Nat Rev Mol Cell Biol. 2002;3:932-943.

3. Lester RD, Jo M, Montel V, et al. uPAR induces epithelial-mesenchymal transition in hypoxic breast cancer cells. J Cell Biol. 2007;178:425-436.

4. Webb DJ, Thomas KS, Gonias SL. Plasminogen activator inhibitor 1 functions as a urokinase response modifier at the level of cell signaling and thereby promotes MCF-7 cell growth. J Cell Biol. 2001;152:741-752.

5. Hinz B, Phan SH, Thannickal VJ. The Myofibroblast: one function, multiple origins. Am J Pathol. 2007;170:1807-1816.

6. Tredan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst. 2007;99:1441-1451.

7. de Munk GAW, Rijken DC. Fibrinolytic properties of single chain urokinase-type plasminogen activator (pro-urokinase). Fibrinolysis. 1990;4:1-9.

● ● ● ● **IMMUNOBIOLOGY**

Comment on MacFarlane et al, page 131

Inhibitions in NK-cell maturation

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Adaptor molecules serve as intracellular protein-protein interaction platforms that are required to amplify and diversify signals received at the plasma membrane. Accordingly, adaptors play important roles for lymphocyte development and function.

B-cell adaptor for phosphatidylinositol 3-kinase (BCAP) is a cytosolic adaptor that connects the B-cell receptor (BCR) to the phosphatidylinositol 3-kinase (PI3K) pathway.[1] Mice deficient for BCAP have reduced numbers of mature B cells, which expand poorly in response to BCR stimulation.[2] This is accounted for, in part, by an increase in activation-induced B-cell death in vitro, which translates into a reduced life span of mature B cells in vivo.[2] Indeed, the antibody response to T cell–independent antigens is strongly reduced in the absence of BCAP. Thus, in B cells, BCAP deficiency results in a loss-of-function phenotype.

In this issue of *Blood*, MacFarlane and colleagues show that the role of BCAP for natural killer (NK) cells differs substantially from that seen in B cells. The absence of BCAP results in an expanded peripheral NK-cell pool, and more of these cells display a mature phenotype. In further contrast to the B-cell phenotype, BCAP deficiency renders mature NK cells more resistant to apoptosis. Finally, NK cells lacking BCAP show an increase in effector function, including enhanced production of the cytokine IFN-γ.

Clearly, more work will be necessary to understand the molecular basis for how BCAP supports B cells while attenuating NK cells. In B cells, it has been shown that BCAP is needed to maintain normal expression of c-Rel,[2] an NF-κB family protein mediating the survival and the proliferation of mature B cells. Along this line, it will be interesting to see whether BCAP influences the expression of NF-κB family proteins in NK cells. Consistent with this possibility, an enhanced IFN-γ response, as seen in BCAP-deficient NK cells, has also been observed in mice lacking NF-κB1 (p50).[3] Irrespective of the precise basis, the inhibitory effect of BCAP raises the prospect of using BCAP blockade to boost NK-cell reactions. As suggested by the authors, accelerated maturation and increased efficacy of NK cells may enhance graft-versus-leukemia effects in patients receiving hematopoietic stem cell transplants.

The work by MacFarlane and colleagues provides unexpected insights into an additional aspect of NK-cell biology: the role of MHC class I recognition in NK-cell maturation and the acquisition of functional competence (also termed licensing). In the absence of MHC class I molecules, NK-cell maturation (as judged by the down-regulation of CD27) is inefficient, and the ability of NK cells to produce IFN-γ or to kill is low. NK-cell function improves when inhibitory receptors display specificity for self–MHC class I molecules. Surprisingly, BCAP deficiency improved NK-cell maturation and function in the absence of MHC class I molecules. This suggests a model in which BCAP keeps NK cells immature. Inhibition of BCAP function, perhaps due to the engagement of MHC class I receptors during NK-cell development, may allow NK-cell maturation. As usual, unexpected findings raise further questions.

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REFERENCES

1. Okada T, Maeda A, Iwamatsu A, Gotoh K, Kurosaki T. BCAP: the tyrosine kinase substrate that connects B cell receptor to phosphoinositide 3-kinase activation. Immunity. 2000;13:817-827.

2. Yamazaki T, Kurosaki T. Contribution of BCAP to maintenance of mature B cells through c-Rel. Nat Immunol. 2003;4:780-786.

3. Tato CM, Mason N, Artis D, et al. Opposing roles of NF-kappaB family members in the regulation of NK cell proliferation and production of IFN-gamma. Int Immunol. 2006;18:505-513.