EDITORIAL

A new partnership between TGF-β1 and glucocorticoids in the network of inflammation

The past decades have seen the discovery of a myriad of pro- and anti-inflammatory molecules. Interleukins (IL), chemokines, glucocorticoids, and the transforming growth factor beta (TGF-β) superfamily, to name a few, all participate in the process of inflammation. Moreover, it has become quite obvious that the behavior of these molecules tend to act beyond cliches of black and white. Many of the so-called proinflammatory mediators exert under certain circumstances anti-inflammatory effects or play a role in the resolution of inflammation and vice versa. Thus, regulation of the homeostasis of inflammation is complex and depends on a wide range of regulatory loops. A large array of molecules regulate each other, and the effect on the inflammatory process varies, depending on the model and the time course of inflammation.

In this issue of Kidney International, Baud et al [1] describe a new and intriguing mechanism of interaction between TGF-β1 and glucocorticoids in a model of human macrophages. Their data add to the complexity of the process of inflammation and its resolution, but also make it more interesting.

Since its discovery approximately 20 years ago, the TGF-β family of polypeptides has undergone extensive studies. To date, five different members are identified in vertebrates. Three members (TGF-β1, 2, and 3) are expressed in mammals. TGF-β inhibits growth of many hematopoetic and epithelial cells and plays a major role in the production of extracellular matrix. TGF-βs exert pivotal effects on developmental processes, cell cycle regulation, and acute and chronic inflammation. Increased TGF-β formation has been reported and linked to the production of extracellular matrix in a large number of different animal models and human renal diseases. Various stimuli such as angiotensin II, thromboxane A₂, reactive oxygen species and high glucose are known to regulate collagen formation in renal tissue due to effects on TGF-β. Therefore, TGF-β is a central player in initiation and resolution of renal inflammation [2]. Another family of hormones with an even wider range of effects are the glucocorticoids. One very well-known and therapeutically widely used effect of glucocorticoids is the control of transcription of pro- and anti-inflammatory genes. Glucocorticoids have been shown to down-regulate activity of nuclear factor-kappa B (NF-kB) in various models of glomerulonephritis. They ameliorate local inflammation and facilitate apoptosis in mesangial cells. The numerous effects of glucocorticoids are mediated through interaction of their corresponding glucocorticoid receptors with the nucleus.

Glucocorticoids and the TGF-β family interact in many different ways. In human T lymphocytes glucocorticoids increase the expression of TGF-β1 by up-regulation of transcription [3]. In human osteoblast-like cells, steroids augment the levels of functional TGF-β by facilitating the cleavage of the latency associated peptide [4]. In another system, however, glucocorticoids down-regulate TGF-β1 and 2 expression in lung fibroblasts, by the interception of an intrinsic positive feedback control mechanism for TGF-β [5]. A synergy of glucocorticoids and TGF-β exists, however, in fibrotic tissue remodeling [6]. These examples emphasize the complexity and the importance of interactions between glucocorticoids and TGF-β in different cell types and even in more complex pathophysiologic situations.

Baud et al [1] demonstrate in this issue of Kidney International a new direct effect of TGF-β1 on glucocorticoid binding and signaling in human U 937 cells. They show very convincingly that the exposure of U 937 cells to TGF-β1 increases dexamethasone specific binding, which is due to an increase of binding sites. The signal transduction cascade of the TGF-β superfamily has the shape of an hour glass. Signaling is mediated through a tetrameric receptor complex, consisting of two heterodimers of one of seven different type I and one of five type II transmembrane proteins. Receptor Smad proteins (Smad1 to Smad3, Smad5, and Smad8) are then activated via phosphorylation by the type I receptor subunit and accumulate in the nucleus after association with the Co-Smad protein Smad4). Here this heteromeric complex can interact with a wide range of DNA-binding proteins, such as activator protein-1 (AP-1), stimulatory protein-1 (SP-1) and many others, to regulate transcription of a multitude of genes. A great number of interactions between the TGF-β pathway and that of other signal cascades as well as Smad-independent pathways have been reported [7].

Baud et al [1] now demonstrate that both Smad2 and Smad3 are involved in the TGF-β1-mediated up regulation of glucocorticoid binding. The Smads are shown to

Key words: transforming growth factor-β, glucocorticoids, inflammation, Smad, AP-1.

© 2003 by the International Society of Nephrology
act through AP-1 on the up-regulation of glucocorticoid binding and signaling. This is an interesting finding because glucocorticoids have been shown to suppress AP-1 activity in immunocompetent cells by direct binding of the glucocorticoid-receptor complex to AP-1 and by the suppression of c-jun, which is a major component of AP-1 [8]. Since AP-1 is needed for the TGF-β autoinduction [9], the AP-1 down-regulation that follows the TGF-β1-mediated increase in glucocorticoid signaling can induce a negative regulatory loop that might explain the potency of glucocorticoids to attenuate TGF-β self-stimulation [5]. Baud et al [1] furthermore demonstrate that the application of TGF-β1 to differentiated U 937 cells can inhibit glucocorticoid mediated IL-8 production. Hereby, the physiologic relevance of TGF-β1 effects on glucocorticoid signaling is stressed even more.

These studies by Baud et al [1] provide evidence for a new interaction of two well-known players in inflammation and fibrosis, telling us again that our therapeutic strategies and their sometimes unsuccessful results in the treatment of inflammatory injuries may have its reasons in the multiplicity of effects of mediators and that the stage of an inflammatory process might be of great importance.

Oliver M. Steinmetz and Rolf A.K. Stahl
Hamburg, Germany

Reprint requests to Rolf A.K. Stahl, M.D., Medizinische Klinik IV, Zentrum für Innere Medizin University of Hamburg, Martinistr. 52, D-20246 Hamburg, Germany.
E-mail: rstahl@uke.uni-hamburg.de

REFERENCES