In recent years, it has been well established that a dynamic interaction between the skin and the nervous system plays an important role in both skin homeostasis and cutaneous disease. Neuropeptides released from the network of unmyelinated nerve fibers in the skin can interact with specific receptors on cutaneous cells including keratinocytes, Langerhans cells, melanocytes, microvascular endothelial cells, and mast cells to mediate a cascade of inflammatory and proliferative activities. While many investigators have focused on studying the role of neuropeptides secreted from sensory nerve fibers, it is clear that other neurotransmitters and their receptors are also operative in the skin in ways that have yet to be fully understood.

In this issue, there are three papers that further demonstrate the importance of small proteins, primarily thought to be neurotransmitters, in mediating a variety of biological activities in the skin. Merighi et al examine the role of adenosine receptors in the proliferation and cell death of cultured human melanoma cells. Adenosine has been reported to display a variety of contradictory biological effects including both the induction and inhibition of cell proliferation as well as pro-apoptotic and cytoprotective effects in different situations. Furthermore, adenosine affects the immune system by exerting immunosuppressive and anti-inflammatory activities. Using the cultured A375 human melanoma cell line, these studies attempt to sort out how adenosine could both promote the growth and proliferation of tumor cells as well as induce cell death. The answer may in part be due to the relative expression of different adenosine receptors on the malignant melanoma cells. Four different adenosine receptors have been identified and pharmacologically characterized: A1, A2A, A2B, and A3. These receptors are seven trans-membrane glycoprotein coupled G protein receptors that are widely distributed on different tissues. A2A and A2B receptors are coupled to adenylylate cyclase activity and their stimulation increases intracellular cAMP concentrations. A1 and A3 receptor stimulation decreases cAMP concentration and raises intracellular Ca2+ levels by a pathway involving PLC activation. It was determined that treatment of the A375 melanoma cells with an A2A specific agonist led to cell death, whereas the A3 receptor agonist had a cytoprotective effect. This basic observation may help explain the apparent conflicting effects of adenosine on malignant melanoma cells by the activation of the A2A and/or A3 adenosine receptors. The authors hypothesize that increased extracellular adenosine is released in tumors such as melanoma due to localized hypoxia, tissue inflammation, and cell death. The increased peritumoral adenosine could then facilitate tumor progression by acting as an immunosuppressant agent and a cytoprotective agent in tumor cells expressing high relative levels of the A3 adenosine receptor compared to the A2A receptor. It is proposed that this observation may lead to the development of a potentially novel class of pharmacological agents to target a variety of different tumor types with specific adenosine receptors.

In a related paper, Slominski et al further examine the neuroendocrine activities in the skin. This group and others have identified the presence of various neuroendocrine factors in the skin that have commonly been associated with the systemic response to stress, including the proopiomelanocortin (POMC)-derived peptides MSH, ACTH, and (-endorphin, corticotropin-releasing hormone (CRH) and urocortin. Specifically, this paper presents a series of studies to determine if the skin expresses the enzymes required for serotonin biosynthesis and/or metabolism. Serotonin has powerful vasodilator, immunomodulator, and growth factor actions. In this study, Slominski’s laboratory found that hamster skin and melanoma cells express the genes required for the synthesis and metabolism of serotonin. Although it has been appreciated for a number of years that serotonin is an important neuromediator in the central nervous system and some peripheral tissues, its role in modulating various biological processes in the skin remains to be determined.

In a third paper in this issue, Haberberger et al examine the cholinergic system in the skin. Specifically, they present a series of studies in which they examine the expression of the high-affinity choline transporter (CHT1) in the HaCaT keratinocyte cell line and in human skin. The skin contains elements of the neuronal and a non-neuronal cholinergic system. Eccrine sweat glands receive cholinergic nerve fibers, and keratinocytes have been found to synthesize and release acetylcholine (Ach). The uptake of choline is the rate-limiting step in Ach synthesis and requires a transporter to enter the cells. It has been proposed that CHT1 is unique to cholinergic neurons but not non-neuronal tissues. This paper for the first time demonstrates the localization and distribution of the high affinity choline transporter, CHT1, in the skin of man and rat. In addition to nerve fibers, CHT1 is present in non-neuronal structures such as keratinocytes of the epidermis and hair shafts. Therefore, this study supports the presence of a choline recycling pathway in keratinocytes similar to that found in neurons. Since previous work indicates that keratinocytes are also capable of synthesizing, processing, and releasing Ach, the epidermis is fully capable of localized production of this potent neuromediator independent of the neurological system. These studies therefore extend our knowledge of the neurobiological capacity of the skin by both cutaneous neuronal and non-neuronal cells in the skin.