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Roles of vitronectin in central nervous system

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Vitronectin (VN) is one of extracellular matrix (ECM) proteins, and plays roles in the adhesion between cells and ECM, the regulation of blood coagulation and fibrinolysis, and the regulation of cell behavior such as migration, proliferation, and differentiation. Since the roles of VN in brain was reported for the first time in 1998, various functions of VN, such as the regulation of neuronal proliferation, differentiation, and neurite outgrowth have been observed in the cell culture system. However, there was no report about VN function *in vivo*. In this study, I analyzed the effects of VN loss on the proliferation and differentiation of cerebellar granule cell precursors (CGCPs) *in vivo* using VNKO mice to clear the roles of VN on the development of cerebellum. The loss of VN suppressed the neuronal differentiation to cerebellar granule cells (CGCs) in the external granule layer and the internal granule layer at postnatal day 8, however, the loss of VN did not significantly affect the proliferation of CGCPs. In addition, the loss of VN increased the expression levels of transient axonal glycoprotein 1, a marker of neurons in the initial differentiation stage, in the cerebella, indicating that the loss of VN accumulates the CGCPs in the initial differentiation stage. Taken together, these results demonstrate that VN promotes the progress of the initial differentiation stage of CGCPs.

The process of tissue regeneration is similar with that of tissue development, because both include the cell proliferation and differentiation processes. As mentioned above, I revealed that VN promotes the progress of the initial differentiation stage during the maturation into CGCs, suggesting that VN might contribute to the mechanisms of the brain regeneration including the neuron regeneration. However, there is no report whether VN contributes to the regeneration of brain tissue. When brain is damaged by external force, various mechanisms for wound healing, such as the coagulation and fibrinolytic

system, regeneration of neurons, inflammatory and anti-inflammatory actions, and recovery from blood brain barrier (BBB) breakdown, begin to work. Here, I focused on fibrinolytic system, one of the brain regeneration mechanisms, and investigated whether VN promotes the wound healing after the cerebral cortex injury through fibrinolysis using VNKO mice. As a result, I cleared that VN deficiency inhibited the recovery from BBB breakdown. In addition, VN deficiency impaired the activity of plasminogen activator inhibitor-1, an inhibitor of the fibrinolytic system, at 3–7 days after the stab wound (D3–7). Furthermore, VN deficiency up-regulated the mRNA and protein expression levels of tissue-type plasminogen activator, and urokinase-type plasminogen activator. These results demonstrate that VN contributes to the regulation of the fibrinolytic system and recovery from BBB breakdown in the wounded brain.

In this doctoral dissertation, it is cleared that VN promotes the progress of the initial differentiation stage of neuron, and that VN contributes the recovery from BBB breakdown in the wounded brain through the regulation of the fibrinolytic system. Therefore, it is suggested that VN plays roles for not only the regulation of central nervous system formation, but also the homeostasis of central nervous system. I hope that this dissertation should contribute to the understanding of the mechanisms of central nervous system development and reformation, and the role of ECM in central nervous system.