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Characterization of c-Kit receptor function in cardiac regeneration by using transgenic mouse models

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Background. Cardiac stem cells expressing the tyrosine kinase receptor c-kit have been recently used in in vivo and in vitro cardiac regenerative studies. However, it remains to be clarified whether the c-kit receptor itself plays a critical role in the process of cardiac regeneration. In order to clarify this point, we will explore whether c-Kit receptor affects cardiac stem cells proliferation, survival, migration and differentiation after heart injury.

Methods and Results. We have generated transgenic mice in which an activatory point mutation (c-KitD814Y mice) has been introduced in the kinase domain of the c-kit gene. Initially, we have analyzed c-kit expression in tissues and organs at different stages of embryonal and post-natal development through immunohystochemical and biochemical analyses. We have found that in two transgenic lines the receptor is highly expressed and activated in heart, testis and cerebellum, compared to wild type mice. In order to follow the fate of the c-Kit transgenic stem cells we crossed c-KitD814Y mice with mice expressing GFP under c-Kit regulative sequences control. By cytofluorimetric and fluorescence microscopy analyses, we observed a 2 fold of increase in the number of c-kit positive cells on heart samples from double transgenic mice at different ages. To verify the c-kit role in cardiac regeneration we performed a necrotic heart damage in vivo and monitored cardiac repair in transgenic mice versus wild-type mice. After 9 days the wounded hearts of transgenic mice presented a larger connectival tissue area compared to wild-type mice. On the contrary, after 45 days a consistent reduction of fibrotic area was observed in transgenic mice. These preliminary results suggest a faster repair of damaged heart area that contain stem cells with an activated c-kit receptor. Further in vitro and in vivo experiments will be performed to assess whether transgenic c-kit cells directly transdifferentiate into cardiomyocytes or whether they act in a paracrine manner. In summary, the generation of transgenic mice carrying a constitutively activated c-kit in cardiac stem cells, will allow to investigate the role of the receptor and to highlight the molecular mechanism underlying heart regeneration.

Keywords: C-kit, cardiac regeneration, stem cells, transgenic mice.