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Response to Sadek et al. and Kotlikoff et al.

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In our recent publication in *Stem Cell Reports* (Andersen et al., 2014), we resected neonatal mouse hearts and examined their ability to regenerate. As described previously (Porrello et al., 2011), we found that all hearts healed but, unexpectedly, this was accompanied with profound scarring of the apex, much like in damaged adult hearts, and little neomyogenesis. In their letter to the editor, Kotlikoff et al., 2014, emphasize the importance of distinguishing between regeneration and neomyogenesis. As we mentioned in our paper, normal postnatal cardiac development may actually replenish some of the cardiomyocytes removed by resection. Kotlikoff et al. provided evidence for such a scenario in their recent study (Jesty et al., 2012) on cryoinjured neonatal mouse hearts in which they observed incomplete "repair or regeneration." Overall, our results (Andersen et al., 2014) suggest that neomyogenesis as a repair mechanism is limited following apex resection, and complete regeneration of the resected apex did not occur in our hands. The discrepancies between our study (Andersen et al., 2014) and that of Sadek and colleagues (Porrello et al., 2011) regarding the apex resection model raise several issues that will be interesting to pursue, because they may help to identify factors and mechanisms that lead to complete versus incomplete heart regeneration. In their letter to the editor, Dr. Sadek and others not associated with the original study (Sadek et al., 2014) suggest that either surgical technicalities or assessment procedures may vary between the two studies. We carefully examined their original surgery protocol (Porrello et al., 2011) and failed to identify any major differences between the procedures. Particularly, we took great care to resect identical tissue amounts based on heart-to-body weight.

In their letter, Sadek et al. refer to other studies showing robust and reproducible regeneration. However, none of the studies published to date (Haubner et al., 2012; Heallen et al., 2013; Jesty et al., 2012; Naqvi et al., 2014; Strungs et al., 2013) actually performed apex resection on postnatal day 1 mice. As we have already stated in our paper (Andersen et al., 2014), we cannot exclude that cardiac regeneration may occur following other types of damage, such as myocardial infarction or cryoinjury (Haubner et al., 2012; Jesty et al., 2012; Naqvi et al., 2014; Strungs et al., 2013), that could leave a matrix beneficial for the repair process. Although it is possible that other surgery-related procedures not described in the published apex resection studies (Andersen et al., 2014; Mahmoud et al., 2014; Porrello et al., 2011) may actually diverge, we believe that the differences could be explained by how the amount of myocardium/fibrosis is assessed or interpreted. At P21, we observed that the scar in the heart located either posteriorly or anteriorly but seldom throughout the apex, which is in contrast to day 1–7 post surgery. We examindd more than 800 sections per heart and noted scarring in only 19.5%; hence, the damaged area could have been overlooked in other studies, including that of Porrello et al., 2011, where 140 sections per heart were examined (we apologize for stating "one heart" instead of "per heart" erroneously in our article [Andersen et al., 2014]).

In conclusion, we would very much like to examine and discuss these issues in a collaborative manner with the Sadek group. We look forward to seeing the apex resection results from other ongoing studies, so that we may pursue approaches that could release the heart from its inert state of repair.

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