6 OUTLOOK

Congenital heart diseases are the most common birth defects with an incidence of approximately 1% of live births. The diseased phenotype originates from disturbances of the complex regulatory networks that direct heart development. Severe cardiac malformations are known to develop if enzymes are lost that mediate the placement of histone modifications or if mutations in cardiac transcription factors or their binding sites occur. It is therefore mandatory to gain a better understanding of the role of histone modifications and transcription factors in heart development. It has become clear, that the majority of cardiac diseases cannot be traced to one single mutation. Therefore, a deeper understanding can only emerge when interactions of multiple factors (i.e. histone modifications and transcription factors) are considered as a whole.

The results presented here show that the properties of histone modifications can only be fully understood when combinations are considered; as currently more than 100 different modifications are known and this number is still growing. However, as could already be demonstrated in this study not all possible combinations actually occur. A first step in this direction would be the integration and reanalysis of currently existing data.

Recent studies have revealed that histone-modifying enzymes have major functions in the development of pathological cardiac growth. In case of Mef2 it is known that it is bound by Class II histone deacetylases (HDACs), whereby normal cardiac size and function are maintained. In response to stress signals the HDACs are exported from the nucleus leaving Mef2 free to activate genes involved in cardiac growth. However, the mechanisms linking histone modifications to transcription factors and cardiac disease are just beginning to emerge[363]. Understanding and ultimately controlling these mechanisms represent potentially powerful therapeutic approaches for normalizing gene expression in the failing heart.

Identifying the main players in cardiac regulatory networks has made it possible to test for cardiac disease genes. However, the variability in penetrance and expressivity of human phenotypes indicate a major influence of modifier genes and environmental factors. Understanding the molecular basis for such variability will necessitate integration of different networks and present a challenge for the future.

Some lower animals such as amphibians can replace lost cardiac myocytes through regeneration, suggesting that cardiac regeneration is a primordial metazoan attribute that was lost. There is some evidence for recruitment of stem cells to injured mammalian myocardium, even if it is not sufficient to restore function. It has been suggested that the mechanisms may closely resemble developmental programs[364] and members of the Mef2 family as well as

Gata4 and Nkx2.5 are redeployed after injury to the adult heart. These findings add a new dimension to the study of these transcription factors. Ultimately, there is great interest in therapeutically manipulating the activities of these TFs in the adult heart to promote cardiac repair, including the genesis of specialized cardiac cell types from stem cells[365].