Editorial

"Regenerative and Restorative Biology"

Margaret Buckingham and Fatih Kocabaş

Stem cells are an underlying theme of developmental biology the cells from which all tissues and organs "stem". This begins with the pluripotent cells of the early embryo and progresses towards multipotent stem cells which have increasingly restricted cell fates, and which will give rise to tissue specific stem cells. These cells are responsible for the initial formation and subsequent growth of the tissue as development proceeds. We now know that they also ensure the maintenance of the adult tissue and its capacity for repair.

Stem cells present in adult tissues have not undergone tissue differentiation, but remain as reserve cells for tissue maintenance and repair. In most cases it has been shown that these cells are closely related to the tissue specific stem cells of the embryo, both in their origin and their molecular regulation. In the hematopoietic system or the intestine, the presence of such stem cells has been known for a long time, although the cellular hierarchy, which underlies the production of mature cells, was not known. This is now better understood, with important implications also for the advent of cancer stem cells due to deregulation of a critical stem cell type, particularly in tissues undergoing constant renewal to maintain homeostasis. While the capacity of some tissues to regenerate after injury was well established, with examples like the skin or skeletal muscle, the nature of the quiescent stem cells and how they become activated is only now becoming clear. Some tissues, like the brain, were thought to be incapable of regeneration but here too a reserve of stem cells has now been shown to be present and capable of undergoing neurogenesis in some regions of the adult brain. Current challenges are how to activate these cells more efficiently in a controlled manner for tissue repair, in the face of degenerative diseases, for example, and how to promote their maintenance in permanently damaged or aged tissues.

Prof Margaret Buckingham
Department of Developmental and Stem Cell Biology,
Pasteur Institute, Paris, France

Assist Prof Dr Fatih Kocabaş
Regenerative Biology Research Laboratory, Department of Genetics and Bioengineering,
Yeditepe University,
İstanbul, Turkey

Recent studies have identified pluripotent cells, which can be cultured and multiplied in vitro. These were initially derived from the early embryo and have been successfully cultured to form permanent cell lines. These embryonic stem (ES) cells, both mouse and human, will proliferate and can be directed into a tissue pathway by manipulation of the culture conditions. In this way, cardiomyocytes or neuronal cells, for example, can be produced efficiently. A major breakthrough in this approach, for which Shinya Yamanaka was awarded a Nobel prize in 2012, was the demonstration that differentiated cells from adult tissues can be converted to a pluripotent state by the expression of pluripotency factors, identified by their presence in the early embryo. Such induced pluripotent stem (iPS) cells, like ES cells, can then be re-directed into the tissue pathway of choice. Not only do iPS cells avoid the ethical problems that arise from work with human embryos, but they also circumvent problems of immune rejection when cells are re-introduced for therapeutic purposes into damaged human tissue. Ideally iPS cells can be derived from a small sample of human skin cells, for example, and then directed to stem cells of the tissue that requires repair and re-introduced into this tissue of the same individual. The derivation of tissue specific cells can be problematical. Some lineages are more easily produced than others and the question of the maturity of the resultant cells, even for tissues like the heart, remains open. The other major question is how to introduce them into the damaged tissue without cell death and with functional integration.

These different types of stem cell are the subject of intense research directed towards fundamental questions about their cellular properties and molecular regulation. The other important area of research concerns their utilisation for therapeutic purposes. This means the controlled stimulation of endogenous stem cells or the re-introduction of stem cells, either derived from pluripotent cells or from adult tissues, to restore tissue function. If the stem cell field has assumed such importance it is in large part due to the medical expectations of stem cell therapy. A word of warning is necessary in this context. Many unscrupulous companies and clinics propose miracle 'cures', largely advertised on the web, with little scientific proof of principle and of course for large sums of money. However, the potential is there and this is indeed an exciting area of research.

This special issue of the *Turkish Journal of Biology* is devoted to regenerative biology and potential approaches for tissue restoration. Most of the research articles focus on how to increase the therapeutic potential of stem cells. This can be achieved by adding compounds that have in some cases shown to be the active principle of traditional treatments, for wound healing for example. Other examples for skin or for the corneal epithelium of the eye, depend on the development of bioengineered materials which promote stem cell growth and tissue formation in culture for subsequent transplantation into the injured tissue in vivo. Bone maintenance and repair is another important area of stem cell biology. Again new biomaterial approaches to combat osteoporosis or the use of substances that increase the differentiation of dental pulp cells of interest for tooth, or even bone, repair are presented here. Mesenchymal stem cells present in bone marrow form bone and electrostimulation of these cells grown on bioengineered supports is shown to increase osteogenic differentiation. Bone marrow derived mesenchymal stem cells have excited considerable interest because of their general therapeutic properties, related to the growth factors that they produce. Thus it is now shown how they stimulate brain repair after stroke, a beneficial effect which is increased by application of a neuroprotective agent. In another article in this issue it is shown that these mesenchymal stem cells also reduce neuroinflammation in the brain and thus reduce functional deterioration. The Sca1-positive fraction of mesenchymal stromal cells also affects hepatopoietic cell lineages that derive from bone marrow, promoting type-M2 macrophage commitment with an increase in phagocytosis, important for the removal of harmful agents from the body. A class of mesenchymal stem cells derived from human adipose tissue shows interesting properties when cultured on a biomaterial in the presence of a cocktail of growth factors and other compounds. This leads to the formation of cardiomyocytes, which are not normally derived from these cells. In another study, bioengineered scaffolds and modified culture medium result in cardiomyocyte-like cells formed from the mesenchymal cells of bone marrow. Most of these examples underline the major therapeutic interest of stem cell manipulation in regenerative medicine.

This theme and the underlying regeneration processes are also addressed in the five review articles presented in this special issue. The theme of bone maintenance and repair is discussed in the context of mechanical load and the beneficial effects of low intensity vibrations, with potential clinical applications. Bone is again the object of a review on the delay in fracture repair, the function of metalloproteinases in the extracellular matrix and how insulin plays a role in the context of type 1 and 2 diabetes. Metalloproteinases, notably the ADAMTS class, and their function in the turnover of extracellular matrix proteins are the subject of another review, which stresses their role in inflammation, fibrosis, and disease states ranging from arthritis and atherosclerosis to cancer. Caspases are enzymes that are implicated in cell death, but also in counteracting apoptotic signals and in promoting cell differentiation, reviewed in the context of their essential role in tissue repair mechanisms. Finally, a review on cardiac regeneration points to the lessons that can be learned from lower vertebrates which respond to cardiac injury by partial de-differentiation and proliferation of cardiomyocytes. This capacity for repair is also seen in newborn mammalian hearts. There is some understanding of the signalling pathways that lead to this phenomenon and the major therapeutic question is how to reactivate this regenerative potential in the damaged adult human heart.

We hope that the research presented here will be both informative and stimulating for the scientific community in general and for the readers of the *Turkish Journal of Biology*.