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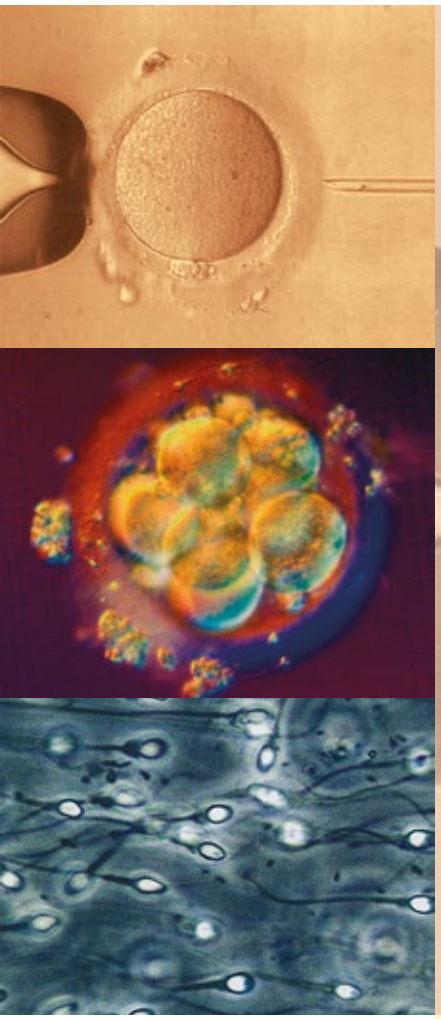

Plasticity of Stem Cells: Cell-fusion Versus Transdifferentiation

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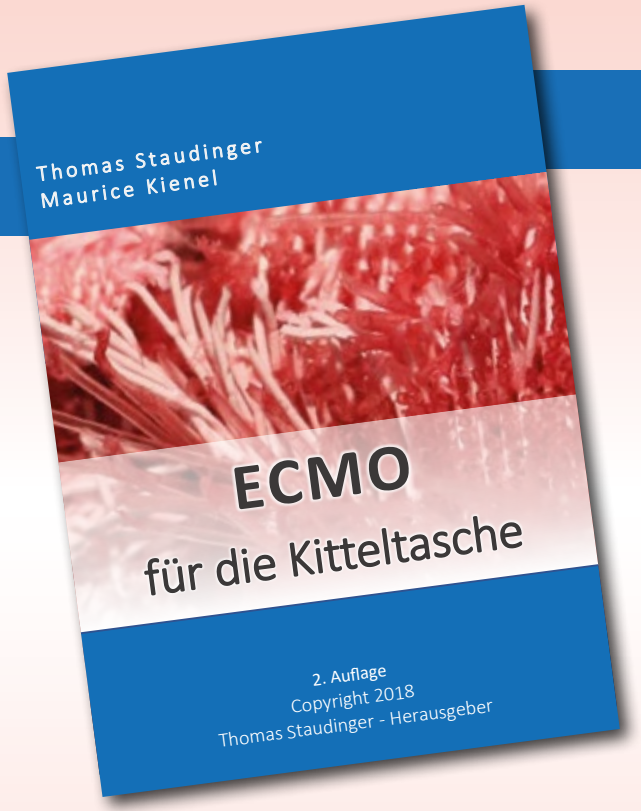

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Plasticity of Stem Cells: Cell-fusion Versus Transdifferentiation

N. H. Zech

Stem cell research is still at a very early stage of its development and we are only beginning to unravel how stem cells influence the organism to keep its balance. There are many regulation systems involved which dictated the replacement of damaged, aged or diseased tissues with new cells. This review will focus on the hotly debated issue, whether the observed plasticity needed for tissue regeneration and replacement results from cell fusion or if transdifferentiation prevails. First, some basics of stem cell biology will be revised, followed by defining the terms of chimerism, fusion and transdifferentiation. A suggestion will be made on how and when the three terms should be used when dealing with the topic of stem cell based therapy. With the help of some selected publications, this review wants to convince the reader that fusion of cells does occur in organisms for various reasons, but that transdifferentiation of stem cells seems to prevail when speaking of tissue regeneration and maintenance of homeostasis. Some comments will be devoted to the linkage between stem cells and aging, diseased or tumourigenic tissues. ***J Reproduktionsmed Endokrinol 2005; 2 (4): 239–45.***

Key words: *stem cells, plasticity, fusion, transdifferentiation, chimerism, tumour, aging*

Stem cell research is still in its infancy. We are only beginning to understand and unravel how stem cells influence the organism to keep its balance. There are many regulation systems involved which dictate the replacement of damaged, aged or diseased tissues with new cells.

For example, only recently it was demonstrated that a specific locus on chromosome-2 regulates, as a cell-intrinsic aging mechanism, the aging of stem cells [1]. This locus was described to have dual function: regulating progenitor cell numbers in young animals and stem cell numbers in old animals. Stem cell aging may thus perturb the homeostasis of the organism, having a direct influence on longevity. Besides this, the environment also has a major influence on the "if and how" stem cells help in tissue maintenance and replacement. In the work by Conboy et al. [2] a heterochronic parabioses model was utilised. In this system, a shared circulatory system was established between young and old mice exposing old mice to factors present in young serum and vice versa. With their model they showed how systemic factors are involved in modulating molecular signalling pathways critical to the activation of tissue-specific progenitor cells. Of importance, the systemic environment of a young animal promoted successful regeneration, whereas that of an older animal either failed to promote or actively inhibited successful tissue regeneration. The decline of tissue regenerative potential with age could be reversed through the modulation of systemic factors.

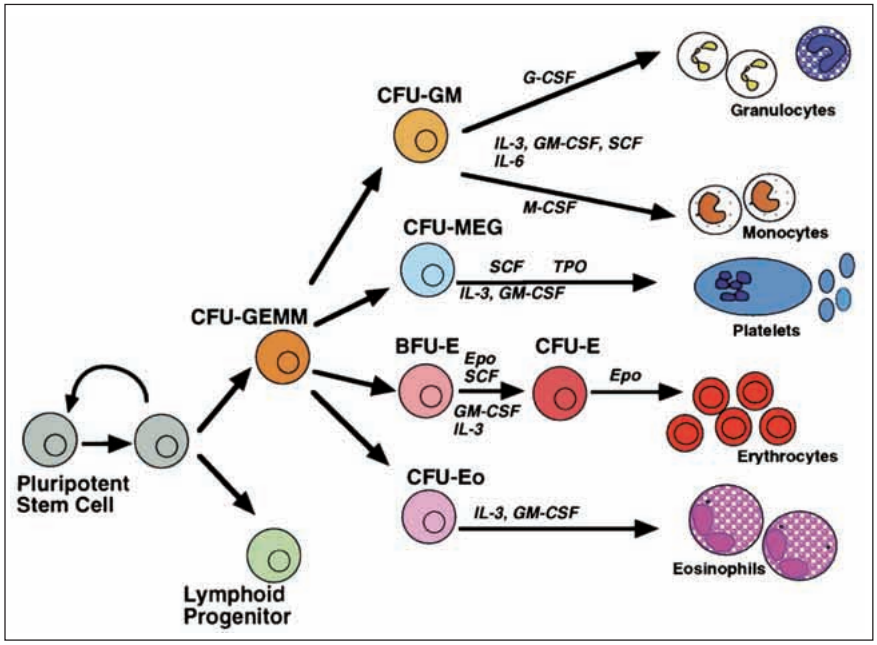

Figure 1. Plasticity of haematopoietic stem cells: these cells have the potential to differentiate to all the cell types of the haematopoietic lineage. M-CSF = macrophage colony stimulating factor; SCF = stem cell factor; Epo = erythropoietin; Tpo = thrombopoietin; CFU-GEMM = CFU granulocyte-erythroid-monocyte-megakaryocyte; CFU-GM = CFU granulocyte-monocyte; CFU-MEG = CFU megakaryocyte; CFU-E = CFU erythroid; CFU-Eo = CFU eosinophil; BFU-E = burst-forming unit erythroid. Reprint with permission from [Socolovsky M, Lodish HF, Daley GQ. Control of haematopoietic differentiation: lack of specificity in signalling by cytokine receptors. Proc Natl Acad Sci USA 1998; 95: 6573–5. Copyright 1998, National Academy of Sciences, U.S.A.].

It seems that stem cells retain much of their intrinsic proliferative potential even when old, but that age-related changes in the systemic environment and niche in which progenitor cells reside preclude full activation of these cells for productive tissue regeneration. Earlier, in 2004, Fraidenraich and his group [3] already showed – besides short range effects – long range-curing effects of embryonic stem cells on embryos with a heart defect when embryonic stem cells were injected intraperitoneally into pregnant mice. This implies, that there are factors secreted by stem cells that act from the distance on the curing of certain defects. That trophic factors might play a crucial role in tissue regeneration was already demonstrated by Borlongan et al. [4], when he nicely could show how therapeutic molecules secreted by injected adult stem cells and crossing the blood-brain barrier – after permealising it for a short interval by mannitol – contrib-

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uted in the regeneration of a cerebral infarction. This type of treatment significantly increased brain levels of neurotrophic factors, which correlated positively with reduced cerebral infarcts and improved behavioural functions.

This review will focus on the hotly debated issue, if the observed plasticity needed for tissue regeneration and replacement – after tissue specific stem and progenitor cells are depleted or exhausted – is a result of cell fusion or if true transdifferentiation potential of stem cells exists. To come to appreciate stem cell plasticity, first some basics of stem cell biology have to be outlined.

Definition and Classification of Stem Cells

It is known for some time that stem cells undergo multiple, self-renewing cell divisions which is a prerequisite for sustaining their population. This is done by symmetric cell divisions where two stem cells are being generated.

It is also characteristic for stem cells, that single stem cell-derived daughter cells differentiate into more than one cell type. This is also known as pluripotency. The two daughter cells, of which one stays a stem cell and the other cell starts the differentiation process, are derived by an asymmetric cell division.

Stem cells can be classified either with regard to their *in vivo* developmental potential **(a)** or with regard to their origin **(b)**.

Ad a)
The classic embryological concept for totipotency, which seems nowadays to somehow evade precise definition, is, when a single cell has the potential to create a living being. This is said to be true for a fertilised oocyte and blastomeres up to the 4- to 8-cell stage embryo. Furthermore, it has been shown, that conglomerates of embryonic cells at a later stage of development (e.g. a conglomerate of cells isolated from the inner cell mass) can develop to an individual if they are kept or combined with intact trophoblast cells (Table 1). Otherwise, cells are termed pluripotent when they are capable to differentiate into various tissue types. It is important to note, that, by definition, out of such cells a living being can never develop. For in-depth reading, the comprehensive overview on this topic by Beier [5] is recommended.

Table 1. The phenomenon of totipotency in embryology as well as in experimental, reproductive biological and genetic science (translated and modified from [5])

Totipotency of a cell	**Natural totipotency** – Fertilised oocyte (zygote) – Isolated blastomere up to the 8-cell stage **Experimental generation of totipotency** – Nucleus transfer into a enucleated oocyte (nuclear transfer cloning)
The ability for regulation to a harmonic whole being (Kind of totipotency of a conglomerate of cells e.g. from the inner cell mass of a blastocyst, which is kept or combined with intact trophoblast cells)	**Natural ability for regulation to a harmonic whole being** – Monocygotic twinning in humans – Monocygotic quadruplets in the armadillo **Experimentally generated ability for regulation to a harmonic whole being** – Embryo splitting in live-stock breeding to generate identical siblings – Cell-cluster growth from embryonic stem cell lines to produce identical siblings and transgenic animals with the help of tetraploid embryo complementation [6]

Ad b)
- Embryonic stem cells (derived from embryonic disk) → pluripotent
- Fetal stem cells (derived from fetal tissues) → pluripotent
- Adult stem cells (derived from adult tissues) → pluripotent

Figure 1 gives an impression of the plasticity of haematopoietic stem cells. These cells have at least the intrinsic potential to differentiate to all the cell types of the haematopoietic lineage and thus are termed pluripotent adult stem cells.

Commonly Used Methods to Examine Adult Stem Cell Plasticity and to Discriminate Fusion from Plasticity

Claims for so called adult stem cell plasticity often rely on the appearance of Y chromosome-positive cells in a female recipient of a bone marrow transplant from a male donor. However, cell fusion may be missed because not all chromosomes might be visible in the tissue sections.

Female to male transplantation with marked XX cells is more suitable for detecting fusion events. Marked bone marrow-derived cells with a Y chromosome have definitely been formed by fusion with host cells (Fig. 2). Alternatively, markers such as green fluorescent protein or LacZ have been used, and these techniques are usually combined with lineage markers in attempts to demonstrate that there has been a switch in the fate, meaning transdifferentiation of the transplanted cells (Fig. 3).

It has to be noted, that each technique used alone is not able to robustly discriminate between cell fusion and transdifferentiation because they all are prone to error. The more of the techniques are combined in an experiment, the better the discrimination potential.

There are three termini to be kept in mind when discussing the topic of fusion and transdifferentiation:
(1) chimerism, also known as mosaicism
(2) fusion
(3) transdifferentiation

Ad 1) Chimerism
Some of the first reports on chimeras were the papers by Tarkowski [7] and Mintz [8]. When combining early stage embryos of two different inbred strains, they produced mice harboring cells of the two different strains. The cells, brought together in a very early stage of development, differentiated into various organs. These cells do not need to transdifferentiate or to fuse to contribute to or

participate in organ formation. These mice are so called chimeras, with cells of different origin but having a normal chromosome composition and a normal karyotype, except that they have a mixture of XX and XY cells all with a normal karyotype in various amounts in the different organs.

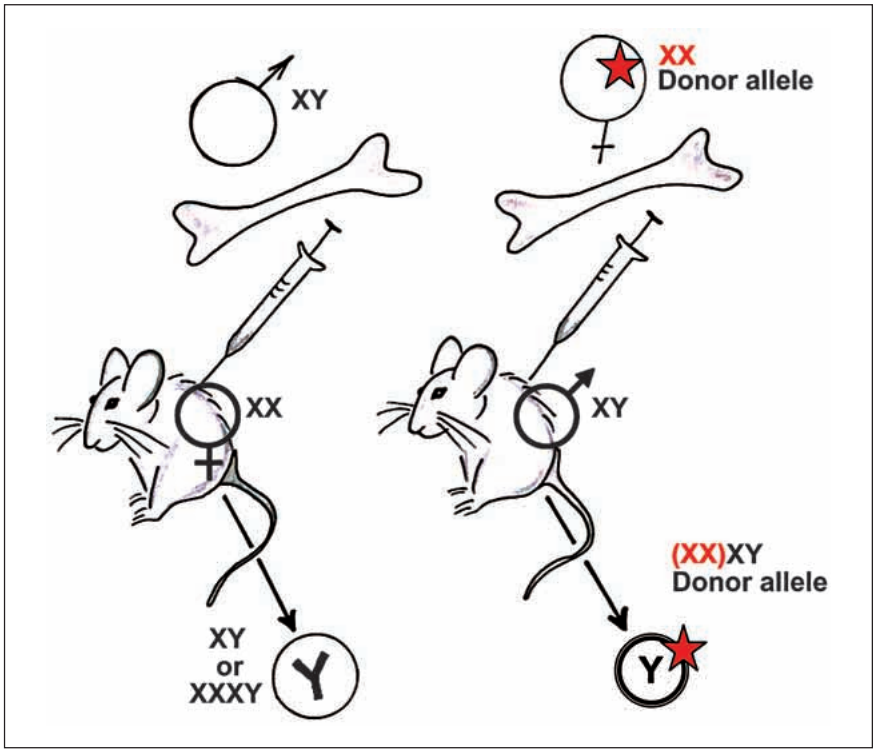

Figure 2. Sex mismatched stem cell transplantation to track progeny cells: claims on the plasticity of stem cells often rely on the appearance of Y-positive cells in female recipients of male bone marrow transplant donors (left). Injection of marked bone marrow cells from female donors into male recipients is more suitable to demonstrate fusion events because marked Y chromosome-positive cells found in the recipient must have been formed by a fusion event (right).

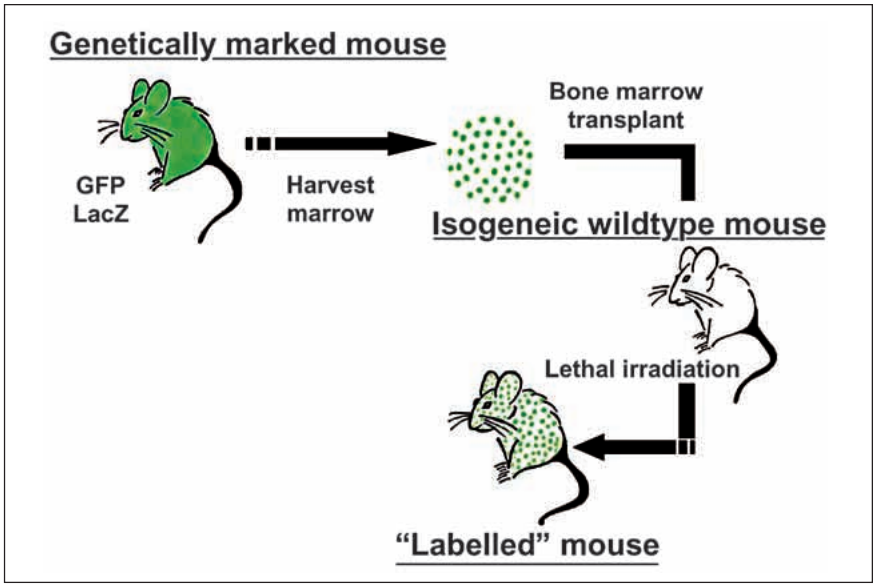

Figure 3. Commonly used methods to examine adult stem cell plasticity and to discriminate fusion from plasticity: cells of transgenic mice expressing markers such as green fluorescent protein (GFP) or LacZ, which are expressed in all cells of transgenic mice, are frequently used to demonstrate the plasticity potential of certain cells, originally belonging to a given cell lineage. For example, when GFP-positive bone marrow cells are injected into wildtype mice and these cells are found in tissues not related to the tissue of origin, it is believed that a lineage switch has occurred. In the case of transplantation of bone marrow cells, lethal irradiation of the recipient should guarantee that no stem cells of the wild type mouse contributes to the observed transdifferentiation or fusion.

Ad 2) Fusion

In cell fusion, as described for example by Terada [9], where genetically altered bone marrow from green fluorescent protein transgenic mice were mixed with embryonic stem cells and a very small proportion of the bone marrow cells fused with embryonic stem cells, the fusion product, seen as a new cell type, expressed genes of both fusion partners in various degrees. Here the chromosomes of the fused cells are mosaic, presenting as a mixture of chromosomes of different origin. In the work by Terada, these newly formed cells could subsequently adopt many of the phenotypes typical of embryonic stem cell differentiation. But in general, this all is more or less a random process and depends on which genes of the fusion partners are being silenced and which are being expressed. Historically seen, spontaneous fusion was already mentioned by Lewis [10], when he described the occurrence of "spontaneous" cell fusion as a mechanism for generating multinucleated cells from both tumour and normal tissue cells placed *in vitro*. Fusion is also a natural occurrence in multicellular organisms such as in egg and sperm during fertilisation, formation of multinucleated myotubes by fusion of myoblasts or generation of osteoclasts by fusion of mononuclear phagocytic precursor cells. Cell fusion may also be observed under pathological conditions such as in cell injury, certain viral or bacterial infections or during malignant cell growth. A comprehensive review by Ringertz and Savage 1976 [11] led to the conclusion that spontaneous fusion occurs in 1:100 to 1:1 million cases, depending on the cell types and culture conditions used.

Ad 3) Transdifferentiation

Traditionally stem cells have been viewed as reaching a point of no return, an irreversible switch. The evolving view is, that cells have a recruitable but decreasing propensity to act as stem cells as they differentiate.

There can be a transdifferentiation into cell types of the same blastodermic layer [12–14] as well as a transdifferentiation into cell types of a different blastodermic layer [15, 16].

Chimerism vs. Fusion vs. Transdifferentiation

Let us point out once again, because this is very important: the difference between the three termini chimerism, fusion and transdifferentiation.

We should keep the term chimerism to what it was originally meant to be, namely, resulting from the intermix of cells coming from different early stage embryos, from where they start their differentiation program along a regular path into the various organs. The cells, brought together in a very early stage of development, differentiate into various organs. These cells do not need to transdifferentiate or fuse to contribute to or participate in organ formation. We also tend to speak of chimeras when feto-fetal transfusion (FFT) occurs in twin pregnancies of opposite sex, but sharing one placenta, as is known for freemartin cattles [17], in some rare cases of dichorionic twins [18–21] as well as in a transplantation-setting such as in gender-mismatched allogene bone marrow transplantation, where XX and XY cells can be found in the same organism. Here, the donor cells do not differentiate but rather fuse or transdifferentiate to have a share in an organ.

Instead, in FFT the same as in a stem cell therapy setting we should refer to the term mosaicism or otherwise "graft-host-cell-interrelation" instead of using terms such as "blood-group chimerism" [18] and more closely point out if it is a result of fusion of cells with a mosaic of chromosomes [21] or transdifferentiation of cells bearing a normal karyotype [22, 23].

Cell Plasticity

Cell plasticity is a central issue in stem cell biology. The first successful publication on mammalian cloning by Wilmut [24] demonstrated that cloning is a reproducible technique in multiple species, clearly indicating that somatic nuclei can be reprogrammed into a totipotent status when placed into enucleated oocytes. Recent publications claim that somatic stem cells can convert into developmentally-unrelated cell types both *in vivo* and *ex vivo* without cloning.

These exciting possibilities of "transdifferentiation" have become of great interest in recent stem cell research for multiple reasons: they call into question traditional concepts of cell lineage and development and they raise the possibility, that stem cells could be used to repair organs from which stem cells are not easily isolated.

A rapidly growing number of papers, starting in 1999, suggest that pluripotent adult cells can differentiate into many types of tissues [25–28]. These and other observations opened the door to a new and very promising field in future medicine.

In the following years, doubts have been cast upon claims that certain adult stem cells can jump lineage boundaries to generate completely new types of cells. Were these the results of fusion or transdifferentiation?

Studies by Clarke [29] and Galli [30] have shown that myoblast cells or embryoid bodies co-cultured with neuronal stem cells labelled with β-galactosidase produced β-galactosidase labelled muscle cells. This was interpreted as evidence that stem cells received signals that caused them to transdifferentiate into muscle cells (Fig. 4).

The paper by Ying [31] as well as other papers alerted investigators to the possibility that perhaps all instances of transdifferentiation were the result of fusion. In Ying's experiments, a low frequency of fusion was observed when mouse central nerve stem cells were mixed with embryonic stem cells, and here the derived hybrid cells were able to show multilineage potential when injected into blastocysts. They could show that the interpretations by Clarke and Galli was wrong, and that there were no signals, but that a fusion had occurred.

Selected Publications on Fusion vs. Transdifferentiation: Talking in Favour of Transdifferentiation

If adult stem cells naturally fused with other cell types, we might all have substantial complements of polyploid cells in many organs caused by fusion. Now, this simply is not the case. Only mentioned aside, as stated by Alison [32], polyploidy in the liver, which develops early in life, is not generated by cell fusion but rather a widespread failure of cytokinesis appears to be responsible. She points out that, for example, in the rat, the 4th postnatal week signals a change in cell composition, with the emergency of binucleate hepatocytes with two diploid nuclei through a failure of cytokinesis, at a time when mononuclear diploid hepatocytes are disappearing. During further developmental growth, cytokinesis arrest yields daughter cells with 4n nuclei and so on. In addition, functional polyploidy is a common feature of liver cells in any significant stress situation of this organ.

One method to look for fusion and transdifferentiation in humans is to examine cells for the presence of X and Y chromosomes in cases of sex mismatched bone marrow transplantation. In the paper by Tran [22] almost 10.000 buccal cells were analysed. The number of Y and cytokeratin 13 (a marker for buccal cells) doubly positive buccal cells in the female recipients ranged from 0.8 % to 12.7 %, with only one XXY cell (0.01 %) and one XXXY cell (0.01 %) detected, both of which could have arisen by fusion. The authors concluded that bone marrow-derived cells could transdifferentiate directly into buccal cells in the absence of cell fusion. Caplice [33] examined the contribution of bone marrow-derived cells to atherosclerotic plaques in human coronary arteries in sex mismatched allogene bone marrow transplantation. His team found, that up to 10 % of intimal smooth muscle cells were derived in this way. In diseased segments of the same vessels this figure was even 100-fold greater. Using probes for X, Y, and chromosome 18 they failed to find evidence of polyploidy among thousands of smooth muscle cells.

Also relating to the cardiovascular system, Bardoff [34] demonstrated that endothelial progenitor cells can be derived *in vitro* from human peripheral blood mononuclear cells, and these endothelial progenitor cells will transdifferentiate into functional cardiomyocytes when co-cultured in contact with rat cardiomyocytes. Fusion was discounted because this also occurred when endothelial progenitor cells were in contact with fixed (dead) cardiomyocytes. Only recently, Yoon and his team [35] have isolated single cells within the adult human

bone marrow, which renew themselves without a loss in multipotency and which exhibit the capacity to transdifferentiate into cells of all three germ layers. This is the first demonstration that a specific population of multipotent human bone marrow-derived stem cells can induce both therapeutic neovascularisation and endogenous as well as exogenous cardiomyogenesis.

A population of bone marrow-derived hepatocyte stem cells has been identified in a rat model in the paper published by Avital [36]. These cells were found to be more numerous in damaged liver and express albumin, even in the bone marrow. After these cells were cocultured with cholestatic hepatocytes, separated by a semipermeable membrane, so that no fusion could occur, they differentiated into hepatocytes, and were able to metabolise ammonia into urea as efficiently as existing hepatocytes. Thus, here we have another situation where fusion could not be responsible for the observed transdifferentiation. Brittan [23] established that bone marrow-derived epidermal cells are proliferative and, moreover, demonstrated for the first time that bone marrow-derived cells can localise or home into a known stem cell niche: the CD34-positive bulge region of mouse hair follicles. In addition, engraftment of bone marrow cells into the epidermis was significantly increased in wounded skin.

The excellent paper only recently published by Yokoo [37] demonstrated how human mesenchymal stem cells in rodent whole embryo culture are reprogrammed to contribute to kidney tissue. They could be detected in various segments of the developing kidney and the cells also expanded over time. Only a negligible number of cells (< 0.1 %) were doubly Y chromosome-positive, suggesting that the occurrence of cell fusion during *in vitro*-culture is rare. Sigurjonsson [38] could show how human adult stem cells from the bone marrow transdifferentiated into neurons and integrated into the spinal cord in chicken embryos, thus helping to repair intentionally set lesions. In nearly 60 % of the embryos exhibiting full regulative regeneration, adult human stem cells had integrated into the regenerated spinal cord. The efficiency of neuronal differentiation by adult human stem cells was in the range between 9.6 % up to 16 %. Furthermore, fusion of human stem cells with host chicken cells was not a contributing factor to the neuronal differentiation seen after transplantation. Houghton [39] published that gastric cancer can originate from bone marrow-derived cells and their data support the view that stable fusion between the bone marrow-derived cells and the gastric mucosa does not occur. Only shortly after Houghton's article was published, another publication followed [40] demonstrating that there is a significant contribution of bone marrow-derived myofibroblasts to the tumour microenvironment in a murine model of pancreatic cancer. Here the bone marrow-derived cells also fused with insulin-producing cells within tumours. Unfortunately it was not mentioned how many of the bone marrow-derived myofibroblasts fused with the host cells.

Figure 5, a drawing taken from a publication by Korbling and Estrov [41], shows the possible roles of bone mar-

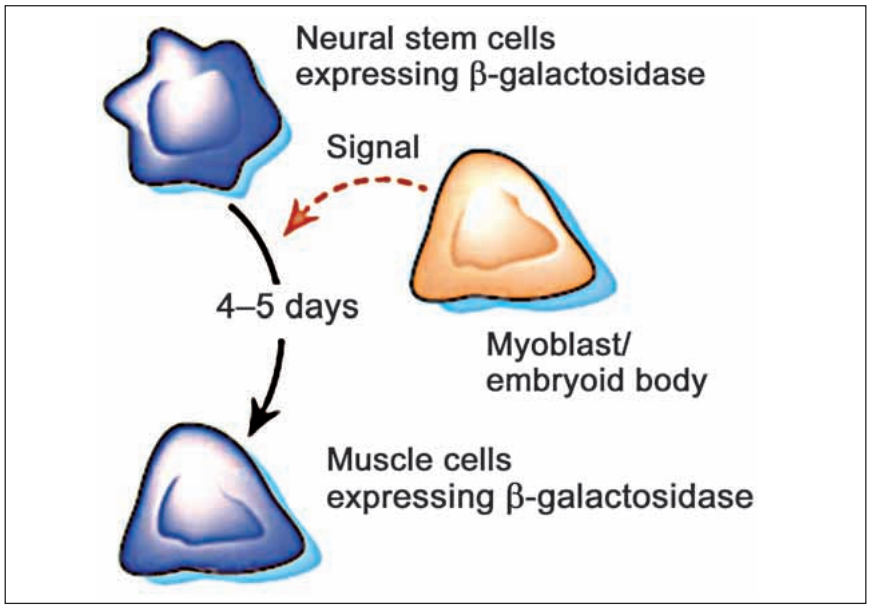

Figure 4. Drawing of a false interpretation of the studies by Clarke [29] and Galli [30]: The detection of β-galactosidase labelled muscle cells after myoblast cells or embryoid bodies were cocultured with neuronal stem cells labelled with β-galactosidase was interpreted as evidence that stem cells received signals that caused them to transdifferentiate into muscle cells. Reprint with permission from [Wurmser AE, Gage FH. Stem cells: cell fusion causes confusion. Nature 2002; 416: 485–7].

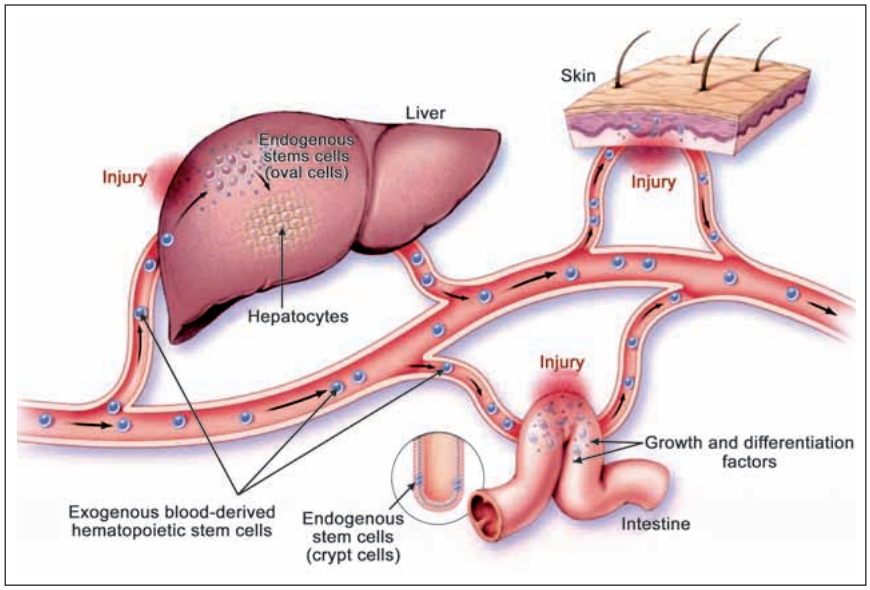

Figure 5. Possible roles of bone marrow-derived and circulating cells in the repair of solid-organ tissue. Reprint with permission from [41]. Copyright © 2003 Massachusetts Medical Society. All rights reserved.

row-derived and circulating cells in the repair of solid-organ tissue: after tissue injury, stem cells that are intrinsic to the tissue replace necrotic cells as a first line of defence. If the pool of endogenous stem cells is exhausted, exogenous circulating stem cells are signalled to replenish the pool and participate in tissue repair. Thus, circulating stem cells may serve as a backup rescue system. In the short term, this could help in regeneration, but in the long run it could also bear danger for the organism. For example, it could play a role in tumour-formation.

That tissue environment plays an important role in tumourigenesis was shown in the publication by Krtolica et al. [42]. They found that senescent human fibroblasts stimulated hyperproliferation and progression of preneoplastic epithelial cells and accelerated tumourigenesis by neoplastic epithelial cells. Ceradini et al. [43] indicated that the tumour-associated microenvironment could possibly continuously recruit circulating stem cells, effectively "hijacking" the body's capacity for tissue regeneration. Could there also be a link to cachexia, a term describing the loss of body weight and muscle mass and which is frequently seen in patients with cancer? The exact mechanism in which cancer and various other diseases cause cachexia is poorly understood, but it is in general believed to be a result of inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), which is also nicknamed cachectin for this reason. What if the "hijacked" stem cells are helping in building up the tumour instead of keeping the normal bodies balance of tissue repair? Could this also result in cachexia? It seems to me to be a very likely hypothesis.

In aging, fusion could play an increasing role, when more and more fused cells are observed in repaired tissues as demonstrated by Weimann and his colleagues [44] where the team provides unexpected evidence that the mechanism whereby bone marrow-derived cells contribute to Purkinje neurons in adult mice is fusion. Such Purkinje neurons as a result of fusion increased in frequency with the aging of the mouse. The same could be true for aged humans. Because in cell fusion, we have genes of both fusion partners expressed and silenced randomly and the overall gene-dose might be greater, this could become an important effect on the organism with increasing age.

There is still a big ongoing debate between those, who believe that fusion is the main mechanism of the observed plasticity of stem cells and those, who believe in true transdifferentiation potential of stem cells. We only begin to understand how transdifferentiation is achieved, but the mechanisms start to be unravelled and understood as exemplified by the work of Pearton [45], where it was shown how differentiated cells of the corneal epithelium are converted to hair, along with their associated stem cells, then interfollicular epidermis, by means of a multistep process triggered by dermal developmental signals.

In summary, in light of the data presented in this review, it can be deduced that fusion of cells does occur in organisms for various reasons, but transdifferentiation of stem cells seems to prevail when speaking of tissue regeneration and in maintenance of homeostasis. Most likely, fusion of cells happens particularly in aging and may have its role in pathological and diseased states.

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