

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300

Open access books available

130,000

International authors and editors

155M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Bone Marrow Microenvironment Defects in Fanconi Anemia

---

Wen Xing, Mingjiang Xu and Feng-Chun Yang

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/52729>

---

## 1. Introduction

In 1927, the Swiss pediatrician Guido Fanconi first reported a family with aplastic anemia and physical anomalies known as FA now, as reviewed by Lobitz et al (Lobitz and Velleuer 2006). FA is a chromosomal fragility disorder characterized by cytopenia, progressive bone marrow failure (BMF) under production, variable developmental anomalies and a strong propensity for cancer. The prevalence of FA is 1 to 5 per million, and heterozygous carrier frequency is about 1 in 300. Clinically, FA patients develop heterogeneous manifestations. 80% of FA patients develop progressive BMF with a mean age of death occurring at 19 years (D'Andrea, Dahl et al. 2002; Bagby and Alter 2006; Giri, Batista et al. 2007). The other 20% of patients usually die of malignancies resulting from the acquisition of myeloid cell leukemia particularly acute myelogenous leukemia and myelodysplastic syndrome. In addition, FA Patients are susceptible to solid tumors, including gynecologic squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal carcinoma, liver tumors, brain tumors, skin tumors, and renal tumors (Kutler, Singh et al. 2003).

To date, at least 15 distinct *FANC* genes, including *FANCA*, *FANCB*, *FANCC*, *FANCD1/BRCA2*, *FANCD2/BRCA1*, *FANCE*, *FANCF*, *FANCG/XRCC9*, *FANCI*, *FANCI/BRIP1*, *FANCL*, *FANCM/HEF*, *FANCN/PALB2*, *FANCO/RAD51c* and *FANCP/SLX4*, are found in FA patients, and *FANCA*, *FANCC*, *FANCG* and *FANCD2* are the most frequent in clinic (Moldovan and D'Andrea 2009; Vaz, Hanenberg et al. 2010; Kim, Lach et al. 2011; Stoepker, Hain et al. 2011). Except for *FANCB* which is on the X chromosome (Meetei, Levitus et al. 2004), all these *FANC* genes are located on autosomes.

FA pathway is inactive in normal cells but turned on during the S phase of cell cycle or in the presence of DNA damage proteins, and it also plays a pivotal role in DNA repair pathway in cellular defense against DNA interstrand crosslinkers (Moldovan and D'Andrea 2009;

Kee and D'Andrea 2010). Following the activation, eight of 15 *FANC* gene products, including FANCA, B, C, E, F, G, L and M proteins assemble into a nuclear E3 ubiquitin ligase complex. This complex is known as FA core complex and one of the main functions of this core complex is to monoubiquitinate and to activate the proteins of FANCD2 and FANCI, which co-localizes with BRCA1 and BRCA2, at the sites of DNA repair (D'Andrea 2010). The monoubiquitinated FANCD2/FANCI is then translocated to chromatin and interacts with other downstream FA proteins FANCD1, J, N and O to form a nuclear DNA-repair complex (D'Andrea 2010). FA patients display spontaneous chromosomal breakage and chromosomal abnormalities (Schroeder, Anschutz et al. 1964; Sasaki 1975). In addition, these DNA instability can be significantly enhanced by DNA cross-linking agents, such as mitomycin C (MMC) (Schroeder, Anschutz et al. 1964; Sasaki 1975).

## 2. *FANC* genes regulate HSC/HPC functions

Because of the earlier bone marrow failure and the predisposition to malignancy, especially the high risk of developing acute myeloid leukemia (AML), FA has been clinically categorized as a hematopoietic disease due to hematopoietic dysfunction. The defective hematopoietic functions are known related to an excess of genetic instability. FA bone marrow cells have clonal evolution, which predispose patients to the development of malignancies. Vinciguerra et al reported an increased number of ultrafine DNA bridges and binucleated cells in both bone marrow stromal cells from FA patients and in primary murine FA pathway-deficient hematopoietic stem/progenitor cells (HSCs/HPCs) (Vinciguerra, Godinho et al. 2010). Using primary and immortalized cell cultures as well as *ex vivo* materials from patients, multiple studies showed oxidant hypersensitivity of these FA cells as reviewed by Du et al. (Du, Adam et al. 2008).

## 3. Murine models of FA

To our best knowledge, 9 of 15 *Fanc* genes have been inactivated in mice, resulting in *Fanca*, *Fancc*, *Fancg*, *Fancd1*, *Fancd2*, *Fancl*, *Fancm*, *Fancn* and *Fancp* knockout mice.

Cheng et al first created *Fanca*<sup>-/-</sup> mice by deletion of *Fanca* exons 4-7 (Cheng, van de Vrugt et al. 2000). The *Fanca*<sup>-/-</sup> mice developed a significant thrombocytopenia, while no other severe hematological abnormalities were observed. Using the same murine model, Rio and colleagues reported that megakaryocyte progenitors, but not granulocyte-macrophage progenitors from the bone marrow of the *Fanca*<sup>-/-</sup> mice have impaired proliferation *in vitro* (Rio, Segovia et al. 2002). In addition, embryonic fibroblasts (MEFs) derived from these knockout mice are hypersensitive to the crosslinker MMC and both male and female mice showed reduced fertility due to hypogonadism (Cheng, van de Vrugt et al. 2000; Rio, Segovia et al. 2002). Different from FA patients, these knockout mice do not spontaneously develop congenital anomalies (Cheng, van de Vrugt et al. 2000; Rio, Segovia et al. 2002). Later, Wong and

colleagues established another *Fanca*<sup>-/-</sup> murine model by deletion of exons 1-6 of *Fanc* gene (Wong, Alon et al. 2003). The homozygous germline-line deletion of the functionally exons 1-6 of *Fanc* leads to multiple developmental deficits, including growth retardation, microphthalmia, craniofacial malformations, as well as hypogonadism, resembling those observed in FA patients (Wong, Alon et al. 2003).

Two different *Fancc*<sup>-/-</sup> murine models were generated by deletion of *Fancc* exon 9 or exon 8 (Chen, Tomkins et al. 1996; Whitney, Royle et al. 1996). Similar to *Fanca*<sup>-/-</sup> mice, these mice do not spontaneously develop peripheral hematological abnormalities. However the bone marrow HSCs/HPCs of these mice display impaired functions *in vitro*, such as abnormal colony forming capacity, hypersensitive to interferon- $\gamma$ . Furthermore, these *Fancc*<sup>-/-</sup> mice also have impaired fertility and increased incidence of a congenital microphthalmia without skeletal abnormalities, replicating some of the features of the FA patients (Chen, Tomkins et al. 1996; Whitney, Royle et al. 1996).

*Fancg*<sup>-/-</sup> mice were generated by deletion of *Fancg* exons 2-9 (Yang, Kuang et al. 2001; Koomen, Cheng et al. 2002). Similar to *Fanca*<sup>-/-</sup> and *Fancc*<sup>-/-</sup> mice, *Fancg*<sup>-/-</sup> mice do not develop spontaneously hematological abnormalities and congenital anomalies either, although MEFs of *Fancg*<sup>-/-</sup> mice are hypersensitive to MMC (Yang, Kuang et al. 2001; Koomen, Cheng et al. 2002).

*BRCA2* has a close functional relationship with the classical FA pathway. Genetic deletion of *Fancd1/Brca2* in mice results in embryonic lethality (Sharan, Morimatsu et al. 1997). Using mice with hypomorphic mutations in *Brca2* (*Brca2* <sup>$\Delta$ 27/ $\Delta$ 27</sup>), Navarro et al reported that bone marrow cells of *Brca2* <sup>$\Delta$ 27/ $\Delta$ 27</sup> mice display spontaneous chromosomal aberrations and are more hypersensitive to MMC (Navarro, Meza et al. 2006), consistent with FANCD1/BRCA2 as downstream of FA core complex in FA pathway and plays a critical role in DNA repair process. Different from *Fanca*<sup>-/-</sup> mice, *Fancd1*<sup>-/-</sup> mice are hypersensitive to ionizing radiation and do not have defect in fertility (Navarro, Meza et al. 2006).

*Fancd2* undergoes monoubiquitylation by the complex and is targeted into nuclear foci and co-localizes with *Brca1*. *Fancd2*<sup>-/-</sup> mice were generated by targeted deletion of *Fancd2* exons 26 and 27 (Houghtaling, Timmers et al. 2003). *Fancd2* mutant mice display cellular sensitivity to DNA interstrand cross-links and germ cell loss, which is similar to human FA patients and other FA mouse models. Interestingly, different from other mice carrying disruptions of proximal FA genes, these *Fancd2* mutant mice exhibited phenotypes including microphthalmia, perinatal lethality, and epithelial cancers. There is similarity between *Fancd2* mutant mice and *Brca2/Fancd1* hypomorphic mutation mice, implying a common function for both proteins in the same pathway.

Although *Fancg*<sup>-/-</sup>, *Fancc*<sup>-/-</sup>, and *Fancd2*<sup>-/-</sup> mice do not develop spontaneous hematopoietic malignancies seen in FA patients, HSCs/HPCs from *Fancg*<sup>-/-</sup>, *Fancc*<sup>-/-</sup>, and *Fancd2*<sup>-/-</sup> mice have defective engraftment and reconstitution of the short and long term hematopoiesis in a competitive transplantation assay (Haneline, Gobbett et al. 1999; Parmar, Kim et al. 2010; Barroca, Mouthon et al. 2012). The defective homing and reconstitution may associated with an impaired cell migration and adhesion of *Fancg*<sup>-/-</sup> hematopoietic cells as reported by Barro-

ca et al (Zhang, Shang et al. 2008; Barroca, Mouthon et al. 2012). In addition, the mobilization of HSCs/HPCs in *Fanca*<sup>-/-</sup> mice in response to G-CSF was defective in the absence of bone marrow failure (Milsom, Lee et al. 2009).

*Fancl*, also known as *Pog* (proliferation of germ cells), belongs to the multisubunit FA complex. *Fancl*<sup>-/-</sup> mice were generated by deletion of *Pog* gene exons 4-14 (AgoulNIK, Lu et al. 2002). *Fancl*<sup>-/-</sup> mice have defects in fertility, growth retardation, although no obvious hematological abnormalities (AgoulNIK, Lu et al. 2002). *Fancm*<sup>-/-</sup> mice were generated by deletion of *Fancm* exon 2 (Bakker, van de Vrugt et al. 2009). Similar to other FA mouse models, *Fancm*<sup>-/-</sup> mice do not spontaneously develop hematological abnormalities and congenital anomalies, whereas, *Fancm*<sup>-/-</sup> mice showed increased cancer incidence.

*Fancn/Palb2*<sup>-/-</sup> mice were generated by insertion of a gene trap construct located between exon 1 and exon 2 of the *Palb2* gene (Rantakari, Nikkila et al. 2010; Bouwman, Drost et al. 2011). Homozygous deletion of *Palb2* leads to embryonic lethality which die at E9.5 at the latest (Rantakari, Nikkila et al. 2010; Bouwman, Drost et al. 2011)

As described above, differing from FA patients who often spontaneously develop bone marrow failure in their lives, most of the models have relatively normal hematological function. It is possible that FA proteins have divergent functions which are independent of FANCD2/FANCI monoubiquitination in hematopoietic cells. To test if deletion of multiple *Fanc* genes would result in a more aggressive hematopoietic phenotype, Pulliam-Leath and colleagues generated *Fancc*<sup>-/-</sup>; *Fancg*<sup>-/-</sup> (DKO) mice by genetically intercrossing *Fancc*<sup>+/-</sup> mice with *Fancg*<sup>+/-</sup> mice (Pulliam-Leath, Ciccone et al. 2010). Combined inactivation of *Fancc* and *Fancg* leads to a defective hematopoietic stem cell function, supporting the hypothesis that besides their common role in FANCD2/FANCI monoubiquitination, FANCC and FANCG function in divergent molecular pathways of relevance to hematopoiesis. This DKO model best recapitulates the spontaneous clinical hematopoietic phenotypes of human FA, including hematopoietic malignancies and bone marrow aplasia.

#### 4. Bone marrow microenvironmental abnormalities in hematopoietic diseases

Hematopoiesis is a dynamic and highly regulated process, which relies on the ordered self-renewal and differentiation of HSCs/HPCs within the bone marrow (BM) (Kotton, Ma et al. 2001; Krause 2002; Zhang, Niu et al. 2003; Li and Li 2006; Yin and Li 2006). This process involves intrinsic and extrinsic cues including both cellular and humoral regulatory signals generated by the HSC microenvironment, also known as "niche". The concept of hematopoietic niche has been proposed in the 1970s (Schofield 1978). Studies have shown that the cellular composition of this "niche" contains heterogeneous populations, including endothelial cells, osteoblasts, adipocytes (Calvi, Adams et al. 2003; Zhang, Niu et al. 2003; Arai, Hirao et al. 2005; Sacchetti, Funari et al. 2007), and mesenchymal stem/progenitor cells (MSPCs) (Badillo and Flake 2006), a common progenitor for many of these cells composing the HSC niche. The regulatory signals of the BM microenvironment represent a demarcated anatomical

cal compartment that provides stimulatory signals to HSCs via the following mechanisms: (1) cell/cell direct interactions, (2) secreting soluble factors, and (3) extracellular matrix. These cellular and humoral regulatory signals dictate HSC cell fate, such as self-renewal, proliferation, differentiation, and apoptosis.

The osteoblastic niche and the vacular niche are well described by independent groups (Heissig, Hattori et al. 2002; Calvi, Adams et al. 2003; Zhang, Niu et al. 2003; Avezilla, Hattori et al. 2004). Studies have shown that BM microenvironment is critical for the physiologic as well as pathologic development of hematopoiesis through the following mechanisms: cell/cell interactions, soluble factors and extracellular matrix (Koh, Choi et al. 2005; Williams and Cancelas 2006). There is increasing evidence suggesting a role of the hematopoietic microenvironment in initiating hematopoietic disorders, such as myeloproliferative disorders (MPD).

Recently, using a murine model in which *Dicer1* was specifically deleted in osteoprogenitors, Raaijmakers et al demonstrated that bone marrow microenvironment plays a causative role in the development of myelodysplasia and secondary leukaemia (Raaijmakers, Mukherjee et al. 2010). The vascular microvessel density is increased in the bone marrow of many hematopoietic disorders including AML, acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). The adipocytes are also found to be accumulated in BMF (Li, Chen et al. 2009). Although the mechanism for the accumulation of adipocytes in bone marrow is still largely unknown, the accumulated adipocytes may act as negative regulators in the hematopoietic microenvironment (Naveiras, Nardi et al. 2009).

## 5. Dysregulated bone marrow microenvironment in FA patients and FA murine models

Besides the hematopoietic defects, mesenchymal tissue-derived congenital malformations are also prevalent in FA patients, such as the renal/limb abnormalities and short stature. Despite these clinical observations suggesting multiple mesenchymal defects, little attention has been directed to the association between the pathological HSC functions and the microenvironment in FA.

Using a murine model with targeted disruption of the *Fancg* gene (*Fancg*<sup>-/-</sup>), Li and colleagues first reported that *Fancg*<sup>-/-</sup> MSPCs have decreased clonogenic growth, diminished proliferating capability and increased apoptosis and senescence (Li, Chen et al. 2009). *Fancg*<sup>-/-</sup> MSPCs have impaired function in supporting the proliferation, recruitment, adhesion and homing of HSPCs *in vitro* and *in vivo*. Importantly, some cellular defects such as survival and proliferation of murine MSPCs can be restored by introduction of human *Fancg* cDNA (Li, Chen et al. 2009).

Consistently, study by Zhang et al showed that MSPCs derived from the bone marrow of *Fancd2*<sup>-/-</sup> mice showed less support for progenitor growth than that from wild type mice in a CAFC assay (Zhang, Marquez-Loza et al. 2010).

Using the MSPCs derived from patients with *FANCA* mutation, Lecourt et al showed that human FA MSPCs also have poor proliferation and increased senescence, while no defective hematopoietic supportive activity was observed *in vitro* (Lecourt, Vanneaux et al. 2010), suggesting a species-specific effect between human and murine system.

## 6. Current treatments for FA

The long-term curative therapy for the BMF of FA patients is HSC transplantation, ideally from an HLA-matched sibling (Gluckman, Broxmeyer et al. 1989; Davies, Khan et al. 1996; Guardiola, Pasquini et al. 2000; Kutler, Singh et al. 2003; Mathew 2006). Allogeneic BM transplantation (BMT) or cord blood (CB) transplantation is available to up-to 30% of FA patients. However, allogeneic BMT or CB transplantation is frequently associated with an increased risk of secondary cancers, particularly squamous cell carcinoma of the head and neck (Kutler, Auerbach et al. 2003; Rosenberg, Socie et al. 2005). Since the conditioning regimens such as irradiation clearly heightens the risk of transformation of the ongoing genetic susceptibility of non-hematopoietic tissue. This complication is even more severe in high-risk FA patients, transplanted with non-matched donors and those develop chronic graft-versus-host disease. Therefore, even with successful allogeneic transplantation for BMF, the risk of secondary malignancies results in a high mortality over 10-15 years. Gene therapy using autologous HSCs is a second theoretical modality to correct defects in the HSC compartment. Transplantation of genetically corrected autologous HSCs without genotoxic conditioning regimens could provide a therapeutic strategy that avoids the increased risks of secondary cancer (Si, Ciccone et al. 2006). However, a significant obstacle for this therapy is the limited number of HSCs that can be harvested from mobilized blood or BM. In addition, in preliminary phase 1 clinical trials in FANCC and FANCA patients using retroviral mediated gene transfer, despite an efficient gene transfer of the mobilized progenitors (40-80%), and no long-term engraftment of retroviral marked stem cells was achieved (Liu, Kim et al. 1999; Williams, Croop et al. 2005; Kelly, Radtke et al. 2007). Although inefficient gene transfer of repopulating HSCs can not be excluded, inefficient engraftment and homing of exogenous genetically modified cells could also be contributory, particularly given the low numbers of HSC targets that are available for gene transfer/transplantation (Gothot, Pyatt et al. 1998; Glimm, Oh et al. 2000; Orschell-Traycoff, Hiatt et al. 2000). Since mesenchymal stem/progenitor cells were excluded in these studies, it is possible that the lack of an appropriate microenvironment could have impaired the ability of transduced cells to home and proliferate *in vivo*.

## 7. Biology of MSPCs and their potential clinical application in transplantation therapy for FA patients

Friedenstein and colleagues first reported a rare, plastic-adherent and fibroblast-like subpopulation expanded from the culture of bone marrow in 1970s (Friedenstein, Chailakhjan et al. 1970), this type of stromal cells, now commonly known as MSCs/MSPCs, has captivated

more and more investigators, especially in the past two decades. As a group cells with heterogeneity, three criteria have been proposed to define human MSPCs, including plastic-adherence, surface expression of CD105, CD73 and CD90, and the absence of CD45, CD34, CD14 or CD11b, CD79a, CD19, CD14 or CD11b and HLA-DR, and trilineage differentiation to osteoblasts, adipocytes and chondrocytes *in vitro* (Dominici, Le Blanc et al. 2006).

It is well known that MSPCs lack expression of MHC class II and most of the classical co-stimulatory molecules such as CD80, CD86, or CD40 (Pittenger, Mackay et al. 1999; Tse, Pendleton et al. 2003). This phenotypic characteristic endows MSPCs with nonimmunogenicity, and therefore transplantation of MSPCs into allogeneic host could be implemented without using immunosuppressive agents. MSPCs are known promote the reconstitution of hematopoiesis. We have recently provided evidence for the first time that *Fancg*<sup>-/-</sup> MSPCs exhibited profoundly diminished supportive activity for normal HSCs, and intratibial injection of WT or genetically corrected FA MSPCs enhanced donor HSC reconstitution (Li, Chen et al. 2009). This data suggests that normal MSPCs transplantation may have a potential clinical application in FA patients.

## 8. Future directions

FA is an inherited disease caused by germ-line mutations in *FANC* genes. Investigators are now paying more attentions on the emerging role of the *Fanc* gene inactivation-caused defective bone marrow microenvironment in the pathogenesis of FA. Co-transplantation of HSCs and MSPCs is hypothesized as a potentially more effective option than HSC transplantation alone for treating the hematopoietic abnormalities in FA. Therefore, much more effort is warranted to understand the mechanisms of the utility of MSPCs to treat FA patients. These efforts should include: 1) unveiling the cellular fates of the co-injected MSPCs *in vivo*, such as at what degree these MSPCs are able to reconstitute the marrow microenvironment and how long a significant degree of MSPC engraftment could persist; 2) clarifying whether an immune suppression activity mediated by the injected MSPCs contributes to the enhanced HSC engraftment by co-transplantation of MSPCs; and 3) elucidating at what extend the co-injected MSPCs could normalize the altered marrow microenvironment cytokine/growth factors profiling in FA patients.

## Author details

Wen Xing<sup>1\*</sup>, Mingjiang Xu<sup>2\*</sup> and Feng-Chun Yang<sup>2\*</sup>

1 State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China



2 Herman B Wells Center for Pediatric Research, Indiana University School of Medicine; Indianapolis, Indiana, USA

## References

- [1] Agoulnik, A. I., Lu, B., et al. (2002). A novel gene, Pog, is necessary for primordial germ cell proliferation in the mouse and underlies the germ cell deficient mutation, gcd." *Hum Mol Genet*, 11(24), 3047-3053.
- [2] Arai, F., Hirao, A., et al. (2005). Regulation of hematopoiesis and its interaction with stem cell niches." *Int J Hematol*, 82(5), 371-376.
- [3] Auerbach, A. D., Buchwald, M., et al. (2002). Fanconianemia. In: Vogelstein B, Kinzler KW, eds.", *The Genetic Bases of Human Cancer 2nd Edition*, (New York: McGraw-Hill, Inc.);, 289-306.
- [4] Avecilla, S. T., Hattori, K., et al. (2004). Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis." *Nat Med*, 10(1), 64-71.
- [5] Badillo, A. T., & Flake, A. W. (2006). The regulatory role of stromal microenvironments in fetal hematopoietic ontogeny." *Stem Cell Rev*, 2(3), 241-246.
- [6] Bagby, G. C., & Alter, B. P. (2006). Fanconianemia." *SeminHematol*, 43, 147-156.
- [7] Agoulnik, A. I., Lu, B., et al. (2002). A novel gene, Pog, is necessary for primordial germ cell proliferation in the mouse and underlies the germ cell deficient mutation, gcd." *Hum Mol Genet*, 11(24), 3047-3053.
- [8] Arai, F., Hirao, A., et al. (2005). Regulation of hematopoiesis and its interaction with stem cell niches." *Int J Hematol*, 82(5), 371-376.
- [9] Auerbach, A. D., Buchwald, M., et al. (2002). Fanconianemia. In: Vogelstein B, Kinzler KW, eds.", *The Genetic Bases of Human Cancer 2nd Edition*, (New York: McGraw-Hill, Inc.);, 289-306.
- [10] Avecilla, S. T., Hattori, K., et al. (2004). Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis." *Nat Med*, 10(1), 64-71.
- [11] Badillo, A. T., & Flake, A. W. (2006). The regulatory role of stromal microenvironments in fetal hematopoietic ontogeny." *Stem Cell Rev*, 2(3), 241-246.
- [12] Bagby, G. C., & Alter, B. P. (2006). Fanconianemia." *SeminHematol*, 43, 147-156.
- [13] Bagby, G. C., Jr , , Segal, G. M., et al. (1993). Constitutive and induced expression of hematopoietic growth factor genes by fibroblasts from children with Fanconianemia." *ExpHematol*, 21(11), 1419-1426.

- [14] Bakker, S. T., van de Vrugt, H. J., et al. (2009). Fancm-deficient mice reveal unique features of Fanconianemia complementation group M". *Hum Mol Genet*, 18(18), 3484-3495.
- [15] Barroca, V., Mouthon, M. A., et al. (2012). Impaired functionality and homing of Fancg-deficient hematopoietic stem cells". *Hum Mol Genet*, 21(1), 121-135.
- [16] Bouwman, P., Drost, R., et al. (2011). Loss of 53 partially rescues embryonic development of Palb2 knockout mice but does not foster haploinsufficiency of Palb2 in tumour suppression". *J Pathol*, 224(1), 10-21.
- [17] Calvi, L. M., Adams, G. B., et al. (2003). Osteoblastic cells regulate the haematopoietic stem cell niche". *Nature*, 425(6960), 841-846.
- [18] Chen, M., Tomkins, D. J., et al. (1996). Inactivation of Fac in mice produces inducible chromosomal instability and reduced fertility reminiscent of Fanconi anaemia". *Nat Genet*, 12(4), 448-451.
- [19] Cheng, N. C., van de Vrugt, H. J., et al. (2000). Mice with a targeted disruption of the Fanconianemia homolog Fanca". *Hum Mol Genet*, 9(12), 1805-1811.
- [20] D'Andrea, A. D. (2010). Susceptibility pathways in Fanconi'sanemia and breast cancer". *N Engl J Med*, 362(20), 1909-1919.
- [21] D'Andrea, A. D., Dahl, N., et al. (2002). Marrow failure". *Hematology Am SocHematolEduc Program.*, 58-72.
- [22] Davies, S. M., Khan, S., et al. (1996). Unrelated donor bone marrow transplantation for Fanconianemia". *Bone Marrow Transplant*, 17(1), 43-47.
- [23] Dominici, M., Le Blanc, K., et al. (2006). Minimal criteria for defining multipotentmesenchymal stromal cells. The International Society for Cellular Therapy position statement". *Cytotherapy*, 8(4), 315-317.
- [24] Du, W., Adam, Z., et al. (2008). Oxidative stress in Fanconianemiahematopoiesis and disease progression". *Antioxid Redox Signal*, 10(11), 1909-1921.
- [25] Friedenstein, A. J., Chailakhjan, R. K., et al. (1970). The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells". *Cell Tissue Kinet*, 3(4), 393-403.
- [26] Giri, N., Batista, D. L., et al. (2007). Endocrine Abnormalities in Patients with FanconiAnemia". *J ClinEndocrinolMetab*, 92(7), 2624-2631.
- [27] Glimm, H., Oh, I. H., et al. (2000). Human hematopoietic stem cells stimulated to proliferate in vitro lose engraftment potential during their S/G(2)/M transit and do not reenter G(0)". *Blood*, 96(13), 4185-4193.
- [28] Gluckman, E., Broxmeyer, H. A., et al. (1989). Hematopoietic reconstitution in a patient with Fanconi'sanemia by means of umbilical-cord blood from an HLA-identical sibling". *N Engl J Med*, 321(17), 1174-1178.

- [29] Gothot, A., Pyatt, R., et al. (1998). Assessment of proliferative and colony-forming capacity after successive in vitro divisions of single human CD34+ cells initially isolated in G0." *ExpHematol*, 26(7), 562-570.
- [30] Guardiola, P., Pasquini, R., et al. (2000). Outcome of 69 allogeneic stem cell transplantations for Fanconianemia using HLA-matched unrelated donors: a study on behalf of the European Group for Blood and Marrow Transplantation." *Blood*, 95(2), 422-429.
- [31] Haneline, L. S., Gobbett, T. A., et al. (1999). Loss of FancC function results in decreased hematopoietic stem cell repopulating ability." *Blood*, 94(1), 1-8.
- [32] Heissig, B., Hattori, K., et al. (2002). Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand." *Cell*, 109(5), 625-637.
- [33] Houghtaling, S., Timmers, C., et al. (2003). Epithelial cancer in Fanconianemia complementation group D2 (Fancd2) knockout mice." *Genes Dev*, 17(16), 2021-2035.
- [34] Kee, Y., & D'Andrea, A. D. (2010). Expanded roles of the Fanconianemia pathway in preserving genomic stability." *Genes Dev*, 24(16), 1680-1694.
- [35] Kelly, P. F., Radtke, S., et al. (2007). Stem cell collection and gene transfer in Fanconianemia." *MolTher*, 15(1), 211-219.
- [36] Kim, Y., Lach, F. P., et al. (2011). Mutations of the SLX4 gene in Fanconianemia." *Nat Genet*, 43(2), 142-146.
- [37] Koh, S. H., Choi, H. S., et al. (2005). Co-culture of human CD34+ cells with mesenchymal stem cells increases the survival of CD34+ cells against the 5-aza-deoxycytidine or trichostatin A-induced cell death." *BiochemBiophys Res Commun*, 329(3), 1039-1045.
- [38] Kook, H. (2005). Fanconianemia: current management." *Hematology 10 Suppl*, 1, 108-110.
- [39] Koomen, M., Cheng, N. C., et al. (2002). Reduced fertility and hypersensitivity to mitomycin C characterize Fancg/Xrcc9 null mice." *Hum Mol Genet*, 11(3), 273-281.
- [40] Kopen, G. C., Prockop, D. J., et al. (1999). Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains." *ProcNatlAcadSci U S A*, 96(19), 10711-10716.
- [41] Kotton, D. N., et, B. Y., & al, . (2001). Bone marrow-derived cells as progenitors of lung alveolar epithelium." *Development*, 128(24), 5181-5188.
- [42] Krause, D. S. (2002). Plasticity of marrow-derived stem cells." *Gene Ther*, 9(11), 754-758.
- [43] Kutler, D. I., Auerbach, A. D., et al. (2003). High incidence of head and neck squamous cell carcinoma in patients with Fanconianemia." *Arch Otolaryngol Head Neck Surg*, 129(1), 106-112.

- [44] Kutler, D. I., Singh, B., et al. (2003). A 20-year perspective on the International FanconiAnemia Registry (IFAR)". *Blood*, 101(4), 1249-1256.
- [45] Lecourt, S., Vanneaux, V., et al. (2010). Bone marrow microenvironment in fanconianemia: a prospective functional study in a cohort of fanconianemia patients". *Stem Cells Dev*, 19(2), 203-208.
- [46] Li, Y., Chen, S., et al. (2009). Mesenchymal stem/progenitor cells promote the reconstitution of exogenous hematopoietic stem cells in *Fancg*<sup>-/-</sup> mice in vivo". *Blood*, 113(10), 2342-2351.
- [47] Li, Z., & Li, L. (2006). Understanding hematopoietic stem-cell microenvironments". *Trends BiochemSci*, 31(10), 589-595.
- [48] Liu, J. M., Kim, S., et al. (1999). Engraftment of hematopoietic progenitor cells transduced with the Fanconianemia group C gene (FANCC)". *Hum Gene Ther*, 10(14), 2337-2346.
- [49] Lobitz, S., & Velleuer, E. (2006). Guido Fanconi (1892-1979): a jack of all trades". *Nat Rev Cancer*, 6(11), 893-898.
- [50] Mathew, C. G. (2006). Fanconi anaemia genes and susceptibility to cancer". *Oncogene*, 25(43), 5875-5884.
- [51] Meetei, A. R., Levitus, M., et al. (2004). X-linked inheritance of Fanconianemia complementation group B". *Nat Genet*, 36(11), 1219-1224.
- [52] Milsom, M. D., Lee, A. W., et al. (2009). *Fanca*<sup>-/-</sup> hematopoietic stem cells demonstrate a mobilization defect which can be overcome by administration of the Rac inhibitor NSC23766". *Haematologica*, 94(7), 1011-1015.
- [53] Moldovan, G. L., & D'Andrea, A. D. (2009). How the fanconianemia pathway guards the genome". *Annu Rev Genet*, 43, 223-249.
- [54] Munoz-Elias, G., Marcus, A. J., et al. (2004). Adult bone marrow stromal cells in the embryonic brain: engraftment, migration, differentiation, and long-term survival". *J Neurosci*, 24(19), 4585-4595.
- [55] Navarro, S., Meza, N. W., et al. (2006). Hematopoietic dysfunction in a mouse model for Fanconianemia group D1". *Mol Ther*, 14(4), 525-535.
- [56] Naveiras, O., Nardi, V., et al. (2009). Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment". *Nature*, 460(7252), 259-263.
- [57] Orschell-Traycoff, C. M., Hiatt, K., et al. (2000). Homing and engraftment potential of Sca-1(+)lin(-) cells fractionated on the basis of adhesion molecule expression and position in cell cycle". *Blood*, 96(4), 1380-1387.
- [58] Parmar, K., Kim, J., et al. (2010). Hematopoietic stem cell defects in mice with deficiency of *Fancd2* or *Usp1*". *Stem Cells*, 28(7), 1186-1195.

- [59] Pittenger, M. F., Mackay, A. M., et al. (1999). Multilineage potential of adult human mesenchymal stem cells." *Science*, 284(5411), 143-147.
- [60] Pulliam-Leath, A. C., Ciccone, S. L., et al. (2010). Genetic disruption of both *Fancc* and *Fanccg* in mice recapitulates the hematopoietic manifestations of Fanconiane-mia." *Blood*, 116(16), 2915-2920.
- [61] Raaijmakers, M. H., Mukherjee, S., et al. (2010). Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia." *Nature*, 464(7290), 852-857.
- [62] Rantakari, P., Nikkila, J., et al. (2010). Inactivation of *Palb2* gene leads to mesoderm differentiation defect and early embryonic lethality in mice." *Hum Mol Genet*, 19(15), 3021-3029.
- [63] Rio, P., Segovia, J. C., et al. (2002). In vitro phenotypic correction of hematopoietic progenitors from Fanconianemia group A knockout mice." *Blood*, 100(6), 2032-2039.
- [64] Rosenberg, P. S., Socie, G., et al. (2005). Risk of head and neck squamous cell cancer and death in patients with Fanconianemia who did and did not receive transplants." *Blood*, 105(1), 67-73.
- [65] Sacchetti, B., Funari, A., et al. (2007). Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment." *Cell*, 131(2), 324-336.
- [66] Sasaki, M. S. (1975). Is Fanconi's anaemia defective in a process essential to the repair of DNA cross links?" *Nature*, 257(5526), 501-503.
- [67] Schofield, R. (1978). The relationship between the spleen colony-forming cell and the haemopoietic stem cell." *Blood Cells*, 4(1-2), 7-25.
- [68] Schroeder, T. M., Anschutz, F., et al. (1964). Spontaneous chromosome aberrations in familial panmyelopathy." *Humangenetik*, 1(2), 194-196.
- [69] Sharan, S. K., Morimatsu, M., et al. (1997). Embryonic lethality and radiation hyper-sensitivity mediated by *Rad51* in mice lacking *Brca2*." *Nature*, 386(6627), 804-810.
- [70] Si, Y., Ciccone, S., et al. (2006). Continuous in vivo infusion of interferon-gamma (IFN-gamma) enhances engraftment of syngeneic wild-type cells in *Fanca*<sup>-/-</sup> and *Fanccg*<sup>-/-</sup> mice." *Blood*, 108(13), 4283-4287.
- [71] Stoepker, C., Hain, K., et al. (2011). *SLX4*, a coordinator of structure-specific endonu-cleases, is mutated in a new Fanconianemia subtype." *Nat Genet*, 43(2), 138-141.
- [72] Tse, W. T., Pendleton, J. D., et al. (2003). Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation." *Transplantation*, 75(3), 389-397.
- [73] Vaz, F., Hanenberg, H., et al. (2010). Mutation of the *RAD51C* gene in a Fanconiane-mia-like disorder." *Nat Genet*, 42(5), 406-409.

- [74] Vinciguerra, P., Godinho, S. A., et al. (2010). Cytokinesis failure occurs in Fanconianemia pathway-deficient murine and human bone marrow hematopoietic cells." *J Clin Invest*, 120(11), 3834-3842.
- [75] Whitney, M. A., Royle, G., et al. (1996). Germ cell defects and hematopoietic hypersensitivity to gamma-interferon in mice with a targeted disruption of the Fanconianemia C gene." *Blood*, 88(1), 49-58.
- [76] Williams, D. A., & Cancelas, J. A. (2006). Leukaemia: niche retreats for stem cells." *Nature*, 444(7121), 827-828.
- [77] Williams, D. A., Croop, J., et al. (2005). Gene therapy in the treatment of Fanconianemia, a progressive bone marrow failure syndrome." *Curr Opin Mol Ther*, 7(5), 461-466.
- [78] Wong, J. C., Alon, N., et al. (2003). Targeted disruption of exons 1 to 6 of the Fanconianemia group A gene leads to growth retardation, strain-specific microphthalmia, meiotic defects and primordial germ cell hypoplasia." *Hum Mol Genet*, 12(16), 2063-2076.
- [79] Yang, Y., Kuang, Y., et al. (2001). Targeted disruption of the murine Fanconianemia gene, *Fancg/Xrcc9*." *Blood*, 98(12), 3435-3440.
- [80] Yin, T., & Li, L. (2006). The stem cell niches in bone." *J Clin Invest*, 116(5), 1195-1201.
- [81] Zhang, J., Niu, C., et al. (2003). Identification of the haematopoietic stem cell niche and control of the niche size." *Nature*, 425(6960), 836-841.
- [82] Zhang, Q. S., Marquez-Loza, L., et al. (2010). *Fancd2*<sup>-/-</sup> mice have hematopoietic defects that can be partially corrected by resveratrol." *Blood*, 116(24), 5140-5148.
- [83] Zhang, X., Shang, X., et al. (2008). Defective homing is associated with altered Cdc42 activity in cells from patients with Fanconianemia group A." *Blood*, 112(5), 1683-1686.

IntechOpen

