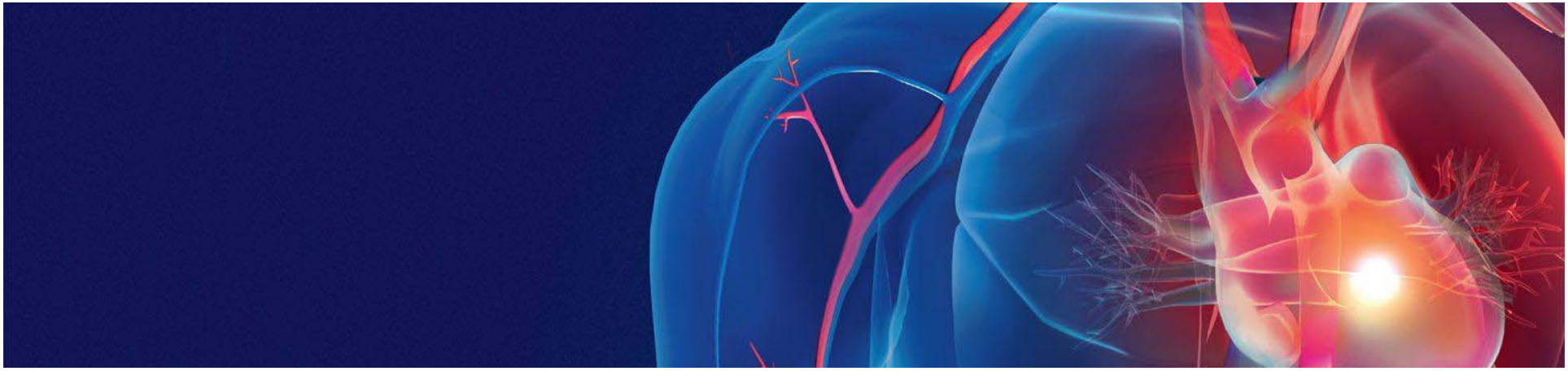
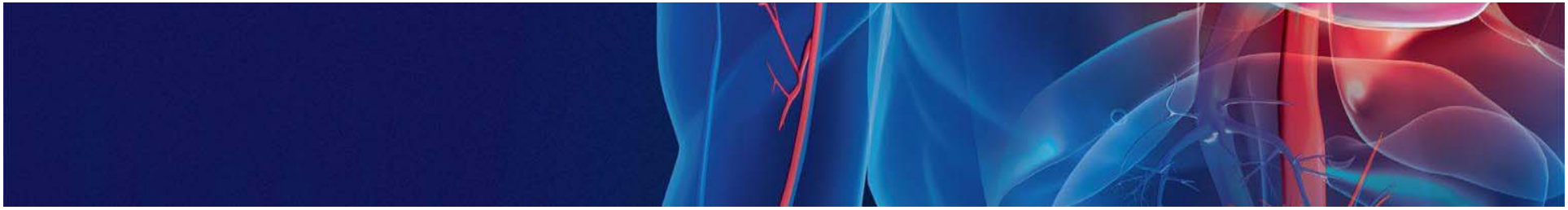
When mutations in blood cells damage the heart





Do cancer and cardiovascular diseases have a common cause?

Mutations in blood stem cells do not necessarily have to result in leukaemia. It was only recently discovered that clones of mutated blood cells can be identified in many healthy people in old age. Nonetheless, clonal haematopoiesis, as scientists baptised this finding, is far from innocent. It is a formidable risk factor for cardiovascular diseases – on par with smoking, excess weight or high blood pressure. Why this is, is still a riddle to be solved.

More than half of all deaths in the Western world are due to cancer or cardiovascular diseases and the trend is rising. The reason for this is our aging society. The probability of dying from heart diseases or cancer increases with age. Interestingly, the occurrence of both of these types of illness in a single patient is not rare. One obvious explanation are common risk factors for cancer and heart diseases, such as age, smoking, excess weight, lack of exercise, or an unhealthy lifestyle. Clinicians and scientists at the Frankfurt University Hospital, at the Excellence Cluster Cardio-Pulmonary Institute (CPI) and at the LOEWE Center Frankfurt Cancer Institute (FCI) are on the trail of

Clonal haematopoiesis is not a disease in and of itself. Only recently, modern DNA sequencing technologies made it possible to demonstrate that clonal haematopoiesis is no rarity (Genovese et al. 2014; Jaiswal et al. 2014). In fact, the harder we look with ever increasing DNA sequencing technologies, the more often we find at least a small mutated clone in the blood of almost every 60 year-old. So far, it looks as if these people are completely healthy. However, since almost no 60 year-old is without some ailment, scientists started to look carefully at whether there was any association between clonal haematopoiesis and disease.

As a result, the leukaemia risk is higher for people with clonal haematopoiesis, although it is not as drastic as was originally thought. This is probably because only a small portion of the mutations that can occur in clonal haematopoiesis are linked to an increased leukaemia risk. In addition, the size of the clone and the number of mutated genes correlate positively with the risk of leukaemia. This is extremely fascinating for scientists, because they hope to be able to predict the occurrence of leukaemia using the sequencing of blood cells (Abelson et al. 2018). We might then find ways to eradicate the prelaeukemic clone to prevent the outbreak of the disease

Cancer Institute (FCI) are on the trail of another possibility: that one event may lead to both illnesses.

Mutated blood stem cells and their clones

Blood cells are constantly being formed anew. This lifelong regeneration is called haematopoiesis and it occurs in the bone marrow. Every second, five million new blood cells are created to replace aging cells. Only a few thousand of blood stem cells in the bone marrow are responsible for achieving this enormous number of diverse cells that constitute our blood. If in only one of these stem cells the genetic material is changed in a way that gives this cell only a slight production advantage, the number of its direct descendants increases. This leads to a collection of blood cells carrying this genetic alteration (a genomic mutation) – a clone that can be identified because we can trace genomic mutations. This type of blood formation is therefore called clonal haematopoiesis.

And they found that these clones are probably not innocent, especially if they are made up of many cells. The first thing that is notable about these mutations is that they also occur in leukaemia cells. Secondly, laboratory experiments had shown that these mutations change cells; mutated blood stem cells are fitter. The mutation provides them an advantage both in cell survival and growth.

This advantage is small, however, making it doubtful that a single mutation alone really drive detrimental leukaemia cell development, but enough to make “their” clone more and more predominant in the bone marrow. In order to really cause leukaemia, the frequently encountered mutations of clonal haematopoiesis need other, independently occurring mutations. It requires a real cocktail of different mutations to convert a normal blood cell into a malignant leukaemia cell. Factors such as smoking, nutrition and exercise also play an important role.

prevent the outbreak of the disease.

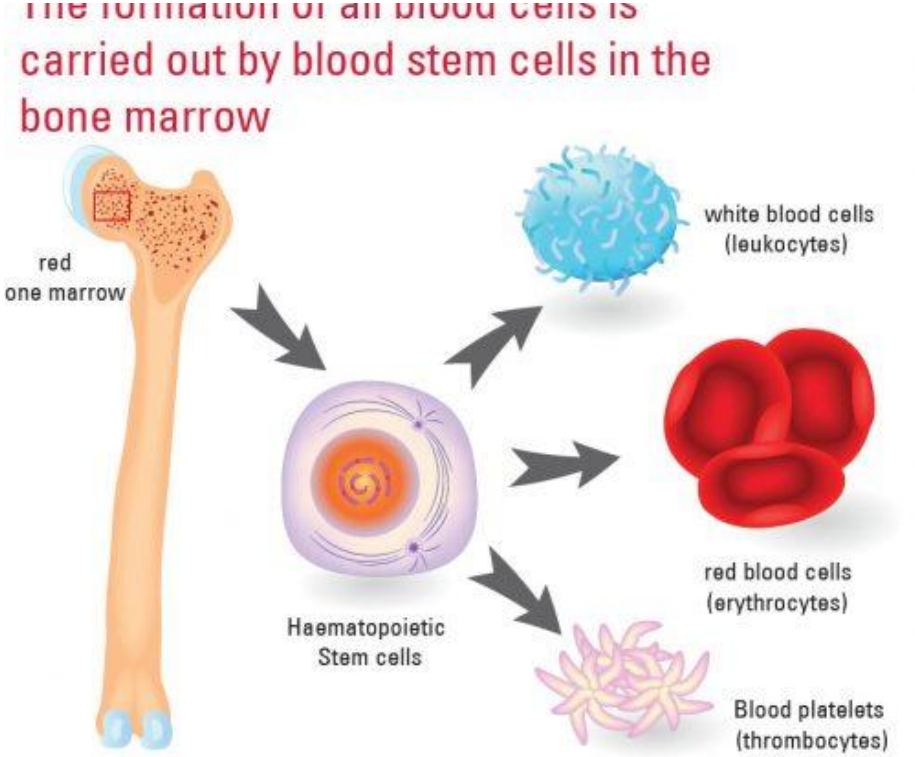
Interestingly, an increased positive association was also found between the occurrence of clonal haematopoiesis and other kinds of cancer that do not arise in the blood. Why this is, however, we do not understand. One hypothesis that scientists follow is that mutated blood cells may change the immune system, making it less effective to fight cancer.

Clonal haematopoiesis: a new risk factor in cardiovascular diseases

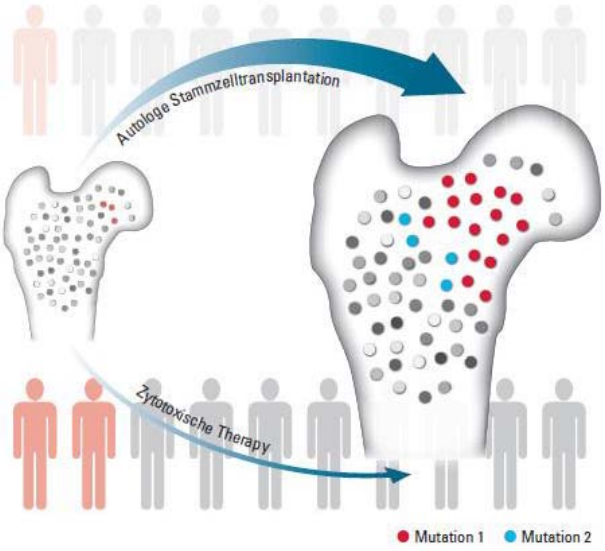
Shortly after the discovery of clonal haematopoiesis several years ago, an astonishing and unexpected connection with the occurrence of cardiovascular diseases was discovered. People with clonal haematopoiesis are more likely to suffer from atherosclerosis and more frequently have heart attacks or strokes (Jaiswal et al. 2017). What influence do gene changes in blood have on the occurrence of these cardiovascular diseases?

The formation of all blood cells is

Haematopoietic stress



Mutated stem cells are activated in stress situations such as chemotherapies and stem cell transplantation, and dominate blood cell regeneration. This leads to the accumulation of mutated blood cells and to clonal haematopoiesis. These therapies lead to a higher number of patients with clonal haematopoiesis and the affected mutated blood cell clone expands as well. This can have an effect on future cardiovascular diseases.



To find out, scientists and clinicians at the University Hospital Frankfurt from diverse fields and disciplines came together to bundle their expertise in cancer research, blood stem cell research and cardiovascular research. A few months ago, we were able to demonstrate that patients at the hospital with chronic heart failure triggered by a heart attack also had more frequent occurrences of clonal haematopoiesis (Dorsheimer et al. 2019).

Some mutations caused by clonal haematopoiesis change the pattern of the messenger substances of macrophages, increasing the production of pro-inflammatory cytokines. This in turn might aggravate chronic inflammation that can damage the heart and blood vessels, and the disease worsens.

It has long been known that former cancer patients who have successfully

Clonal haematopoiesis should be regularly monitored in patients with this development. To reduce the enormous effort of DNA sequencing, an intensive search for clinical parameters that would indicate clonal haematopoiesis is currently underway.

Close interdisciplinary collaboration between cardiologists and oncologists, such as practiced at the University Hospital Frankfurt in research and

(Dorsheimer et al. 2019).

Patients with blood stem cell mutations in the most often affected genes, DNMT3A and TET2, had a significantly worse prognosis, and their heart failure progressed much faster than in the other patients. The size of the mutated blood cell clone had a significant impact on the course of the illness. We also found that patients with aortic valve stenosis who undergo an implantation of an artificial aortic valve via catheter have a worse course of illness, if they display clonal haematopoiesis driven by a mutation in the genes DNM3A or TET2 (Mas-Peiro et al. 2019). Now we are heavily working to unlock the mechanisms with which mutated blood cells influence cardiovascular diseases.

Results from laboratory experiments have shown that some mutations can change the function of monocytes and macrophages. These cells are part of the native immune defence system, and they work everywhere in the body as scavengers. They “eat” bacteria and kill them, but they also play an important role as messengers to other cells of the native and the more specialized, adaptive immune system by secreting

overcome their disease have a higher risk of contracting cardiovascular diseases. Undoubtedly, the protracted and draining cancer therapies (chemotherapy, radiation therapy) contribute to this, but the discovery of clonal haematopoiesis places these observations in a new light. After successful leukaemia therapy, most patients retain clonal haematopoiesis. Recently, we showed that lymphoma patients who received chemotherapy combined with stem cell transplantation, a procedure that preserves the blood production to survive this type of therapy, but poses high stress onto haematopoiesis, had an increased occurrence of clonal haematopoiesis (Ortmann et al. 2019). If these patients displayed clonal haematopoiesis before the therapy, the size of the mutated blood cell clone, and with it the risk for leukaemia and cardiovascular diseases, was also increased significantly by the therapy. Could the same mutations be the source for the disease progression of both diseases? Patients with myelodysplastic syndrome, a kind of precursor stage of leukaemia triggered by similar genetic changes, also

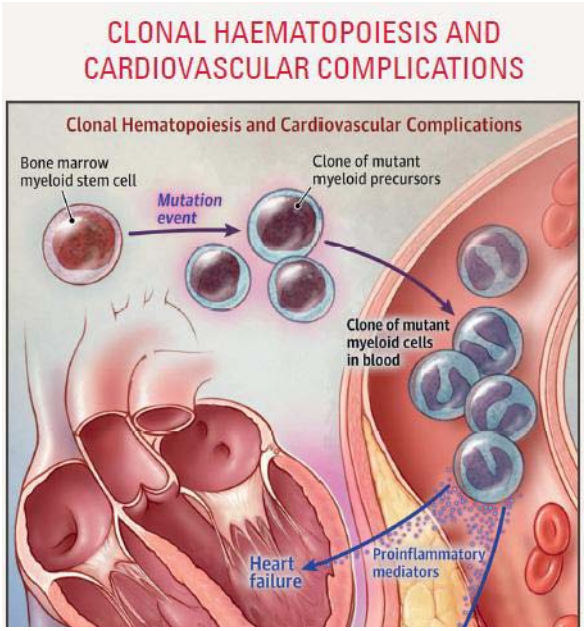
patient care, will play a major role in the future in the successful treatment of cancer patients and patients with cardiovascular diseases. The risks of both diseases have to be discussed individually for each patient before, during, and after therapy, and disease-preventing measures determined as early as possible.

Hope for new therapies

Clonal haematopoiesis has become a hot topic in medicine. The phenomenon is recognised as a new risk factor for cardiovascular diseases. It is at least as significant as other known risk factors such as smoking, excess weight, high blood pressure, and diabetes. We have to understand the mechanism of action of each individual gene change in order to determine precise therapeutic and preventive measures. It is probable that mutated blood cells send signals via messenger substances that affect both the centre of inflammation in the affected organ, as well as the stem cells and blood formation. Thus begins a vicious cycle: mutated stem cells produce more mutated blood cells due to these messenger substances, which in turn

adaptive immune system by secreting substances to influence the growth, activity and movement of various immune cells.

They can recruit other cells to a site of inflammation, and they can have either anti- or pro-inflammatory effects, dependent on the cell types they attract, and by dampening or inciting their activity. Depending on the messenger substances they transmit, macrophages can even heavily promote or suppress the growth of cancer. What has all this to do with clonal haematopoiesis?



frequently suffer from cardiovascular diseases.

Clinical consequences

Routine testing for mutations that cause clonal haematopoiesis could make the early detection of leukaemia, of worsening chronic heart failure, and of cardiovascular diseases possible. This testing is not currently being carried out, because it only makes sense if disease-preventive measures are clinically established. Clonal haematopoiesis is currently being detected above all in patients with haematological diseases as accompanying condition.

Clonal haematopoiesis arises from mutated blood stem cells that attain a growth advantage. Out of these mutated blood stem cells, a clone of mutated precursor cells is formed in the bone marrow, which matures into mutated myeloid cells and released into the blood.

The mutated myeloid cells (monocytes macrophages) produce signal substances (cytokines, chemokines) that induce inflammation

produce more messenger substances, and the clonal haematopoiesis and tissue inflammation increase. We are putting enormous effort into researching the influence of clonal haematopoiesis on other chronic inflammatory sicknesses of the heart and lung. The Excellence Cluster “Cardio-Pulmonary Institute” offers an ideal platform for this work.

If the findings on clonal haematopoiesis continue to keep coming at such a rapid pace, we can soon use them to the therapeutic benefit of patients.

In a nutshell

Clonal haematopoiesis has been identified as a new risk factor for cardiovascular diseases. Following a heart attack, patients with particular mutations in blood stem cells have a worse prognosis.

There is a greater risk for leukaemia if the number of mutations in blood stem cells and the size of their clones increase.

and attract other immune cells. In this way, clonal haematopoiesis leads to the development and worsening of cardiovascular diseases such as atherosclerosis and aortic valve stenosis, and heart failure.

The inflammatory signals also support the formation of additional mutated blood cells, resulting in a vicious cycle in patients with clonal haematopoiesis.

Clonal haematopoiesis is also being increasingly scrutinized as an effect of cancer therapy. The importance of monitoring cancer survivors for cardiovascular diseases is growing.

Once we fully understand the mechanism and find ways to interfere, screening of individuals for clonal haematopoiesis may give us new tools for patient risk assessment and early intervention for cardiovascular disease, leukaemia, and possibly also for other diseases.

The authors

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Professor Andreas Zeiher, born in 1955, is a cardiologist and has been the director of the Medical Clinic III (cardiology, angiology, haemostasiology) since 1995. From 2008 to 2012 he was co-speaker of the excellence cluster Cardio-Pulmonary Systems. Since 2010 he has been the speaker of the LOEWE Centre for Cell and Gene Therapy and since 2011 the speaker of the German Centre for Cardiovascular Research Rhein-Main. In 2019 he was elected president of the German Society for Cardiology.

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