Defects in phagocytes

To get a view about immunodeficiencies the figure shows how these are distributed. Half immunodeficiencies take place in antibodies. But with 18 % also phagocytes have a very important role especially in primary immune response. [1] The consequence of a deficit could be the spread of bacterial infections in the body.
There are 3 types of phagocyte immunodeficiencies, caused by genes encoding proteins that concern phagocyte production, phagocyte interaction and phagocyte killing of microorganisms.
Inherited deficiencies of neutrophil production are called neutropenias and are classified as severe congenital neutropenias or as cyclic neutropenias. In the first case the number of neutrophils is always extreme low in contrast to the second case, where the number fluctuates from near normal to very low or none. The cycle time is about 21 days.
Defects in the interaction/migration of phagocytic cells to extravascular sites of infection can cause serious immunodeficiency.
There are 4 different phases. The rolling adhesion to endothelial cells, tight binding, diapedesis and migration. Fundamental in this process are molecules on the surface of leukocytes. Deficiencies in these molecules can prevent neutrophils and macrophages from reaching sites of infection to ingest and destroy bacteria.
As an example, one step in the biosynthesis of Sialyl-Lewis x is the fucosylation. A genetically caused lack of GDP-fucose transporter leads to a deficiency of Sialyl-Lewis x and consequently to a reduced rolling adhesion. [2]
There are several genetic defects which cause a dysfunction of intracellular killing of microorganisms. Glucose-6-P-Dehydrogenase and Myeloperoxidase are two enzymes necessary for intracellular killing. Glucose-6-phosphate dehydrogenase leads to the production of NADPH, which causes the formation of superoxide anion. And Myeloperoxidase leads to the production of Hypoclorous acid. Both molecules have a antibacterial function and can destroy bacterias. A deficiency in these enzymes can lead to chronic infections. [3]

Chronic granulomatous disease

Chronic Granulomatous Disease is the most commonly encountered disorder of phagocytes. The disease is the result of a disorder of the NADPH oxidase system, culminating in an inability of the phagocyte to generate superoxide, leading to the defective killing of pathogenic organisms. [1]
NADPH oxidase is composed of cytochrome-b558 heterodimer located in the membrane which consists of the **gp91phox** and **p22phox** units, and three cytosolic components: **p67phox** , **p47phox** , and a **p40phox**. Following cellular activation, the soluble cytosolic components, p67phox, p47phox, and a p40phox, move to the membrane and bind to components of the cytochrome-b558 heterodimer. This is also accompanied by the binding of the GTPase protein, **Rac**. This catalyzes the transfer of electrons from NADPH to oxygen, resulting in the formation of **superoxide(O2-)** in the extracellular component. Subsequent reactions via superoxide dismutase (SOD), catalase or myeloperoxidase (MPO), occurring in the phagolysome, can result in formation of H2O2, H2O, or HOCl- respectively. [1]

X-linked CGD arises due to mutations in the gp91phox gene and is responsible for 65-70% of the clinical cases in the United States. Deletions, frameshift, missense, nonsense, and splice site mutations have been described in this gene. Autosomal recessive CGD, seen in the remaining 35% cases, arise due to mutations in genes encoding p22phox , p67phox and p47phox. [4]
Clinical Features:
The disease manifests as repeated, severe bacterial and fungal infections resulting in the formation of inflammatory granulomas.The infections include: Staphylococcus aureus, Pseudomonas species, Nocardia species, and fungi (such as Aspergillus species and Candida albicans). Due to involvement

of vital or large organs, such infections can lead to significant morbidity and/or mortality in the affected patients. [1]

Biotechnological applications: Gene therapy

Current and past clinical trials of gene therapy rely on viral delivery and addition of a functional copy of the defective gene. Over the past decades target-specific nuclease enzymes have been investigated to follow a strategy of targeted insertion of a functional copy and correction of the dysfunctional gene. Engineered nuclease enzymes comprise Zinc-finger nucleases (ZFN), transcriptor activator-like effector nucleases (TALENs) and clustered regulatory interspaced short palindromic repeats CRISPR-associated (CRISPR/Cas) based RNA-guided DNA endonucleases. [5] These nucleases catalyse a site-specific double-strand break and the addition of a target gene/sequence by means of homologous recombination, which allows the integration of the correct gene and its further expression.Gene-targeting approaches have been recently published, applying ZFN, TALEN and CRISPR/Cas9 technology to iPSCs from CGD patients, among others. [6]

References:

[1] Song E , et al, Clinical and Molecular Allergy 2011
[2] Murphy K, et al, Garland Science 2008
[3] Satyanarayana U,et al, Journal of Dr. NTR University of Health Sciences 2014
[4] Assari T , et al , Medical Immunology 2006
[5] Ghosh S, et al, British Journal of Haematology 2015
[6] Flynn R , et al, Experimental Hematology 2015