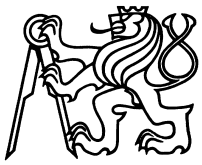
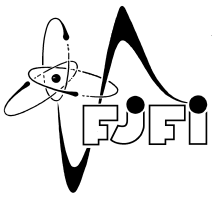


Czech Technical University in Prague
Faculty of Nuclear Sciences and Physical Engineering



Estimating patient's life expectancy after a successful kidney transplant using machine learning methods

Odhad délky života pacienta po úspěšné transplantaci ledviny pomocí metod strojového učení

Bachelor's Degree Project

Author: **Kyrylo Stadniuk**

Supervisor: **Ing. Tomáš Kouřim**

Consultant: **Ing. Pavel Strachota, Ph.D.**

Language advisor: **PaedDr. Eliška Rafajová**

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ZADÁNÍ BAKALÁŘSKÉ PRÁCE

Student:	Kyrylo Stadniuk
Studijní program:	Aplikovaná informatika
Název práce (česky):	Odhad délky života pacienta po úspěšné transplantaci ledviny pomocí metod strojového učení
Název práce (anglicky):	Estimating patient's life expectancy after a successful kidney transplant using machine learning methods

Pokyny pro vypracování:

1) Prozkoumejte současný přístup k transplantacím ledvin, jeho problémy a výzvy. /
Investigate the current approach to kidney transplantation, its problems and challenges.
2) Prozkoumejte příslušné metody strojového učení a metody pro hodnocení přesnosti modelu. /
Explore applicable machine learning methods and model accuracy evaluation methods.
3) Vyčistěte, předzpracujte a rozšiřte stávající datovou sadu. /
Clean, preprocess and extend the existing dataset.
4) Vytvořte prediktivní model strojového učení pro odhad délky života pacienta a ohodnoťte jeho přesnost. /
Create a predictive machine learning model estimating a patient's life expectancy and evaluate its accuracy.
5) Navrhněte úpravy skórovacího algoritmu pro transplantace ledvin na základě výsledků prediktivního modelu. /
Design an updated kidney matching compatibility scoring algorithm based on the prediction model.
6) Prozkoumejte možnost integrace dosažených výsledků do nástroje pro správu transplantací TX Matching. /
Evaluate the possibility of integrating achieved results into kidney transplantation management tool TX Matching.

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Jméno a pracoviště vedoucího bakalářské práce:

Ing. Tomáš Kouřim
Mild Blue, s.r.o., Plzeňská 27, Praha 5

Jméno a pracoviště konzultanta:

Ing. Pavel Strachota, Ph.D.
Katedra matematiky, Fakulta jaderná a fyzikálně inženýrská, České vysoké učení technické v Praze, Trojanova 13, 120 00 Praha 2

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V Praze dne 31.10.2022

garant oboru

vedoucí katedry

děkan

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Author's declaration:
I declare that this Bachelor's Degree Project is entirely my own work and I have listed all the used sources in the bibliography.

Prague, August 2, 2023 Kyrylo Stadniuk

Název práce:

Odhad délky života pacienta po úspěšné transplantaci ledviny pomocí metod strojového učení

Autor: Kyrylo Stadniuk

Obor: Aplikovaná Informatika

Druh práce: Bakalářská práce

Vedoucí práce: Ing. Tomás Kourim Mild Blue, s.r.o., Plzenská 27, Praha 5

Konzultant: Ing. Pavel Strachota, Ph.D. Katedra matematiky, Fakulta jaderna a fyzikálne inzenyrska, Ceské vysoké udeni technické v Praze, Trojanova 13, 120 00 Praha 2

Abstrakt: Abstrakt max. na 10 řádků.

Klíčová slova: klíčová slova (nebo výrazy) seřazená podle abecedy a oddělená čárkou

Title:

Estimating patient's life expectancy after a successful kidney transplant using machine learning methods

Author: Kyrylo Stadniuk

Abstract: Max. 10 lines of English abstract text.

Key words: keywords in alphabetical order separated by commas

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Introduction

Chapter 1

Medical Background

1.1 The history of kidney transplantation.

1.1.1 Early animal experiments

Advancements in surgical methods and techniques at the beginning of the 20th century eventually led to experiments with organ transplantation. On March 1st, 1902, Emerich Ullman, a physician at the Vienna Medical School, performed the first recorded organ transplantation. He performed an autograft, meaning the transplantation where the donor and the recipient are the same individual. Ullmann utilized the method of vascular suturing developed by Ervin Payr, to connect the dog's kidney to the vessels of its neck. The transplant was successful - the kidney produced urine. The dog was presented the same day to Vienna medical society eliciting significant interest and discussion.

The same year other similar transplantations were made. Another physician, Alfred von Decastello, performed a dog-to-dog kidney allograft at the Institute of Experimental Pathology in Vienna. The kidney produced urine for a while but then stopped working. Later Ullman performed a dog-to-goat kidney xenograft (cross-species transplant), and to his surprise kidney produced some urine, but later stopped.

In Lyon in the department headed by Mathieu Jabourday, his assistants Carrel, Briau and Villard were working on new methods of vascular suturing. In 1902, Alex Carrel published the method of vessel anastomosis now referred to as Carrel's seam. This technique represented a significant improvement over existing methods and effectively addressed the common issues of thrombosis, hemorrhage, stricture, and embolism[5].

Later Carrel moved to the United States where he continued his research on vessel suturing and organ transplantations at The Rockefeller Institute for Medical Research. There he perfected his method and while performing autografts and allografts documented what later would be recognized as "rejection". For his works in 1912, he got the Nobel Prize in Medicine. By this time, his method of suturing had been widely adopted in human surgeries[6].

1.1.2 Early human transplantation

The first recorded human renal xenograft was performed by Mathieu Jaboulay in 1906. He chose a pig and a goat as donor animals and performed two xenografts. One kidney was transported to the arm and the second to the thigh. Each kidney functioned for one hour[1, 4].

The second and third human transplants performed by Ernst Unger were far more known. On December 10, 1909, he performed a kidney transplant from a stillborn baby to a baboon. Even though the kidney produced no urine, the postmortem showed that vascular anastomosis (connection of vessels) was

performed successfully. This inspired Unger to perform another transplantation that same month, but this time monkey-to-human xenograft. The kidney was transplanted from an ape to dying from renal failure young woman. The kidney never worked.

These early experiments demonstrated that technically kidney transplantation was possible, but the mechanism of rejection was not yet fully understood. Carrel in his famous lecture about the future of transplantation (1914) to the International Surgical Society mentioned that the works of his colleague at the Rockefeller center J.B. Murphy might seriously impact the development of the field. Murphy found that irradiation and benzol treatment increased the graft survival of cancer in mice. This observation inspired Carrel to conduct his own experiments, wherein he irradiated recipients and found prolonged graft survival, but these experiments were never formally published[3].

The period of the 1930s and 1940s was rather stagnant compared to the beginning of the century. European surgical centers that studied transplantology before were in decline. Moyo Clinic in the US was conducting some cautious experiments without considering Carrol's works and attempts at immunosuppression.[5] However, there was a notable event during this period - the first human-to-human transplantation. It was performed by Yurii Voronyi (in literature for some reason he is referred to as Voronoy) on March 3, 1933, in Kherson, Ukraine. The recipient was a 26-year-old woman admitted to the hospital on March 3, 1933, with mercury chloride poisoning induced by a suicide attempt the previous day that resulted in acute renal failure. Transplantation seemed the only viable option. It was known from previous experiments by other scientists that no xenograft ever was successful so human-to-human transplantation was the only feasible choice. The option of injuring a living person by organ removal was not even considered. It was known from the physiology that kidneys save their function a couple of hours after the reperfusion with ringer-solution and that organs keep some sterility a couple of hours after the host's death. So temporary cadaver transplantation until the woman's own kidneys would regenerate seemed to be a reasonable option. The transplantation was performed to the thigh's artery and vein using Carrel's seam with some modifications. After some time the kidney started to produce urine for a while but then eventually the allograft failed and 48 hours after the surgery the patient dies. The reason for graft failure was blood group mismatch and too long warm ischemia time - 6 hours, so the kidney began to degrade, resulting in an immune reaction to dead kidney cells and kidney blood cells. Voronyi performed another 5 such transplantations, which he considered as a bridge therapy until the recipient's own kidneys would recover. Kidneys produced urine for different durations from 1 to 7 days with 2 patients eventually recovering and living normally thereafter[4].

1.1.3 First successes

In 1946, at the Peter Bent Brigham Hospital in Boston, a group of surgeons: Hufnagel, Hume, and Landsteinerhuman performed kidney transplantation under local anesthetic on the arm vessels. The short period of kidney functioning may have helped the patient to recover from acute renal failure. It ignited the hospital's interest in renal transplantation.

Simonsen in Denmark, Dempster in London, and Küss in Paris concluded that it is preferable to place the kidney in the pelvis. Further, both Simonsen and Dempster deduced that the immune response was responsible for graft failure and both hypothesized that the humoral mechanism of rejection was probable.

In the early 1950s, two groups of surgeons based in Paris and Chicago performed pelvic kidney transplants without immunosuppression. In Paris, Jean Hamburger reported the first live-related kidney transplant between a mother and her child. he transplanted kidney began to function immediately. It functioned for 22 days until it was rejected.

A series of nine transplantations with the thigh position of the allograft was closely studied in Boston and the first usage of hemodialysis for the preparation was recorded in Boston by David Hume in 1953. In

some of these cases, mild successes were achieved using the adrenocorticotropic hormone (more known as cortisone). It was hypothesized that the endogenous immunosuppression of uremia was responsible for the results rather than the drug regimen. Hume's findings were substantial as he concluded that prior blood transfusions, blood group matching between the donor and recipient, and host bilateral nephrectomy could be beneficial for the success of the transplant. These conclusions were later confirmed by subsequent studies.

These attempts in the early 1950s taught technical aspects of kidney transplantation and with increased confidence on December 23, 1954 in Boston Joseph Murray performed kidney allograft from one identical twin to another, bypassing the rejection barrier. From that time many similar surgeries were performed in Boston. This caused a lot of talks and predictions but all of them were negated when one of such recipients got pregnant and gave birth to a completely normal infant. However, in retrospective, it didn't bring anything new scientifically, because the technical possibilty of kidney transplantation was evident and the cases of successful skin allografts between identical twins were known for decades, but nonetheless it was an important milestone that aroused the interest in further experiments [1, 4].

1.1.4 Attempts in immunosuppression

In 1948 at Mayo Clinic patients handicapped by rheumatoid arthrytis were given already mentioned cortisone, adrenal cortical hormone with mild immunosuppressive properties, that relieved their condition. This popularized the research on adrenal cortical hormones, but later it was concluded that the steroid effect was clinically insignifficant for transplantation. After that, the experiments with irradiation, abandoned by Carrel and Murphy, were revitalized. Joan Main and Richmond Prehn showed that weakening of the immune system of adult mice by radiation and consequent skin and bone marrow transplantation from the same donor resulted in skin transplant acceptance. This encouraged teams in Boston and Paris to pursue the similar approach in humans.

In 1958, Murray's team transplantation on humans utilizing the Main-Prehn method conducted lethal total body irradiation (TBI) on two patients with additional bone marrow transplant. Ten more recipients were irradiated with sub-lethal TBI, but without donor bone marrow transplant. As a result 11 patients passed away within a month, the only survivor had sub-lethal TBI without transplanted bone marrow and he got kidney from his non-identical twin brother. This was rather revolutionary - for the first time kidney was not rejected from non-identical twin. The kidney functioned for 20 years. Jean Hamburger and his team performed another fraternal twin transplant utilizing the same irradiation technique. The transplant functioned for 26 years finishing with the recipient's death for rejection-unrelated reason.

Between 1960 and 1962 Kuss and Hamburger performed four successful transplantations between non-twin patients with following TBI. This gave promise that the transplantations could be done in non-twins and potentially between anybody. The research continued.

It was obvious that TBI is not the best choice and that it is necessary to find a substitution. In 1959, Schwarz and Damesehek from Tufts University published paper that described how an anticancer drug 6-mercaptopurine (6-MP) lowered immune response to foreign proteins in rabbits. Roy Calne, a training surgeon at Royal Free Hospital, London, dissapointed with TBI in prolongation of kidney allograft survival in dogs, noticed Schwarz and Dameshek's paper and performed his own experiment in dogs and found that it signifficantly prolonged dog's survival. Charles Zukoski and David Hume found the same outcomes.

6-MP was used in three tranplantations at Royal Free Hospital, but without success, However Kuss and assosiates reported one prolonged graft survival from a nonrelated donor. The TBI was main agent and intermittent usage of azathioprine and prednisone was used as an additional therapy.

Gertrude Elion and George Hitchings provided Roy Calne with the 6-MP derivative - azathioprine. Calne showed even longer graft survival with azathioprine. Both Elion and Hitchings were awarded with

the Nobel Prize for the development of 6-MP and azathioprine. In 1961 Azathioprine became available for human use.

1.1.5 Gloom then revolution

In 1963 National Research Council organized a small conference constisting of 25 transplant clinitians and scientists to review the status of kidney transplantation at the moment.'the discussion was quite depresive. Clinitians presented their results, that were rather discouraging: less that 10% of hundreds performed transplantations survived for more than three months, from patients with TBI only six got to the one year mark. Murray reported that from his first ten patients on 6-MP one survived for a year, others passed away within 6 months, so it was concluded that drugs were not more effective than radiation.

The gloom continued untill Tom Starzl, until then unknown, did his presentation where he described his protocol that allowed graft survival for more than one year in 70% of cases. He was not believed at first, but then he showed medical records of his patients and he was eventually believed. The only thing that differed from other protocols with 6-MP was that addition of prednison. This was a sensation. In the first year after the presentation, 50 new tranplantation programs were founded in US alone. And his protocol became medical world standard for the next 20 years.

1.1.6 Plateau

During the period from 1964 to 1980 nothing groundbreaking had happened, although the steady development was seen. Dialysis become available and thanks to the acumulated exprerience the dosages became more precise. The brain death was accepted and the body was supported for a while to save organs for transplantation.

Hemodialysis for renal failure was created by Willem Kolff from Holland during WWII. But it couldn't be used for chronic renal failure untill 1960 when was invented Teflon arteriovenous conduits for long-term vascular access.

Acceptance of brain death as a real death. Before the mid 60s the kadaver transplantation was limited by the ischemic damage. Now the additional organs were available from "heartbeating kadavers".

Cold for organ preservation. This was suggested in 1905 by Carrel's colleague Charles Guthrerie. Initially, Starzl used total body hypothermia to protect donor organs, but by 1960 switched to infusing cold solution into the portal vein to protect donor livers. In 1963 the infusion of cold solution intravenous in the transplanted kidney has become a standard.

As the organ preservation for more than 6 hours was achieved in mid 60s the exchange of organs between centers has became practical. Initially sharing was local and informal, that roused the worry that the organs could be distributed unequally and that they could be transported outside of the US. This led to Congress passing the National Transplant Act in 1984. The Southeastern Organ Procurement Foundation (SEOPF), founded in 1969 and eventually composed of 12 hospitals in several cities, served as the template for the United Network of Organ Sharing (UNOS) that controls organ allocation and placement, monitors performance of transplant centers and organ procurement organizations, collects data, and controls quality. They kindly provided us with data for this paper.

1.1.7 Tissue typing

Although tissue typing was suggested by Alexis Carrel in the beginning of 20th century it could not be proven and used until 1958 when Jean Dausset discovered the first human leukocyte antigen (HLA). Testing for antibodies was not reliable until 1964 when Paul Terasaki invented a microxytotoxicity assay. Test included mixing donor's lymphocytes and recipient's serum and quickly has became the standard

and was name crossmatch. For a couple of years Terasaki performed typing for most of U.S. transplant centers and found a couple of observations: 1) Positive cross-match test predicts hyperacute rejection. 2) matching can reliably identify optimal donor within a family. It was assumed that the same would work for non-related recipients.

However, when in 1970 Terasaki reviewed his large database of cadaver renal allografts he found no correlation with the typing. This raised a lot of agitation in tissue typing community and his grant even was temporalily suspended until others didn't report the same. Now it is conclded that the

1.1.8 Antilymphocyte serum

Next mark was cyclosporine, a fungal derivative with immunosuppressive properties discovered in 1976 by Jean-François Borel. It revolutionized the renal and extrarenal transplants, proving to be much better than the previous drug azathioprine. However it also had to be combined with prednisone to gain those results. It was used until 1989 when even more potent drug was discovered - Tacrolimus. It helps even when the cyclosporine with prednisone has no effect.

Tom Starzl discovered that donor leukocyte chimerism was present in patients who had maintained successful kidney or liver grafts for up to three decades.

chimerism is an important cause (not the consequence) of successful transplantation,

successful engraftment is the result of the responses of coexisting donor and recipient cells each to the other causing reciprocal clonal exhaustion followed by peripheral clonal deletion

1.1.9 Conclusion and challenges of the field

The ultimate goal is immunosuppression without drugs because drugs are often toxic and the proper dosing might be tricky.

1.2 Immunology

The immune system is a sophisticated defense mechanism that evolved to protect multicellular organisms from pathogens such as bacteria, fungi, viruses, and parasites. It consists of many cells and tissues that compose a complex system that detects, evaluates, and responds to the invader. The immune system is divided into humoral and cell-mediated immunity. Humoral is mediated by soluble immunoglobulin proteins referred to as antibodies, while cell-mediated involves pathogen-specific T Lymphocytes that either destroy the invader or assist other cells in doing so. Both are essential for a complete immune response.

Lymphocyte is a type of white blood cell that is responsible for both humoral and cell-mediated immune responses. There are two types of lymphocytes: T lymphocytes (T cells) and B lymphocytes (B cells). B cells mediate humoral response by producing antigen-specific antibodies. An antigen is any molecular structure that binds to an antibody or specific surface T cell receptor, triggering an immune response. Once B-cell encountered an antigen it starts to produce antibodies specific to it, antibodies then bind to it, marking the invader for destruction. T cells when encountering an antigen start to proliferate forming an army of T cells that will eliminate the invader and will form long-term memory about the pathogen.

Physical barriers: epithelia and mucous membranes constitute the first line of defense. To activate the immune system the pathogen must first breach physical barriers. The immune system categorizes pathogens by common characteristics and designs its response accordingly. Pathogen detection and categorization rely on the interaction between pathogen and T-cell receptors, as well as soluble antibodies.

Binders for T cell receptors and antibodies can be the whole pathogen's body, its part, or molecules excreted by it.

Pathogens are recognized and categorized by molecular patterns that are associated with a particular pathogen and are referred to as pathogen-associated molecular patterns (PAMPs). Pathogen recognition receptors (PRRs), which are excreted by white blood cells, bind to PAMPs initiating the cascade of events that will mark a pathogen for destruction.

Pathogen-host interaction is a continuous arms race, as pathogens usually have a short life cycle and can modify their DNA to elude the host's recognition systems. The generation of diversity in developing cells is designed to combat this. When lymphocytes are developing in bone marrow random PRRs are generated, then cells are tested on non-reactivity to host cells. If the test is passed the cell is released into circulation. The principle of recognizing self vs. non-self is called tolerance.

There are two interconnected systems of response: innate and adaptive. Innate includes primitive built-in cellular and molecular mechanisms aimed at preventing infections and quickly demolishing common pathogens. It consists of physical and molecular barriers as well as PRRs that are encoded in DNA and therefore are inherited. Innate immunity provides a fast and effective response which however is not very specific and cannot differentiate small differences. Adaptive immunity is constituted by both humoral, where antibodies neutralize and eradicate extracellular microbes and toxins, and cell-mediated immunity, where T lymphocytes exterminate intracellular invaders.

Adaptive immunity is much slower but more able to recognize small differences. It typically starts to act within 5 to 6 days after initial exposure. Because it takes time to create an army of cells with specific receptors. After pathogen extermination, some of the lymphocytes with the specific receptor become memory cells, making it easier to fight this type of pathogen.[5]

In conclusion, the immune system is a complex network of molecules, cells, tissues, and organs that cooperate in protecting the organism from pathogens. The system can be divided into two main branches: innate and adaptive, which cooperate in protecting the host from infections while developing long-term immunity to specific pathogens. Understanding the mechanisms of the immune system is essential to understanding the domain of kidney transplantation.

1.3 Immunology of kidney transplant

The process of transplantation inevitably includes termination of blood flow, and, as a result, oxygenation. Therefore cell is unable to generate sufficient amount of energy to maintain homeostasis, leading to damage or death. Damage or death is associated with DAMP release that might be detected by both innate and adaptive immunity.

1.3.1 Immune system activation Peritransplant

The process of transplantation inevitably includes termination of blood flow, and, as a result, oxygenation. Therefore cell is unable to generate sufficient amount of energy to maintain homeostasis, leading to damage or death. Damage or death is associated with DAMP release that might be detected by both innate and adaptive immunity. Mostly it is the ancient innate immunity that is activated with its soluble arm - complement system.

Damage signals Many DAMPS are recognized by the same PRRs that mediate response to PAMPs. These DAMPS include molecules that are normally hidden from the immune system and are produced during ischemia, such as extrecellular ATP, heat shock proteins (HSPs), uric acid, etc. Likewise, oxidative stress and decline in intracellular potassium may act as intracellular damage signals.

Complement Complement system is comprised of series of proteine kinases that are sequentially activated resulting in membrane attack complex (MAC) formation. MAC include complement components C5 to C9, which are inserted into pathogen cell membrane resulting in compromising cell integrity leading to cell death.

There are three pathways of complement system activation: the classical pathway, the alternative pathway, and the mannose-binding lectin (MBL) pathway. The classical pathway is activated by IgM and IgG antibodies and participates in antibody-mediated rejection, that will be discussed further. Alternative complement is always active and therefore must be controlled by a regulatory proteins, to prevent inadequate responses. The MBL pathway is activated by damaged endothelium, a cell tissue that covers organs and vessels, and carbohydrates present on pathogens. Either pathway results in C3 convertase that cleaves C3. This cleavage leads to a cascade of reactions that culminate in MAC formation.

Long ischemia time results in endothelial cell damage that is acossiated with ischemia-reperfusion injury (IRI). IRI activates MBL and alternative complement pathways.

Gene silencing using small interfering RNA (siRNA) might be a promising instrument in organ transplantation, because it can be appliend to an allograft during cold reperfusion and it has been shown to mitigate IRI in animal models. Other strategies of supressing local complement activation would also be useful.

1.3.2 Stimulation of Adaptive Alloimmunity

Immune response to a graft occurs in two main stages: afferent and efferent arms. In afferent stage, recipient lymphocytes are stimulated by donor antigens and start to proliterate and send signals to other cells. In efferent arm, leukocytes migrate to the transplanted organ and donor specific antibodies are produced.

For the immune system to be activated graft must express antigens that will be considered by the host's immune system as foreign. These include ABO antigens, human leukocyte antigens (HLA), and polymorphic non-HLA "auto-antigens".

ABO blood group antigens

ABO system is used to group blood into groups, based on presence or absense of antigens on a blood cell surface. There are four major blood groups: A, B, O and AB.[7]

When allocating an organ to transplant the first thing that is considered is ABO blood group antigens compatibility. ABO antigens are expressed almost by any cell in the allograft, and if the transplantation to be carried out in ABO-incompatible donor and recipient it would result in a hyperacute antibody-mediated rejection.

Donors with blood group O are so called "universal donors". Organs from them can be safely transplanted to recipients with any ABO blood group. Whereas, recipient with AB group can safely receive organ from recipient with any ABO blood group and is called a "universal recipient".[1]

HLA

Histocompatibility antigens are genetically encoded antigens that cover cell surfaces. They differ between individuals of the same species and therefore trigger an immune response in case of allograft. In all vertebraes histocompatibility antigens are divided into single major histocompatibility complex (MHC) and numerous minor histocompatibility (miH) systems. In case of either MHC or miH incompatibility the result is an immune response to the graft, more severe in case of MHC than miH. Rejection

Table 1.1: MHC class division

MHC class I	MHC class II
HLA-A	HLA-DR
HLA-B	HLA-DP
HLA-C	HLA-DQ

in MHC-compatible donor-recipient pair is usually delayed, in some cases forever. Although, sometimes miH mismatch might be so severe that it would be comparable to full MHC mismatch.

MHC antigens are proteins that cover cell surfaces to help the immune system to recognize self vs. non-self. Major histocompatibility comples is divided into MHC class I and MHC class II. MHC class I cover surfaces of most cells and are liable for activation of cytotoxic CD8 cells, that help to find and destroy infected cells. MHC class II are found on certain immune cells and play crucial role in immune response coordination. In humans MHC class 1 are divided into three subgroups each, as can be seen on table

In clinical practice, clinicians asses and try to match donors and recipient according to the number of HLA-A, -B, and -DR mismatches, ranging from zero mismatches (0-0-0) to a maximum of 6 mismatches (2-2-2). Generally more emphasis is placed on DR loci due to capability of CD4 T cell activation, which might trigger both humoral and cellular adaptive immune responses.

Minor histocompatibility proteins can act as antigens, although weaker than MHC. However if prior sensitisation exists it could result in severe immune response that might result in graft loss.

1.3.3 T Cell-mediated rejection

T cell-mediated rejection or TCMR is the most common type of allograft rejection, as it still happens in 20% of transplantations mostly within first 6 months posttrasplant. Immune system cells migrate through vessels to the graft, become activated and start to attack the organ. Complement may also play role in it.

1.3.4 B Cell-mediated rejection

B cells are immune system cells that produce antibodies. Alloantibodies are antibodies that react to donor-specific HLA antigens and might cause hyperacute rejection, acute antibody-mediated rejection (ABMR), and chronic ABMR. About 30% of patients have sensitivities and have certain HLA antibodies. It might cease transplantation or require antibody suppression strategy. Even low amount of antibodies below crossmatch cutoff doubles the risk of ABMR and increases the risk of graft failure by 76%. Additionally, donor specific antibodies might develop posttransplant and cause an actue ABMR.

Acute AMBR is rarely seen in patients withour prior sensitization and is highly difficult to treat. AMBR is characterized by decline in allograft function, presense of DSA and signs of acute vascular injury. A progressive reduction in graft function over time is observed almost universally.

1.3.5 Transplant tolerance

Taking into account the detrimental effect of long-term immunosuppression one of the primary objectives in transplantation is the induction of immunologic non-responsiveness (tolerance) to an allograft. The are a couple a pathways of immune non-responsivenes generation described in literature, however it haven't gone further animal models yet.

1.3.6 Factors Influencing rejection beyond the graft - microbiome

Human body is very complex system where every subsystem influences other subsystems and the whole system in general. It is clear that gut microbiome has a profound influence on immune system. It is possible microflora on the allograft might cause rejection. Immunosupression, profilactory antibbiotics, diet changes and other restrictions asossiated with organ transplantation result in decrease in gut microbiome diversity that result in systematic inflammation, that might contribute to alloimunnity, as well as autoimunnity.

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Text of the conclusion...

Bibliography

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