Journal of Cell and Tissue Research Vol. 20(1) 6853-6860 (2020)
(Available online at www.tcrjournals.com)
ISSN: 0973-0028; E-ISSN: 0974-0910

Review Article

DEVELOPMENT OF IMMUNE SYSTEM FROM NEW BORN TO ADULT: A NEW INSIGHT

GUPTA, P. D.[1] AND TYAGI, S.[2]

[1]Former Director Grade Scientist, Centre for Cellular and Molecular Biology, Hyderabad
E. mail: pdg2000@hotmail.com, Cell: 080728 91356
[2]European Diplomate in Pediatric Pulmonology, Head Pediatric Department, Metro Hospital, Noida (UP). E. mail: drshalinit@gmail.com, Cell: 098101 54327

Received: April 2, 2020: Accepted: April 23, 2020

Abstract: Certain antibodies can pass through placenta and therefore the new born baby carries some immunoglobulins at the time of birth to protect from worldly pathogens, this natural passive immunisation does not long last and new born has to develop immune system of its own. The fully grown immune system loses its capacity in old age. The immune system modify according to the needs of the body's physiology and pathology. For example during pregnancy, auto immune diseases and cancer the system is not normal.

Key words: Immune system

INTRODUCTION

The immune system is essential to live. More than 1600 genes are involved in innate and adaptive immune responses [1]. *In utero*, the fetal environment demands that the immune system remains tolerant to maternal alloantigens [2]. A child is born with an immature, innate and adaptive immune system. It develops as we age, peaks in young and decline in old age [3]. The recognition of self and non self by the body system and protects the self and destroys the non self is done by our immune system [4]. This all done by joint affords of the thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract and bone marrow), macrophages, lymphocytes including the B cells and T cells. When the body senses foreign substances (called antigens) against which a specific chemicals (antibodies) are produced by B cells that protects the body; Then T cells kill the non self and the cell debris is removed by the macrophages. A baby's immune system is immature when they are born. It develops

Dr. P. D. Gupta, Ph. D.: Former, Director Grade Scientist, (Retired from Centre for Cellular and Molecular Biology, Hyderabad, India).

Dr. Shalini Tyagi MD, DNB, DCH, New born and child specialist, is Head of Pediatric Department, Metro Hospital, Noida, She is running own children clinic at Totmall, Noida. and also European diplomats in pediatric

throughout life as they are exposed to different germs that can cause disease. "An infant's immune system doesn't mature until around 2 to 3 months," Dr. Sabella says [5]. "In those first few months, the immune system — especially cell-mediated immunity — becomes more developed Immunity in newborn babies is only temporary and starts to decrease after the first few weeks or months. Breast milk also contains antibodies, which means that babies who are breastfed have passive immunity for longer(6). Those antibodies stay active for the first few weeks of a baby's life. The major function of the immune system is to protect the host from environmental agents such as microbes or chemicals, thereby preserving the integrity of the body. Breastfeeding can help protect the baby from getting sick, but it cannot completely prevent illness. At some point, your child may get an ear infection, catch a cold, or develop an upset stomach. Breast milk is more likely to stay down and less likely to make diarrhea or vomiting worse.

Naturally acquired passive immunity occurs during pregnancy, in which certain antibodies are passed from the maternal blood into the fetal bloodstream in the form of immunoglobulin G (IgG). Antibodies are transferred from one person to another through natural means such as in prenatal and postnatal relationships between mother and child (Fig. 1). Babies produce their own antibodies every time they are exposed to a virus or germ, but it takes time for this immunity to fully develop. The passive immunity passed on from the mother at birth also doesn't last long and will start to decrease in the first few weeks and months after birth. Breast milk also contains antibodies, which means that babies who are breastfed have passive immunity for longer. A child exposed to colds and viruses earlier in life will develop a stronger immune system and is less likely to become sick in his or her later years. Some experts still say more exposure to germs is better.

The immune system in babies: Antibodies are passed from mother to baby through the placenta during the third trimester (last 3 months of pregnancy). This gives the baby some protection when they are born. The type and amount of antibodies passed to the baby depends on the mother's own level of immunity. Besides frank infections and vaccinations, the newborn is exposed to other antigens. He or she comes from a relatively sterile environment in utero and is then rapidly exposed to multiple microbes [7]. The first major exposure to bacteria is during passage through the birth canal, and then as soon as he/she makes oral, skin and respiratory contact with the exterior. From then on, exposure to microorganisms is continuous. Many of the bacteria that colonize the gut and other mucosal sites are essential for healthy life, including digestion of food and acquisition of vital nutrients. They also impact on the development of the immune system [8].

Research shows that delivery by vaginal canal is better than caesarean section in terms of baby's immune health. New research has found that babies born via caesarean section may have an impaired immune system in later life due to the lack of exposure to maternal bacteria that would occur during the standard birthing process [9].

Babies born by caes are an section have different gut bacteria to those born vaginally – but the differences largely disappear by the time the babies are between 6 and 9 months old. That's according to the largest study into the effects of birth mode on the microbiome.

After birth, more antibodies are passed on to the baby in colostrum and in breast milk. But babies' immune systems are still not as strong as adults'. Premature babies are at greater risk of infection because their immune systems are even more immature and they haven't had as many antibodies passed to them from their mothers. The cells involved are neutrophils, monocytes, macrophages and dendritic cells, which all interact with the adaptive immune system (Fig. 2). Babies produce their own antibodies every time they are exposed to a virus or germ, but it takes time for this immunity to fully develop.

Boost baby's immune system: Each time your baby gets sick, they are developing new antibodies that will protect them in the future. In the meantime, there are some important things you can do to protect your baby.

Breastfeeding: Breast milk contains many elements that support your baby's immune system. These include proteins, fats, sugars and antibodies

and probiotics. When a mother comes into contact with germs, she develops antibodies to help her fight off the infection. These are passed to the baby in breast milk. As mothers and babies are usually exposed to similar germs, this means the baby is protected [6].

Breastfed babies have fewer infections and get better more quickly than formula-fed babies. However, breastfeeding cannot protect your baby from serious, life-threatening infections like polio, diphtheria or measles. Also, for mothers who are unable to breastfeed or who choose not to, infant formula is a healthy alternative.

- Vaccination
- Vaccinating children is the safest and most effective way to protect them against serious disease.
- Vaccination causes an immune response in the same way that a virus or bacteria would. It means that if your child comes into contact with the real disease in future, their immune system will recognise the germ and respond fast enough to fight off the disease or prevent serious complications.
- Pregnant women are vaccinated for whooping cough in their third trimester so they will pass on immunity to their babies.

Your baby will have their first vaccinations at birth, then some more at 6 weeks, 4 months and 6 months and for the first few years of life. Diet and supplements: Once your baby starts on solids, a variety of fresh foods including different types of pureed vegetables and fruits should be enough to keep the immune system healthy. Try to keep breastfeeding while you're introducing solid food. Taking antibiotics can kill some of the gut bacteria that are important for immunity. Probiotics are often suggested as a way of boosting babies' immunity after they have had antibiotics. Probiotics are safe to use in late pregnancy and after the baby is born. However, the evidence is mixed about if they have benefits for children or adults. Talk to your doctor before you consider giving probiotics to your baby [10]. Probiotics for infants are available as supplemental drops as well as in infant formulas. Older children may eat foods that contain probiotics, like yogurt. Probiotics may become less viable over time if dispensed in a bottle.

It's recommended for babies from six months up to three years of age. Many parents report that it has helped relieve gas and other tummy troubles for their little ones. They say babies seem happier overall when taking it, and that older kids can't detect it when it's mixed into their smoothie or other foods and drinks. Research indicates that probiotics are safe and well-tolerated in normal, healthy infants and children. Good tolerance has been observed in premature infants, very low birth weight babies and in HIV-infected children and adults. Probiotics are also safe to use in late pregnancy.

Gripe Water with Probiotic Now Available for Infants. Wellements announced the launch of Wellements Probiotic Gripe Water, the first gripe water to contain probiotics, to help ease a newborn's stomach discomfort often associated with gas, colic, fussiness, and hiccups.

Side effects of gripe water: It was only in 1992 that Britain mandated that alcohol be removed from Gripe water, and in 1993 the United States Food and Drug Administration (FDA) ordered an automatic detention of all shipments of Woodward's Gripe Water into the U.S. on the basis of its being an un approved drug. Some of the side effects are hives, watery eyes, swelling of the lips or tongue, vomiting, itchiness and a change in breathing.

From infancy to old age: The immune system gradually matures during infancy. Critical early protection against many infectious diseases previously experienced by the mother is given by the passive IgG antibody transferred from the mother transplacentally and in milk. Once that fades away, young children become more vulnerable to infections, though by then better armed with the maturing innate and adaptive immune systems (Fig. 3). The young human child is at risk from many pathogenic viruses, bacteria, fungi and parasites. The risks are now much reduced by vaccinations, which stimulate

protective immune responses in the maturing immune system (Fig. 4). Nevertheless, children may still acquire viral, bacterial and parasitic infections that have to be fought off and controlled by immune responses. Besides promoting recovery, such antigen stimulation results in immunological memory [11,12]. Thus, over time, protection provided by the immune response increases, and young adults suffer fewer infections. This accumulation of immunological memory is an evolving feature of the adaptive immune response.

Meanwhile, a complex system of more than 30 proteins develops that act in concert to help eliminate infectious microorganisms. Specifically, the complement system causes the lysis (bursting) of foreign and infected cells, the phagocytosis (ingestion) of foreign particles and cell debris, and the inflammation of surrounding tissue.

The complement system is a part of the immune system, consists of a series of proteins that interact with one another in a highly regulated manner, in order to eliminate pathogens. Complement system was discovered by Jules Bordet as a heat-labile component of normal plasma that causes the opsonisation and killing of bacteria. The complement system refers to a series of >20 proteins, that are synthesized by the liver, and circulate in the blood as inactive precursors, circulating in the blood and tissue fluids. When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages. It helps antibodies and phagocytic cells to clear pathogens and damaged cells; promote inflammation and attack pathogen's plasma membrane. Complement is a system of plasma proteins that can be activated directly by pathogens or indirectly by pathogen-bound antibody, leading to a cascade of reactions that occurs on the surface of pathogens and generates active components with various effector functions. The complement system has four major function, including lysis of infectious organisms, activation of inflammation, opsonization and immune clearance. There are three different complement pathways, the classical complement pathway, the alternative complement pathway, and the mannose-binding lectin pathway [13].

The complement system has the potential to be extremely damaging to host tissues, meaning its activation must be tightly regulated. The complement system is regulated by complement control proteins, which are present at a higher concentration in the blood plasma than the complement proteins themselves. Some complement control proteins are present on the membranes of self-cells preventing them from being targeted by complement. One example is CD59, also known as protectin, which inhibits C9 polymerisation during the formation of the membrane attack complex. The classical pathway is inhibited by C1-inhibitor, which binds to C1 to prevent its activation.

During childhood, Treg cell numbers decline, and memory Th1, Th17 and Th2 cells gradually increase to equal the number of naive T cells [14]. Although some of these memory T cells could have been stimulated by infections with specific pathogens and by vaccinations, many may be primed by the microbiome, not only in the gut but also in the respiratory tract and skin. These primed memory T cells may respond to subsequent infections through cross-reactions [15-17]. For example, adults who have never been exposed to HIV-1 have memory T cells in their repertoire that react with HIV peptides presented at the cell surface by HLA proteins; these T cells are likely to be reawakened should HIV infection occur [15,18], similarly to other microbes [16]. These could easily be responsible for generating the memory T cells specific for pathogen epitopes the person has never encountered.

As the individual gets older, he or she develops an expanding repertoire comprising memory T and B cells triggered by previous infections and vaccinations, but also a naive-memory repertoire shaped by exposure to the microbiome, food antigens and inhaled antigens. Given the great complexity of the T- and B-cell repertoires and a large stochastic element in choosing which cells will respond to a given stimulus, and somatic mutations in B cells, the precise composition will differ in each individual, even in monozygotic twins [19]. Add to this considerable genetic variability in how individuals respond, determined by the highly polymorphic HLA genes [20] and by the genes of innate immunity, and it is not surprising that the immune responses of any single adult vary considerably.

Fig. 1: Natural passive antibodies passed though colostrum and then the breast milk

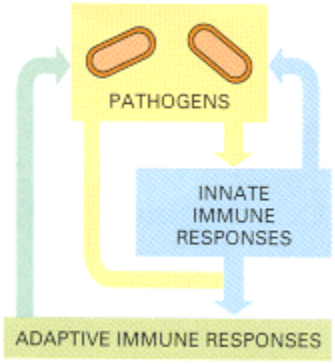

Fig. 3: Adaptive Immune response against pathogens

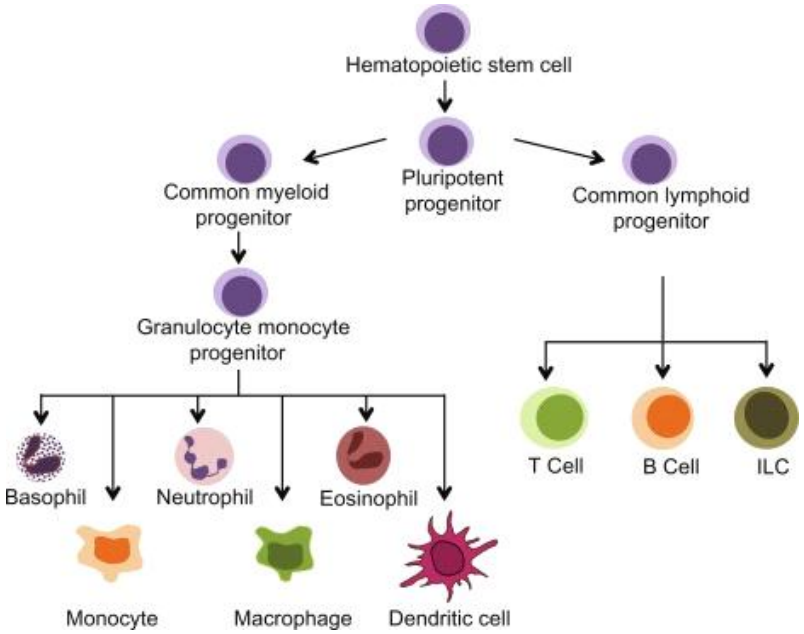

Fig. 2: Ontogeny of immune cells

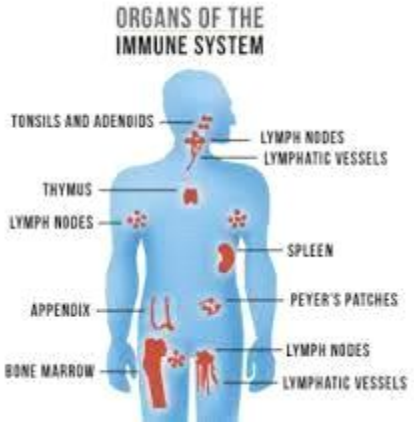

Fig. 4: Organs of Immune System

As age advances, the immune system undergoes profound remodelling and decline, with major impact on health and survival [21,22]. The memory persists into old age [11] but then may fade.

This immune senescence predisposes older adults to a higher risk of acute viral and bacterial infections. Moreover, the mortality rates of these infections are three times higher among elderly patients compared with younger adult patients [23]. Infectious diseases are still the fourth most common cause of death among the elderly in the developed world. Furthermore, aberrant immune responses in the aged can exacerbate inflammation, possibly contributing to other scourges of old age: cancer, cardiovascular disease, stroke, Alzheimer's disease and dementia [24].

During a regular influenza season, about 90% of the excess deaths occur in people aged over 65. Furthermore, poor immune responses account for diminished efficacy of vaccines [21,25]. Immune senescence also results in reactivation of latent viruses.

Deterioration of the immune system with age may compromise the homeostatic equilibrium between microbiota and host. Thus reduced bacterial diversity in the gut has been correlated with Clostridium difficile-associated diarrhoea, a major complication for the elderly in hospitals [26]. Moreover, deviations from the intestinal microbiota profile, which was established in youth, are associated with inflammatory bowel disease [26]. The increase with age in pro-inflammatory pathobionts and the decrease in immune-modulatory species may promote and sustain inflammatory disorders [24].

At the same time, the ageing immune system fails to maintain full tolerance to self-antigens, with an increased incidence of autoimmune diseases. [25]. This is probably due to lymphopaenia occurring with age, leading to excess homeostatic lymphocyte proliferation [26], as well as a decrease in regulatory T-cell function and decreased clearance of apoptotic cells by macrophages [27].

Cancer is most frequent in older people; the median age for cancer diagnosis in industrialized countries is approaching 70 years of age. The main reason is obviously the accumulation of cellular and genetic damage throughout life; however, given the role of the immune response in controlling cancers, reduced immune functions in the elderly must contribute to the higher risk [28]. This immune impairment is in apparent contradiction to the increase in autoimmunity as anti-tumour responses can be directed against self; however, the general decline of the immune system probably prevails and tumours are no longer rejected as efficiently. Moreover, the increased inflammation found with age facilitates cancer emergence.

In nut shell: As a long-lived species, humans have evolved mechanisms of innate immunity and immunological memory to survive recurrent infections. However, over the lifetime of an individual, these immune mechanisms change, first to adapt to the change from fetus to infant, and then to mature and expand during growth, subtly changing in pregnancy and finally decreasing in senescence. The output of naive lymphoid cells and the ability to form new immunological memory becomes increasingly less important as the older individual will have encountered and established a memory bank to many pathogens over its lifetime. There is a possibility that the myeloid bias and the increased secretion of pro-inflammatory cytokines during ageing are essential for improved phagocytosis of an increasing number of senescent cells, raising the question of whether the changes in the ageing immune system might serve a purpose.

The immune system has been primarily moulded by evolution to respond efficiently to acute infections in young people, to adapt to pregnancy and to transmit protection to infants, and is adapted to cope with many chronic infections lasting for decades. Apart from fighting viruses, bacteria, fungi and parasites, the immune system also assumes other roles such as tissue repair; wound healing, elimination of dead and cancer cells, and formation of the healthy gut microbiota. Assuming an absence of a major selective pressure on humans beyond reproductive age, we may have to pay for genetic traits selected to ensure early-life fitness by the later development of immunological phenotypes such as chronic inflammation. Massive ageing and advanced longevity are very recent phenomena occurring in

an optimized environment. As proposed by Hayflick [29], ageing may be an artefact of civilization, and hence changes in the ageing immune system might just be a consequence of evolutionary unpredicted antigenic exposure over the lifetime of an individual.

In some aspects, the immune system of the aged organism resembles that of the newborn, with reduced antimicrobial activity by neutrophils and macrophages, reduced antigen presentation by DCs and decreased NK killing, and somewhat compromised adaptive lymphocyte responses. Both the very young and old immune systems are therefore similarly compromised in coping with a typical viral infection such as influenza, whereas the young (non-pregnant) adult organism seems to be perfectly equipped for this challenge (Fig. 1). The evolution of the immune system within an individual possibly reflects the central role of the young adult in the survival of the species for its procreative potential.

Immune system during pregnancy: It is beyond the scope of this review to explore the immunology of pregnancy in detail (reviewed in [30,31]). However, successful reproduction is of central evolutionary importance and there are immunological issues. How the newborn retains mechanisms by which the fetus minimizes its immune responses to the mother has been discussed above. A bigger puzzle is how the mother tolerates a semi-allogeneic graft without rejecting it and without the immunosuppression necessary to accept an organ transplant [32]. There are features at the trophoblast maternal interface at the site of initial implantation and in the placenta that subvert the normal graft rejection immune response. These include expression only of non-polymorphic non-classical HLA antigens on the trophoblast [33], local immune suppression mediated by infiltrating NK cells [34], monocytes and T regulatory cells [35], and inhibition of T-cell activation by tryptophan catabolism [36]. Around the time of implantation, a local inflammatory response sets up the stable placental site . There is evidence that the mother changes the balance of her T-cell responses to Th2 rather than Th1. Thus pregnant women can show remissions of autoimmune disease [37], and are more susceptible to severe complications of influenza [38] and some other infections. This immune modulation, necessary for the well-being of the fetus, can occasionally be harmful to the mother.

Immune system malignancy and autoimmunity: The primary role of the immune system is probably to protect against infections. Other roles such as destruction of mutated cells may be very important, though more so in old age after reproduction. Many tumours turn off T cells specific for tumour antigens by binding to 'check-point' receptors such as PD-1 or CTLA4, and new treatments that block these receptor–ligand interactions have great therapeutic potential [39,40]. However, the side effects of such therapy and of the passive transfer of anti-cancer T cells include autoimmune reactions, suggesting a balance between anti-self-immune reactions preventing cancer and causing autoimmunity [40]. In adult life, the balance usually works, but one-third of Western humans develop cancer, usually later in life, while 5–10% develop clinical autoimmune disease, so the balance is finely set and may shift over time. The fading immune system in old age (see below) may ameliorate autoimmunity but at the expense of increased cancer risk.

Microorganisms cause about a quarter of all cancers (e.g. EBV, hepatitis B and C viruses, human papilloma virus and Helicobacter pylori). Specific T-cell responses normally hold these microbes in check. However, if immunity is impaired through ageing (see below), immunosuppressive therapy or certain infections, particularly HIV-1, these cancers emerge [41].

CONCLUSION

Therefore, having developed a fully effective immune response in early childhood, this matures as memory accumulates and maintains the health of the individual during critical periods of life, including child bearing. It not only protects against potentially lethal infections but also controls a number of persisting infections, some of which have the potential to cause cancer. It can also deal with mutant cells that have potential for becoming malignant. It can be over-reactive and cause autoimmune disease or allergy, a price paid for the overall benefit.

REFERENCES

[1] Abbas, A.R. et al.: Genes Immun., 6: 319-331 (2005).

[2] Jeff, E. Mold, Jakob Michaëlsson, Trevor, D. Burt, Marcus, O., Muench, Karen P., Beckerman, Michael P. Busch, Tzong-Hae Lee, Douglas F. Nixon and Joseph M. McCune: Science, 322(5907): 1562-1565 (2008).

[3] Katharina Simon, A., Georg, A. Hollander, and Andrew McMichael: Proc. Biol. Sci., 282(1821): 20143085 (2015).

[4] Segundo Gonzalez, Ana Pilar González-Rodríguez, Beatriz Suárez-Álvarez, Alejandro López-Soto, Leticia Huergo-Zapico, and Carlos Lopez-Larrea: Self Nonself., 2(1): 19-25 (2011).

[5] https//health.clevelandclinic.org: Is Your Newborn Baby's Immune System Strong Enough? Health.

[6] Hanson, L.A. and Söderström, T.: Prog. Clin. Biol. Res., 61:147-59 (1981).

[7] Matamoros, S., Gras-Leguen, C., Le Vacon, F., Potel, G., de La Cochetiere, M.F.: Trends Microbiol., 21: 167-173 (2013).

[8] Round, J.L. and Mazmanian, S.K.: Nat. Rev. Immunol., 9: 313-323 (2009)

[9] Josef, Neu and Jona, Rushing: Clin. Perinatol., 38(2): 321–331 (2011).

[10] Andrea T. Borchers, Carlo Selmi, Frederick J. Meyers, Carl L. Keen, and M. Eric Gershwin: J. Gastroenterol., 44: 26-46 (2009).

[11] Walker, J.M. and Slifka, M.K.: Adv. Exp. Med. Biol. 684: 96-107 (2010).

[12] Zinkernagel, R.M.: Phil. Trans. R. Soc. Lond., B 355; 369-371 (2000).

[13] Ricklin, D., Hajishengallis, G., Yang, K. and Lambris, J.D.: Nat. Immunol., 11: 785-797 (2010)

[14] Shearer, W.T. et al.: J. Allergy Clin. Immunol., 112: 973-980 (2003).

[15] Campion, S.L., Brodie, T.M., Fischer, W., Korber, B.T., Rossetti, A., Goonetilleke, N., McMichael, A.J. and Sallusto, F.: J. Exp. Med. 211: 1273-1280 (2014).

[16] Selin, L.K., Nahill, S.R., Welsh, R.M.: J. Exp. Med. 179: 1933-1943 (1994).

[17] Su, Z.J., Chen, H.B., Zhang, J.K. amd Xu, L.: World J. Gastroenterol., 11: 2502-2507 (2005).

[18] Su, L.F., Kidd, B.A., Han, A., Kotzin, J.J. and Davis, M.M.: Immunity, 38: 373-383 (2013).

[19] Hawes, G.E., Struyk,, L. van den and Elsen, P.J.: J. Immunol., 150: 2033-2045 (1993).

[20] Bjorkman, P.J., Saper, M.A., Samraoui, B., Bennett, W.S., Strominger, J.L. and Wiley, D.C.: Nature 329: 512-518 (1987).

[21] Goronzy, J.J. and Weyand, C.M.: Arthritis Res. Ther. 5: 225-234 (2003).

[22] Sheu, T.T., Chiang, B.L., Yen, J.H. and Lin, W.C.: PLoS ONE 9, e89379 (2014).

[23] Yoshikawa, T.T.: Clin. Infect. Dis. 30: 931-933 (2000).

[24] Chung, H.Y., Cesari, M., Anton, S., Marzetti. E., Giovannini, S., Seo, A.Y., Carter, C., Yu, B.P. and Leeuwenburgh, C.: Ageing Res. Rev., 8: 18-30 (2009).

[25] Maslowski, K.M. and Mackay, C.R.: Nat. Immunol., 12: 5-9 (2011).

[26] Biagi, E., Candela, M., Turroni, S., Garagnani, P., Franceschi, C. and Brigidi, P.: Pharmacol. Res., 69: 11-20 (2013).

[27] Weiskopf, D., Weinberger, B. and Grubeck-Loebenstein, B.: Transplant Int., 22: 1041-1050 (2009).

[28] Derhovanessian, E., Solana, R., Larbi, A. and Pawelec, G.: Immun. Ageing 5: 11 (2008).

[29] Hayflick, L.: Nature 408: 267-269 (2000).

[30] Mor, G. and Cardenas, I.: Am. J. Reprod. Immunol., 63**:** 425-433 (2010).

[31] Erlebacher, A.: Annu. Rev. Immunol., 31: 387-411 (2013).

[32] Medawar, P.: Symp. Soc. Exp. Biol., **7:** 320-338 (1952).

[33] Kovats, S., Main, E.K., Librach, C., Stubblebine, M., Fisher, S.J. and DeMars, R.: Science 248: 220-223 (1990).

[34] Moffett, A. and Colucci, F.: J. Clin. Invest. 124: 1872-1879 (2014).

[35] Aluvihare, V.R., Kallikourdis, M. and Betz, A.G.: Nat. Immunol. **5:** 266-271 (2004).

[36] McGaha, T.L., Huang, L., Lemos, H., Metz, R., Mautino, M., Prendergast, G.C. and Mellor, A.L.: Immunol. Rev., 249: 135-157 (2012).

[37] Ostensen, M. and Villiger, P.M.: Semin. Immunopathol. 29: 185-191 (2007).

[38] Memoli, M.J., Harvey, H., Morens, D.M. and Taubenberger, J.K.: Influenza Other Respir. Viruses **7:** 1033-1039 (2013).

[39] Pardoll, D.M.: Nat. Immunol. 13, 1129-1132 (2012).

[40] Zhong, S. et al.: Proc. Natl. Acad. Sci. USA, 110: 6973-6978 (2013).

[41] Morath, C., Mueller, M., Goldschmidt, H., Schwenger, V., Opelz, G., Zeier, M.: J. Am. Soc. Nephrol., **15:** 1582-1588 (2004).