THE IMPACT OF IMMUNOSENESCENCE ON THE IMMUNE RESPONSES: A CHALLENGE ON INFLUENZA VACCINATION IN THE ELDERLY

Firzan Nainu

Faculty of Pharmacy, Hasanuddin University, Makassar

INTRODUCTION

The global population of people older than 65 years is estimated to rise dramatically due to advances in average life expectancy (1). A massive increase in the numbers of elderly persons; from 600 million at present to nearly 2 billion in 2050, is expected to happen worldwide and, approximately, 25 % of the population in developed countries will be older than 65 (1).

To date, the ageing population presents a challenge for the public healthcare system since the elderly suffer from more frequent and severe infections compare to their younger counterparts (2). In addition, poor outcomes from infections tend to be experienced by aged people in comparison to the younger population. Influenza, particularly, is an example of a common infection which causes annual epidemics, and in the elderly, is associated with increased morbidity. In fact, one of the ten major causes of death in the elderly is influenza (2).

One of the main reasons for the increase of infections observed in the elderly is believed to be a gradual deterioration of the immune system that occur with ageing which leads to a decline in the response to infection by both the innate and adaptive immune systems, namely immunosenescence (2,3). Immunosenescence was introduced for the first time by Dr. Roy Walford (4).

Basically, since the immune response in the elderly declines and the outcome of infection is often poor, prevention of infection becomes critically important (3). Vaccination against important infectious pathogens such as influenza, could provide a sufficient protection in the elderly and in this case is recommended by the World Health Organization (5). Unfortunately, immunosenescence not only impairs the ability of the immune system to fend off infection but also its capacity to respond to immunisation, as shown by the reduced efficacy of annual influenza vaccination in the elderly, with an efficacy of 17-53% in the elderly compare to 70-90% in healthy adults (6).

Despite considerable progress in influenza vaccine development and our understanding in immunosenescence mechanisms, we still do not have a clear understanding regarding the impact of immunosenescence on the effectiveness of influenza vaccination in the elderly. It is important to identify this issue since several studies have reported the effectiveness of influenza vaccination in the elderly during seasonal outbreak (7,8,9,10,11) while other studies present contradictory results (12,13,14). Further elucidation of the relationship between immunosenescence and infuenza vaccination efficacy would reveal the way to improve immune response of the aged people and therefore, improve their quality of life during influenza outbreak. In this review, we will discuss on recent advances in innate and adaptive immune response, especially in mucosal immune system, during ageing and this knowledge should eventually lead to the development of more effective influenza vaccines for the elderly

CHANGES IN THE INNATE IMMUNITY DUE TO AGEING

Innate immunity is the first line of defense in immune system, comprises the cells and mechanisms that protect the host from infection by pathogens, in a non-specific manner (15). The innate immune system includes several cellular components such as monocytes/macrophages, natural killer (NK) cells, natural killer T (NKT) cells, dendritic cells (DCs), neutrophils, eosinophils, and basophils, and by the elaboration of proinflammat-ory cytokines, type I interferons (IFNs) and other soluble factors which provide protection against bacterial and viral infections (16,17).

The innate immune system identifies pathogens via pattern-recognition receptors (PRRs), such as toll-like receptors (TLR), which triggering a variety of signalling pathways subsequent to the recognition of specific molecular patterns that present on the surface of the pathogens (16). PRRs have several characteristics. First, PRRs could recognise microbial components, known as pathogen-associated molecular patterns (PAMPs)

that are essential for the survival of the micro-organisms. Different PRRs will respond to specific PAMPs, demonstrate distinct expression patterns, activate specific signaling pathways, and lead to distinct antipathogen responses. Second, PRRs are expressed constitutively in the host and will detect the pathogens despite of their life-cycle stage. Third, PRRs are germline encoded, non-clonal, expressed on all cells of a given type, and independent from immunological memory (15). However, recent studies evaluating the effects of ageing on the innate immune system reveal that the function of innate cellular components declines with age, which might suggest an explanation for the increased frequency of bacterial and viral infections among the elderly (6,16,18,19).

A study in 1994 showed that phagocytic activity did not affected by ageing (20). However, recent evidence suggests that the phagocytic activity and the production of superoxide anion in macrophages had been declined in the elderly (21) as well as their ability to present the antigens to the T cells (22). Several studies had demonstrated the increase of the number of NK cells in the elderly and are associated with an increase in the CD56^{dim} population of NK cells (23,24,25,26). Nevertheless, overwhelming evidence indicates depressed NK function such as impaired NK cell cytotoxicity and decreased production of cytokines and chemokines by activated NK cells are associated with age (21). In addition, evidence indicates the decrease of DCs' ability of aged people to stimulate T-cell proliferation, diminished expression of co-stimulatory molecules, and inadequate production of interleukin (IL)-12 has been reported (22).

CHANGES IN THE ADAPTIVE IMMUNITY DUE TO AGEING

All immune cells arise from the haematopoietic stem cells (HSC) in the bone marrow (27). A study by Aw et al. (2007) shows that a reduced ability of HSC in the production of B-cell precursors is possibly due to an intrinsic and micro-environmental defects at bone marrow level. Simultaneously, intrinsic B-cell defects may occur in the periphery along with age, including low immunoglobulin titer and abnormal B-cell receptor signaling (21). Moreover, even though proliferative capacity of B-cells has been diminished, an increased production of autoantibodies may result from inadequate inhibition by suppressor T-cells (28).

Immunosenescence also affected T-cell's function (28). Maue et al. (2009) have demonstrated the relationship between immunosenescence and significant defects in CD4+ and CD8+ T-cell responses (29). Theoretically, increasing age is predicted to be associated with a well-functioning memory T-cell population that can respond to previously encountered pathogens (2). In other words, we should be able to cope with more infections as we get older. However, a decline production of cytokines such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), IL-1, and IL-6 by T-helper (Th)-1 (30), drastic contraction in CD4+ T-cell diversity (31), and decreased antigen-recognition repertoire of CD8+ T-cells among the elderly (32) have been reported in the elderly. Furthermore, in addition to the vulnerability to new pathogens, the elderly often have difficulties in dealing with pathogens which they have previously encountered, including the annual return of influenza (33).

THE IMPACT OF MUCOSAL IMMUNOSENE-SCENCE ON INFLUENZA INFECTION

Older individuals are much more susceptible to infections (34) including the fact that the severity and mortality caused by the pathogens invading mucosal surfaces such as influenza virus are significantly increased in humans of advanced age (35).

To date, there are three types of influenza viruses are known to be responsible for influenza related diseases: type A, B, and C (36). However, Influenza A virus is the most virulent among influenza viruses and is classified into several subtypes based on the antigenic properties of two viral antigens, Hemagglutinin (HA) and Neuraminidase (NA), which are attached on the surface of the virus (36). HA plays an important role in determining the host specificity and the mechanism of viral entry into the host cells through an interaction with sialic acid (SA) receptor in the upper respiratory tract of the host (37). Therefore, Chen et al. (2009) suggested that hemagglutination inhibition (HAI) antibody is the most accepted immunological protection against influenza A viruses (1).

According to Harriman et al. (1999), effective protection can be provided by pathogen-specific systemic IgG without mucosal IgA responses (38). However, pathogen-specific SIgA responses are a necessary component for providing the first-line barrier of effective immunity against these respiratory pathogens at their entry site in the elderly (39). Recently, an important role of influenza HA-specific SIgA responses in protecting the body against the influenza virus in the upper respiratory tract has been documented. Furthermore, it is also providing a cross-protection against infection caused by a variant of influenza virus within the same subtype when compared with those of serum IgA Antibodies (39).

Up to now, only few studies in the effect of ageing on the upper respiratory tract immune system have been documented (39). Hagiwara et al. (2003) has reported a decrease frequency of naïve CD4+, CD45RB+ T-cells in Nasopharyngeal-associated lymphoreticular tissues (NALT) of ageing mice (40). However, the size and the total lymphocyte count in the NALT of mice increases approximately five- to ninefold during the ageing process through the first year (39). It is suggested that two years old experimental mice could be considered equivalent to aged-humans (40,41,42).

Nevertheless, the differences of the nasal cavity between mice and humans should be considered in any future development of nasal vaccines (39).

IMMUNOSENESCENCE AND INFLUENZA VACCINATION EFFICACY IN THE ELDERLY

Vaccination is critically important in order to prevent infection and to protect people from disease (43). However, the efficacy of a vaccine depends on the quality of the immune responses; therefore, immunocompromised persons such as infants and older individuals are more likely to be insufficiently protected (44).

Regarding disastrous outbreak of "Spanish flu" in 1918, annual vaccination against influenza has been recommended to everybody especially older people aged > 65 years (5,45). Several studies have suggested the benefit of influenza vaccination during seasonal outbreak especially in the elderly (7,8,11,46,47,48,49). However, Chen et al. (2006) identified some of the studies have been criticized in the methodological problems including inadequate consideration of potential bias; variability in the serological match between the vaccine virus strains and the circulating influenza strains and the use of outcome measures with low sensitivity (influenza-like illness rather than laboratory confirmed influenza) (1). In addition, Goodwin et al. (2006) reported that antibody responses following influenza vaccination are lower in elderly persons than in young adults (6). Furthermore, diminished influenza-vaccine related protection against influenza illness is frequently observed in the elderly and is considered, in part, due to ineffectiveness of an ageing immune system (28).

One of the hallmarks of the immunosenescence in aged people is a decline in the antibody production which will impair the status of humoral responses. It is, unfortunately, believed that this event has a negative impact on the effectiveness of many current vaccines, including influenza vaccines, since the goal of the administration of the vaccines into the body is to improve the immune system by increasing the humoral responses, including antibody production (28,29). Declining immune function due to ageing and resultant impairment on the innate immune response could reduce the effectiveness of the vaccination programs due to the decrease of the antigen uptake at the site of injection, resulting from a reduced phagocytosis (44). Improved antigen delivery systems (e.g. liposomes and virosomes), immunostimulatory adjuvants (such as saponins, adjuvants targeting TLRs), or the administration of recombinant cytokines might help overcome these limitations (43).

Since the immunosenescence phenomena occurs earlier in the mucosa than in the systemic compartments, the development of mucosal vaccines against influenza viruses for the elderly (especially A-type) offers both promises and significant challenges. For instance, gaps in the mucosal immunosenescence studies between mouse and human subjects should be revealed, as well as the development of mucosal modulators including novel mucosal adjuvants that can overcome mucosal immunosenescence in the elderly. Furthermore, differences in the immune response of the elderly populations from various countries are influenced by commensal flora, nutritional uptake, genetic background, life style, and so forth (39).

CONCLUSION

In the elderly, many changes happened in both the innate and the adaptive immune responses. These changes are generally viewed as the deterioration of immunity, leading to the use of the term immunosenescence, which is might responsible for the increased susceptibility of elderly to infectious diseases such as influenza. Hence, a better understanding of the immunosenescence and its effects on the influenza vaccination in the elderly would reveal new strategies on the influenza vaccine development.

REFERENCES

1. Chen, W.H., Kozlovsky, B.F., Effros, R.B., Grubeck-Loebenstein, B., Edelman, R., & Sztein, M. 2009, Vaccination in the Elderly: An Immunological Perspective. *Trends in immunol.* (30); *pp.* 351-359
2. Aspinall, R., Giudice, G.D., Effros, R.B., Grubeck-Loebenstein, B., & Sambhara, S., 2007, Challenges for Vaccination in the Elderly. *Immun and Ageing* (4); pp. 9-17
3. McElhaney, J.E., 2003, Overcoming the Challenges of Immunosenescence in the Prevention of Acute Respiratory Illness in Older People. *Conn Med* (67); pp. *469-474*
4. Walford, R.L., 1964, The Immunologic Theory of Aging. *Gerontol* (4); pp. 195-197
5. World Health Organization, 2005, WHO Position Paper on Influenza Vaccines. *Wkly Epidemiol Rec WER* (33); pp. 279-287
6. Goodwin, K., Viboud, C., & Simonsen, L., 2006, Antibody Response to Influenza Vaccination in the Elderly: A Quantitative Review. *Vaccine (*24); pp. 1159-1169
7. Ahmed, A.H., Nicholson, K.G., & Nguyen-Van-Tam, J.S., 1995. Reduction in Mortality Associated with Influenza Vaccine During 1989-90 Epidemic. *Lancet* (346); pp. 591-595
8. Jefferson, T., Rivetti, D., Rivetti, A., Rudin, M., Di Pietrantonj, C., & Demicheli, V., 2005, Efficacy and Effectiveness of Influenza Vaccines in Elderly People: A Systematic Review. *Lancet* (366); pp. 1165-1174
9. Nichol, KL., 2005, Influenza Vaccination in the Elderly: Impact on Hospitalization and Mortality. *Drugs aging* (22); pp. 495-515

10. Rivetti, D. Jefferson, T., Rivetti, A., Rudin, M., Di Pietrantonj, C., & Demicheli, V., 2006, Vaccines for Preventing Influenza in the Elderly. *Cochrane Database Syst. Rev 3:*CD004876

11. Nichol, K.L., Nordin, J.D., Nelson, D.B., Mullooly, J.P., & Hak, E., 2007, Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly. *N. Engl. J. Med.* (357); pp. 1373-1381

12. Goronzy, J.J., Fulbright, J.W., Crowson, C.S., Poland, G.A., O'Fallon, W.M., & Weyand, C.M., 2001, Value of Immunological Markers in Predicting Responsiveness to Influenza Vaccination in Elderly Individuals. *J. Virol.* (75); pp. 12182-12187

13. Simonsen, L., Reichert, T.A., Viboud, C., Blackwelder, W.C., Taylor, R.J., & Miller, M.A., 2005, Impact of Influenza Vaccination on Seasonal Mortality in the US Elderly Population. *Arch. Intern. Med.* (165); pp. 265-272

14. Rizzo, C., Viboud, C., Montomoli, E., Simonsen, L., & Miller, M.A., 2006, Influenza Related Mortality in the Italian Elderly: No Decline Associated With Increasing Vaccination Coverage. *Vaccine* (24); pp. 6468-6475

15. Akira, S., Uematsu, S., & Takeuchi, O. 2006, Pathogen Recognition and Innate Immunity, *Cell* (124); pp.783-801

16. Renshaw, M., Rockwell, J., Engleman, C., Gewirtz, A., Katz, J., & Sambhara, S., 2002, Cutting Edge: Impaired Toll-Like Receptor Expression and Function in Aging. *J. Immunol.* (169); pp. 4697-4701

17. Panda, A., Arjona, A., Sapey, E., Bai, F., Fikrig, E., Montgomery, R.R., Lord, J.M., & Shaw, A.C., 2009, Human Innate Immunosenescence: Causes and Consequences for Immunity in Old Age. *Trends in immunol.* (23); pp. 403-408

18. van deen Biggelaar, A.H., Huizinga, T.W., de Craen, A.J., Gussekloo, J., Heijmans, B.T., Frolich, M., & Westendorp, R.G., 2004, Impaired Innate Immunity Predicts Frailty in Old Age. the Leiden 85-plus study. *Exp. Gerontol.* (39); pp. 1407-1414

19. van Duin, D., Mohanty, S., Thomas, V., Ginter, S., Montgomery, R.R., Fikrig, E., Allore, H.G., Medzhitov, R., & Shaw, A.C., 2007, Age-Associated Defect in Human TLR-1/2 Function. *J. Immunol.* (178); pp. 970-975

20. Fietta, A., Merlini, C., Dos Santos, C., Rovida, S., & Grassi, C., 1994, Influence of Aging on Some Specific and Nonspecific Mechanism of the Host Defense System in 146 Healthy Subjects. *Gerontol.* (40); pp. 273-254

21. Aw, D., Silva, A., & Palmer, D., 2007, Immunosenescence: Emerging Challenges for An Ageing Population. *Immunol.* (120); pp. 435-446

22. DelaRosa, O., Pawelec, G., & Peralbo, E., 2006, Immunological Biomarker of Ageing in Man: Changes in Both Innate and Adaptive Immunity Are Associated With Health and Longevity. *Biogerontol.* (7); pp. 471-481

23. Vitale, M., Zamai, L., Neri, L.M., Galanzi, A., Facchini, A., Rana, R., Cataldi, A., & Papa, S., 1992, The Impairment of Natural Killer Function in the Healthy Aged Is Due to A Postbinding Deficient Mechanism. *Cell. Immunol.* (145);1-10

24. Sansoni, P., Cossarizza, A., Brianti, V., Fagnoni, F., Snellli, G., Monti, D., Marcato, A., Passeri, G., Ortolani, C., Forti, E., Fagiolo, U., Passeri, M., & Franceschi, C., 1993, Lymphocyte Subsets and Natural Killer Cell Activity in Healthy Old People and Centenarians. *Blood* (82); pp. 2767-2773

25. Borrego, F., Alonso, M.C., Galiani, M.D., Carracedo, J., Ramirez, R., Ostos, B., Pena, J., & Solana, R., 1999, NK Phenotypic Markers and IL-2 Response in NK Cells From Elderly People. *Exp. Gerontol.* (34); pp. 253-265

26. Miyaji, C., Watanabe, H., Toma, H., Akisaka, M., Tomiyama, K., Sato, Y., & Abo, T., 2000, Functional Alteration of Granulocytes, NK cells, and Natural Killer T Cells in Centenarians. *Hum. Immunol.* (61); pp. 908-916

27. Janeway, C.A., Travers, P., Walport, M., & Shlomchik, M.J., 2005, *Immunobiology: The Immune System in Health and Disease. 6th ed.* Pub: Garland Science Taylor and Francis Group, New York, p. 3

28. Targonski, P.V., Jacobson, R.M., & Poland, G.A.,2007, Immunosenescence: Role and Measurement in Influenza Vaccine Response Among the Elderly. *Vaccine* (25); *pp.3066-*3069

29. Maue, A.C., Yager, E.J., Swain, S.L., Woodland, D.L., Blackman, M.A., & Haynes, L., 2009, T-Cell Immunosenescence: Lessons Learned From Mouse Models of Aging. *Trends in immunol.* (30); pp. 301-305

30. Fulop, T., Larbi, A., Douziech, N., Levesque, I., Varin, A., & Herbein, G., 2006, Cytokine Receptor Signaling and Aging, *Mechanisms of Ageing and Development* (127); pp. 526-537

31. Naylor, K., Li, G., & Vallejo, A., 2005, The Influence of Age on T Cell Generation and TCR Diversity. *J. Immunol.* (174); pp. 7446-7452

32. Weng, NP., 2006, Aging of the Immune System: How Much Can the Adaptive Immune System Adapt? *Immunity* (24); pp. 495-499

33. Hannoun, C., Megas, F., & Piercy, J., 2005, Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res.* (103); pp. 133-138

34. Shanley, D.P., Aw, D., Manley, N.R., & Palmer, D.B., 2009, An Evolutionary Perspective on the Mechanisms of Immunosenescence. *Trends in immunol.* (30); pp. 374-381

35. Webster, R.G., 2000, Immunity to Influenza in the Elderly. *Vaccine* (18); pp. 1686-1689

36. Poddar, S.K., 2003, Detection of Type and Subtypes of Influenza Virus by Hybrid Formation of FRET Probe With Amplified Target DNA and Melting Temperature Analysis. *J. Virol Meth.* (108); pp. 157-163

37. Thanh, T.T., van Doorn, H.R., & de Jong M.D., 2008, Human H5N1 Influenza: Current Insight Into Pathogenesis. *The International Journal of Biochemistry and Cell Biology.* (40); pp.2671-74

38. Harriman, G.R., Bogue, M., Rogers, P., Finegold, M., Pacheco, S., Bradley, A., Zhang, Y., & Mbawuike, I.N., 1999, Targeted Deletion of the IgA Constant Region in Mice Leads to IgA Deficiency With Alterations in Expression of Other Ig Isotypes. *J. Immunol.* (162); *pp.* 2521-2529

39. Fujihashi, K., & Kiyono, H., 2009, Mucosal Immunosenescence: New Developments and Vaccines to Control Infectious Diseases. *Trends in immunol.* (30); pp. 334-343

40. Hagiwara, Y., McGhee, J.R., Fujihashi, K., Kobayashi, R., Yoshino, N., Kataoka, K., Etani, Y., Kweon, Mi-Na, Tamura, S., Kurata, T., Takeda, Y., Kiyono, H., & Fujihashi, K., 2003, Protective Mucosal Immunity in Aging Is Associated With Functional CD4+ T-Cells in Nasopharyngeal-Associated Lymphoreticular Tissue. *J. Immunol.* (170); pp. 1754-1762

41. Haynes, L., Linton, P.J., Eaton, S.M., Tonkonogy, S.L., & Swain, S.L., 1999, Interleukin 2, But Not Other Common Gamma Chain-Binding Cytokines, Can Reverse The Defect in Generation of CD4 Effector T Cells From Naïve T Cells of Aged Mice. *J. Exp.Med.* (190); pp.1013-1024

42. Kato, H., Fujihashi, K., Kato, R., Dohi, T., Fujihashi, K., Hagiwara, Y., Kataoka, K., Kobayashi, R., & McGhee, J.R., 2003, Lack of Oral Tolerance in Aging Is Due to Sequential Loss of Peyer's Patch Cell Interactions. *Int. Immunol.* (15); pp. 145-158

43. Weinberger, B., Herndler-Brandstetter, D., Schwanninger, A., Weiskopf, D., & Grubeck-Loebenstein, B., 2008, Biology of Immune Responses to Vaccines in Elderly Persons. *Clin. Infect. Dis.* (46); pp. 1078-1084

44. Kalula, S.Z., & Ross, K., 2008, Immunosenescence: Inevitable or Preventable? *Curr. Aller. Clin. Immunol.* (21); pp. 126-130

45. Bridges, C.B., Harper, S.A., Fukuda, K., Uyeki, T.M., Cox, N.J., and Singleton, J.A., 2003, Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* (52); pp. 1-34

46. Fedson, D.S., Wadja, A., & Nicol, J.P., 1993, Clinical Effectiveness of Influenza Vaccination in Manitoba. *JAMA* (270*); pp. 1*956-1961

47. Flemming, D.M., Watson, J.M., & Nicholas, S., 1995, Study on the Effectiveness of Influenza Vaccination in the Elderly in the Epidemic of 1989-1990 Using A General Practice Database. *Epidemiol.Infect.* (115); pp. 581-589

48. Gross, P.A., Hermogenes, A.W., Sacks, H.S., Lau, J., & Levandowski, R.A., 1995, The Efficacy of Influenza Vaccine in Elderly Persons. *Annals. Int. Med.* (123); pp. 519-527

49. Ohmit, S.E., & Monto, A.S., 1995, Influenza Vaccine Effectiveness in Preventing Hospitalization For Pneumonia Among the Elderly During Influenza A and Type B Seasons. *Int. J. Epidemiol.* (24); pp. 1240-1248

Halaman ini sengaja dikosongkan