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THE MOLECULAR MECHANISMS OF IMMUNOSENESCENCE IN NUTRITIONAL DEPRIVATION

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ABSTRACT

A rural Gambian community where alternating periods of food abundance (harvest season) and deprivation (hungry season) exists, season of birth strongly predicts adult mortality from infectious diseases, suggesting permanent programming of immunity. The susceptibility of the thymus to nutritional deprivation and its role in immunity, lead to the prediction that the immune mechanisms involved were of thymic origin.

During the first year of life when exclusive breast feeding was practiced, those born in the harvest season had bigger thymi, which suggested involvement of breast milk factors. IL-7, a cytokine critical for thymic and T cell development was suggested a possible candidate, with the prediction that deficiency in IL-7 during the hungry season may inhibit thymic and T cell development. Accelerated T cell division driven by homeostatic and antigenic pressures could then alter the T cell repertoire and precipitate premature T cell senescence.

The hypothesis was tested by evaluating IL-7 in breast milk in relation to thymic output in infants born in the harvest or hungry season. Thymic and T cell immunity was also analysed in young adults from the same community to investigate season of birth influences on immunosenescence. The role of milk IL-7 was further characterised by use of a mouse model designed to evaluate if thymic and T cell defects following the absence of IL-7 could be rescued by fostering. The results revealed that higher breast milk IL-7 levels were associated with better thymic function as determined by signal joint TCR rearrangement excision circles (sjTREC) measurements, in infants born during the harvest. Although the murine model confirmed that defective T cell development was rescued by fostering IL-$7^{-/-}$ KO pups to lactating IL-$7^{+/+}$ WT dams, thymic function, T cell repertoire and telomere length results could not verify that early immune defects programmed premature immunosenescence.