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EVOLUTION OF LYMPHOCYTES FROM PROTOZOA: THE HYPOTHESIS IS SUPPORTED BY THE SIMILARITY OF AMOEBAPORE AND GRANULYSIN

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ABSTRACT

It is a remarkable mystery as to why both primitive protozoa and mammalian lymphocytes employ similar proteins, to penetrate the membranes of bacteria with lethal consequences for the target.

In the case of the protozoan Entamoeba histolytica the protein is called amoebapore; in the case of the human lymphocyte, it is the protein granulysin. Both of these proteins have the same basic structure based on the SAPLIP motif (saposin-like protein), a molecular arrangement conserved for billions of years. Not only that, but both proteins are designed to function in a similar way. They are thus both SAPLIP DEFENSE PROTEINS, and porcine NK-lysin similarly found in lymphocytes, provides a third example.

The fact that SAPLIP DEFENSE PROTEINS (SDPs) are not present in other animal phyla (apart from platyhelminths), only deepens the mystery; and the 2 billion year gap between the first incarnation of the SDPs, and then their reappearance in mammalian lymphocytes, and no other tissue, not even macrophages leads us to think that protozoa were directly involved in the development of the lymphocyte, possibly to the extent of being direct ancestors.

This hypothesis could be tested by finding SDPs in primitive fish.

KEY WORDS: LYMPHOCYTES, PROTOZOA, EVOLUTION, SAPLIPS, AMOEBAPORE, NK-LYSIN, GRANULYSIN.

SAPLIP proteins are a diverse family of lipid-interacting proteins (Bruhn, 2005). Their name derives from the fact that they are all structurally similar to the protein saposin. Their functions have been summarized in Table 1 of Bruhn's paper: and strikingly, one of the main groups of SAPLIPS, which he describe as *"Defense proteins"*, are only found in protozoa, and vertebrate lymphocytes , and the Platyhelminths Fasciola, and Clonorchis, but not in the other 30 or so phyla of animals!

There is no escaping the significance of this bizarre distribution. As Bruhn himself writes "the fact that the highly specialized and complex immune system of mammals and a primitive phagocyte such as an amoeba use similar molecules to fulfil a similar function appears remarkable." (Bruhn et al, 2003). We submit that not only is this eventuality remarkable, but it also lends support to the hypothesis we have been pursuing for the last several years: namely that lymphocytes evolved from a marine protozoan parasite. (Coulson, 2013, and Coulson and Coulson, 2016)

Some time, about 2 to 3 billion years ago, the ancient protozoan parasite Entamoeba histolytica began to synthesize the SAPLIP termed appropriately amoebapore; this protein works by disrupting the membranes of bacteria, effectively changing them into cerements, (Lieppe, 1995). The SAPLIP Granulysin from human lymphocytes functions in a similar fashion, and so does NK-lysin from porcine NK (natural killer) and cytotoxic T lymphocytes, (Bruhn et al, 2003). One way this situation could have developed, and these homologs come into existence, would be, if about 650 million years ago a marine protozoan parasite evolved into a protective endosymbiont in an early chordate, bringing with it the ability to make these SAPLIP defense proteins. Certainly it is impressive that when lymphocytes first appeared in Lampreys, they were already equipped with a range of biological weapons, (Mayer et al, 2002).

Structurally, the key features of the SAPLIP protein family are: a core of hydrophobic amino acids, and six cysteine residues which form the disulphide bridges; these latter structures are thought to be pivotal to the extraordinary stability of the domains. This, "combined with the common position of the secondary structure of four to five alpha –helices, are sufficient features to result in a common fold, as expected for a family of homologous proteins." (Bruhn, 2005). (Fig 1)

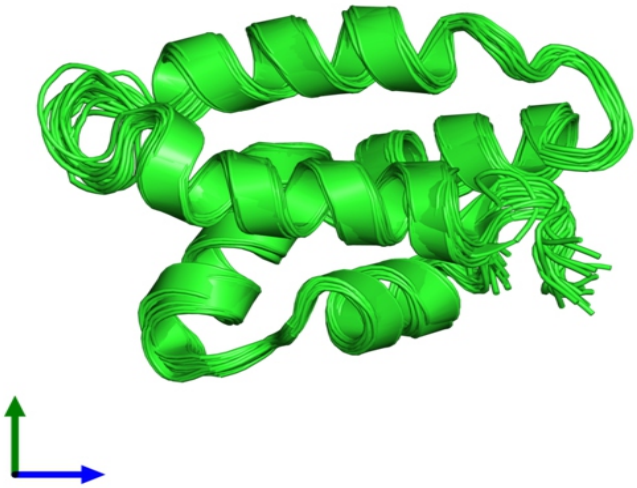

FIGURE 1 A: Amoebapore

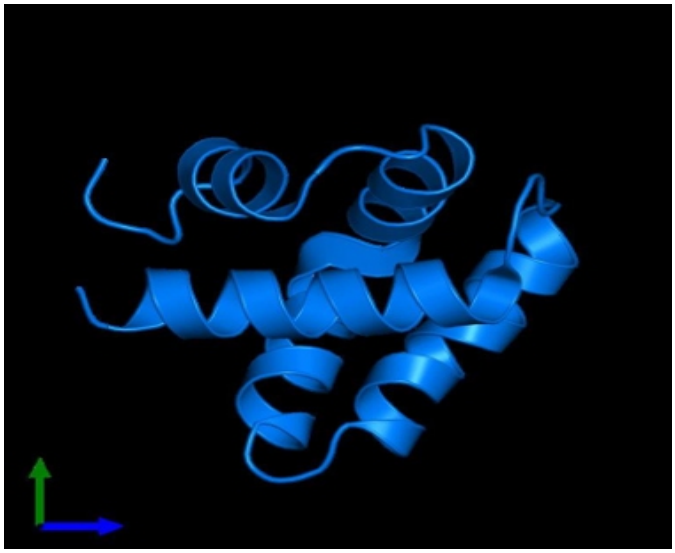

FIGURE 1B: NK-Lysin

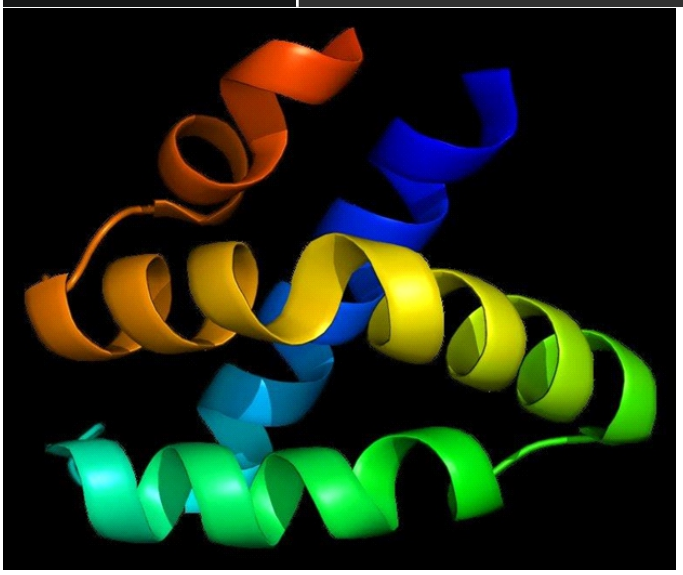

FIGURE 1C: Granulysin

FIGURE 1. Detailed structure of the SAPLIPS, Amoebapore, NK-lysin and granulysin.

The precise mechanism by which amoebapore and NK lysin accomplish lysis of the target cell varies slightly. Briefly, the amoebapores appear to create stable pores (Bruhn and Leippe 1999); while the NK-lysin inflicts damage to the membrane by molecular electropolation, (Miteva et al 1999).

Another consideration to take into account, is that the SDPs are only found in lymphocytes, and not in macrophages or in any other organ, where they could perform a similar lytic and defensive function, such as pancreatic digestive juices, saliva or tears.

The hypothesis that lymphocytes are derived from protozoa, could be tested by finding SAPLIP defense proteins in the lymphocytes of primitive fish, and continuing not to find them in other animal phyla. In addition, if the genes controlling some of the other features peculiar to lymphocyte, such as movement and antigen recognition, were to be located near the SAPLIP genes, this would further strengthen the concept of a protozoan ancestry for the lymphocyte.

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