Structure based understanding of the innate immunity proteins and their explotation for therapeutic applications

T.P. Singh

Department of Biophysics, All India Institute of Medical Sciences, New Delhi
Email: tpsingh.aiims@gmail.com

Abstract

Over a period, the efforts to develop new drugs against infectious diseases declined considerably due to the prevailing notion of low returns. However, the devastating impact of the recent worldwide viral pandemic has forced the scientific community to intensify research for solutions. The desperate efforts include to design new antiviral agents, modify the old ones, intensify the exploitation of known drugs by repurposing, use of natural products, improve the combinatorial chemistry approaches, carry out structure based design and search useful antiviral agents from the synthetic compound libraries. It is needless to say that several vaccines also emerged in a short period which are being administered extensively in the whole world in spite of some known and some unknown concerns. As of now everything, whichever can help or assumed to be helpful is being tried against the deadly COVID-19 pandemic. Making drugs and vaccines against a particular virus or bacteria is not enough as new strains can always emerge. In order to be prepared for any such eventuality, we need to think about better anti-infection weapons that can kill the diverse organisms. It is well known that the first line of defense against invading microbes is provided by innate immunity proteins. In principle, the antimicrobial innate immunity proteins found in the extracellular fluids of mammals including in the plasma, saliva, and airway epithelial lining fluids, nasal lining fluid, milk, tears and gastric juices should be able to protect the hosts but that does not always happen. Also we observe that certain animals protect themselves better than the others indicating that they have better innate immune system. This is the crux and we need to find out the basis of this. If it is quality of the innate immunity proteins, we need to find it out and thus the better proteins can be exploited as therapeutic molecules. We

have extensively, structurally and biochemically studied four members of the innate immune system which use different mechanisms of action. This includes peptidoglycan recognition protein (PGRP), heme-lactoperoxidase (LPO), lactoferrin (LF) and lysozyme-Ca (LYZ-Ca). Due to limited time available for the presentation, the role of one member of the innate immune system will be discussed here. This member is LPO which acts as an oxidoreductase enzyme and uses hydrogen peroxide (H_2O_2) as substrate-1 to convert substrate-2, thiocyanate (SCN^-) into highly potent antimicrobial hypothiocyanite ($OSCN^-$).The enzyme LPO is over expressed at the site of infection and the production of substrate-1, H_2O_2 is always more than required for this reaction but the availability of substrate-2, SCN^- is not always enough. In view of this, we need to provide substrates-2 for the production of antimicrobial agent by LPO system which works with two steps, Step-1: LPO+H_2O_2 to LPO-intermediate + H_2O and Step-2: LPO-intermediate + substrate-2 to LPO + oxidized product.

Unlike the binding of inhibitors to enzymes for blocking the binding site, the substrate binding requires a unique orientation so that it can be converted in to a product. This can only be understood by structural studies. After extensive structural investigations, we have identified iodide, nitric oxide and some organic compounds that work as substrates for LPO. Thus the substrates of LPO are hereby proposed to be used as therapeutic agents for controlling/preventing the microbial infections.