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Mini-Review

Applications of Ezrin Peptide Therapy to Long COVID, Drug Resistant Infections, Chronic Inflammation and in the Support of Healthy Aging

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Introduction

Ezrin peptides amplify adaptive immunity through the RANTES/CCL5 pathways that lead to cures of drug resistant infections due to bacteria, viruses, fungi and protozoans. Ezrin peptides simultaneously suppress chronic pro-inflammatory cytokine and chemokine signalling, leading to cures for chronic inflammatory disease of the muscular-skeletal system (for example; Ankylosing Spondylitis): inflammatory gut diseases (for example; ulcerative colitis): inflammatory liver diseases (for example; HCV induced hepatitis) and inflammatory heart disease (for example; myocarditis).

Ezrin peptide pharmaceutical technology evolved from a prototype HIV peptide vaccine program in London UK and San Antonio TX, USA, established by Dr Rupert Holms in the mid-1980s. In the early 1990s, Dr Holms discovered that the amino-acid sequence at the C-terminus of HIV gp120 mimics part of the Alpha domain of human ezrin, a protein that builds multi-protein cell signalling complexes of adhesion molecules and receptors on the cell surface; with adaptor proteins, kinases and cytoskeletal components attached to the sub-surface of the cell-membrane. Aqueous solutions of Ezrin peptides are active on mucosal membrane surfaces and seem to behave as a ligand for a surface-exposed "receptor" transition conformation of human ezrin, which causes allosteric changes in the submembrane multi-protein complex that triggers intra-cellular signaling [1].

Dr Holms organised development of Human Ezrin Peptide One (HEP1) which was a synthetic peptide copy of the protein sequence between amino-acids 324 and 337 of human ezrin, at The Gamaleya Institute and Institute of Immunology in Moscow. Safety and efficacy of HEP1 was first demonstrated in HIV and AIDS opportunistic infections, and later in drug resistant sex infections. The first ezrin peptide product (HEP1) was launched on the Russian market in 2001 (brand name "Gepon") as an adaptive immune amplifier that simultaneously down-regulated inflammation for treatment of AIDS and other defective immune responses to infection.

A normal course of treatment is 2mg ezrin peptide per day for 5 days. Ezrin peptides have been clinically demonstrated as safe: no adverse reactions, nor adverse drug interactions, nor allergic responses, have been reported. Human Ezrin Peptide One (HEP1) and Regulatory Ezrin Peptide Glycine 3 (RepG3) are closely related fourteen amino acid synthetic peptides, which are highly charged, highly soluble, 4-turn alpha helical peptides, mimicking the Alpha domain of human ezrin. Ezrin peptides are cheap and simple to manufacture and the active substance costs less than one pound per milligram (mg). Ezrin peptides are stable at room temperature in solid form for at least 2 years. In aqueous solution, ezrin peptides degrade at about 1% per month.

Treatment of Drug Resistant Infections

After the registration of HEP1 in the Russian Federation, a large number of clinical trials were performed with ezrin peptide HEP1 in the treatment of drug resistant chronic sex infections. Generally the clinical trials of HEP1 treatment of chronic viral, bacterial, fungal or protozoan infection, demonstrated approximately ninety per cent success rates, either in combination with existing therapy or as monotherapy, and there were no reports of any adverse reactions. Clinical use of ezrin peptide therapy in Russia to treat and prevent Candida, Chlamydia, Trichomonas vaginalis, Syphilis, HPV and Herpes (HSV-1 & 2) revealed a broad clinical potential for this adaptive immunity amplification technology. HEP1 was also used to successfully treat HCV hepatitis in HIV patients and as an adjuvant to increase antibody titres during hepatitis B vaccination of children [2,3].

Treatment of Acute COVID

Between 2020 and 2022, experimental ezrin peptide therapy using generation one ezrin peptide HEP1 or generation three ezrin peptide RepG3, was used to successfully treat acute COVID, based on earlier clinical successes using ezrin peptides to treat acute viral respiratory infections with inflammatory complications [4]. Investigation of the pro-inflammatory cell-signalling problem triggered by spike protein of SARS-CoV-2, identified RAGE, PKC, p38, NFkB & IL-6 hyper-expression as important components of the problem. The understanding of a possible disease mechanism, suggested both ezrin peptide therapy and also vaso active intestinal peptide (VIP) therapy as potential solutions in which suppression of NFkB mediated chronic expression of pro-inflammatory cytokine expression could be achieved by the induction of PKA>CREB signaling [5].

Treatment of Long COVID and mRNA Vaccine Injury

Long COVID, also referred to as Post-Acute Sequelae of COVID (PASC), is probably triggered during acute SARS-CoV-2 infection by Spike protein binding and hyper-activating the cell-membrane expressed Receptor for Advance Glycation End-products (mRAGE) and Toll-Like Receptor 4 (TLR4). SARS-CoV-2 infects lung monocytes by Spike binding to mRAGE (not ACE2). During acute COVID-19, high levels of IL-6 hyper-stimulate S100A8/A9 expression and secretion. Although no viral protein nor mRNA can be detected in half of long COVID (PASC) patients, there is a significant elevation of serum levels of IL-1b, IL-6, TNFa, and S100A8/A9. It appears that a pathological pro-inflammatory feedback loop (the TLR4/RAGE-loop) is established during acute COVID-19, which is maintained by S100A8/A9 > RAGE/TLR4 chronic inflammatory signalling, even after SARS-CoV-2 has been cleared from the body [6].

However, more evidence has emerged of chronic spike expression over long periods of time, both as a result of SARS-CoV-2 infection and the use of mRNA COVID vaccines. NewalR&D established a volunteer experimental ezrin peptide treatment program for Long COVID and COVID vaccine injury in which more than sixty volunteers have been treated on an individual unmet medical need basis (this data is anecdotal and is not a clinical trial). However the general observation is that ezrin peptide therapy is safe in Long COVID and COVID vaccine injury patients, about half report symptom improvement and about ten per cent report a significant benefit. The most common symptomatic improvements suggest reduction of inflammation in the gut, brain and heart. Ezrin peptides have already been shown to be clinically effective as anti-inflammatory therapy for any ulceration or inflammation in the gut, including the treatment and prevention of stomach & duodenal ulcers, and ulcerative colitis [7-9].

During the treatment of a vaccine injury patient, blood results provided new information that ezrin peptide RepG3 was inducing enhanced RANTES/CCL5 expression, providing an explanation for the amplification of adaptive immunity which has been observed with ezrin peptide treatment over the previous thirty years. In addition a second control pathway was identified that had a dominant suppressive effect on pro-inflammatory cytokine expression [10]. Results from individual Long COVID patients with other co-morbidities, also revealed a potent ezrin peptide cure for the inflammatory spine disease Ankylosing Spondylitis, and relief from myocarditis chest pains experienced by COVID vaccine injury patients, in addition to the reduction of symptoms of gut inflammation and "brain fog" due to CNS inflammation.

Current Developments

Research and clinical use of ezrin peptides over three decades has revealed the unusually broad beneficial biological activities of ezrin peptides, in the absence of adverse reactions. The scientific endeavour is to develop an integrated theory to explain these diverse results.

Ezrin peptides induce RANTES/CCL5 amplification of adaptive immunity while simultaneously suppressing pro-inflammatory cytokines and chemokines. Ezrin peptides are effective therapy for drug resistant infection whether viral, bacterial, fungal or protozoan, and are effective as monotherapy or in combination with existing therapy, to over-come Anti-Microbial Resistance (AMR). 17 clinical trials have been performed that showed clinical efficacy in a variety of sexually transmitted infections that failed to respond to existing therapy.

Ezrin peptides amplify adaptive B-cell and T-cell programmed immune responses, mediated via RANTES/CCL5 secondary signalling. Ezrin peptides also suppress pro-inflammatory cytokines (IL1b, IL6, IL8, IL13 & TNFa) and chemokines (MIP1a & MIP1b). Ezrin peptides amplify programmed B-cell responses, increase antibody titres and have vaccine adjuvant effects. Ezrin peptides also induce leukocyte migration and fibroblast activation. They stimulate tissue repair, wound healing, ionization radiation recovery and ulcer healing. Ezrin peptides stimulate NK-cell responses and have anti-solid tumour activity in animal models.

Ezrin peptides activate various cell signalling pathways: such as the Ras>Raf>MEK>ERK growth signalling and PI3K>AKT anti-apoptotic signalling, and possibly the JNK stress response pathway, and "Hippo" cell proliferation control pathway. Observations of anti-solid tumour activity, recovery from ionizing radiation damage and tissue regeneration suggest "Hippo" signalling and JNK signalling may be modulated by ezrin peptides.

Over the thirty years ezrin peptide technology has evolved, the evidence has grown that these peptides are operating at a deep level of living systems. For example, in chronic toxicity-safety studies mice displayed features of a slow-down of the rate of aging (healthier hair and higher fecundity). Ezrin peptides may enhance activity of transcription factor FOXO3: it is already known that some FOXO3 SNPs that enhance its activity are associated with extreme human longevity. Ezrin peptides have potential applications in the treatment of radiation sickness and in the enhancement of healthy aging but much more research needs to be done.

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