Letter to the Editor

TREATMENT OF CHRONIC WOUNDS: TIME FOR IMMUNOLOGIC CONCERN ON DRUG DESIGN?

Dear sirs

Professor Paul Davis has in his article (1) considered advances and improvements in immunology a major contribution towards the therapeutics of diseases, especially wound healing. We have been working along similar lines for more than a decade in drug design and have registered such drugs as patents (2–5).

Several well-known documents indicate that cellular and molecular impairments of immunologic origin are seen in chronic wounds such as diabetic foot ulcers (DFUs) (6). They are cytokine defects (mainly Th-1 mediated), tendency to be associated with other chronic diseases [tuberculosis in diabetes mellitus (DM) (7)], overexpression of matrix metalloproteinases (MMPs) (1,8) etc.

On the basis of worldwide literature, we have been working on reverting or correcting the defects responsible for DFU. We hypothesised that the defect could be corrected by repairing a biologic (immunologic based) mechanism that has been assumed to be impaired in patients with DFU and chronic wounds (6). To prove such a hypothesis, we proposed that factors such as decrease in macrophages and fibroblasts and other cell recruitment impairments and leukocyte function defects might have been defective in these patients. Disturbances in pro-inflammatory and inflammatory cytokines such as interleukin (IL)-1, tumour necrosis factor (TNF)/alpha, and others such as transforming growth factor alfa and beta (TGF), interleukine 8 (IL-8), granulocyte monocyte - colony stimulating factor (GM-CSF), and interferon gamma (IFN/gamma) and many other vital cells and molecules were all indicative of an immunological defect in DFU. On the other hand, based on the nature of the abnormalities, we considered these patients to be relatively immunocompromised, especially with innate immune defects. We postulated that many signs in these patients indicate that they may lack proper cell immunity. Other studies had also shown this to be true. The immune defects included a lack of CD3+ T lymphocytes, macrophage recruitment defect, neutrophils and other phagocytic dysfunctions. Disturbances in neutrophil function such as failure of respiratory burst, INF/gamma, interleukin 12 (IL-12), and deficiency of IL-1, IL-2 receptors (IL-1 R, IL-2 Rs) and some other critical factors led us to confirm that these patients had innate cellular immunity failure, as already discussed in our hypothesis (6). We then suggested the possible importance of gaining the effector functions of some critical cells as phagocytes. In our subsequent works, we postulated that this can be achieved with Th-1 cell activation as the mechanism of cellular and molecular conduction. It could be concluded that one of the defects in DFU might be the non-specific immunity in its cellular and molecular aspects. To achieve our goal in this direction we proposed that Th-1 cells are the major gateway through which the body may refresh itself. In this stage, we used activators of Th-1 cells as adjuvants. The non-specific immunity defects were previously described in some reports. Some interesting features observed apart from the healing of non-healing wounds using the available protocols are blockage of proteolytic activity of enzymes associated with clot formation as an appropriate mechanism for cells and molecules necessary to act on wound healing, autolytic debridement of necrotic lesions without use of surgical tools, control of infection without use of antibiotics and interestingly control of interdigital fungal infection resistant to all used antifungal agents.

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