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New hope on the horizon of chronic pain management; targeting PI3K, proinflammatory cytokines/AKT and nitric oxide

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Pain is one of the most debilitating and unpleasant sensory and emotional condition which present itself in the form of complex phenomena. Safe and effective drug treatment for chronic pain is still a gigantic challenge in the field of research and quality of life. Recently phosphotidylinositide-3-kinase (PI3K) and its downstream regulator emerged as appealing targets for the development of new drugs having immense potential in various major disorders [1]. Researcher's targeted different PI3K downstream signaling components both in central and peripheral level of nervous system using various models of chronic pain. Emphasis must be put on the importance of PI3K and its downstream molecules such as Akt, proinflammatory cytokines and nitric oxide as a potential target for the treatment of chronic pain. Researchers are paying serious efforts to identify those molecules which have high clinical outcome with least chances of side effects. Several compounds have been identified to successfully target PI3K in experimental models of chronic pain [2]. Additional research is needed to uncover the importance of PI3K signaling as potential candidate target for the development of new drugs that warrant in treatment of chronic pain.

As common pain therapy is successful in 20-70% of patients therefore management and treatment of chronic pain itself is high challenge and became one of the main economic burden on the society [3].In the last decade, extensive measures have been taken to confront pain mechanism. Different targets have been proposed with limited success rate in clinical trials to develop effective drugs. However; still we need a definite and reliable target for achieving gold standard therapy. PI3K is a signal transducer enzyme capable to modulate a diverse array of functions including pain in biological system [4]. It is activated as a downstream target tailored to the activation of receptor tyrosine kinase (RTKs) or G protein coupled receptors (GPCRs). Once it is activated it can stimulate various downstream signaling targeting Akt, calcium-calmodulin (CaM), glycogen synthase kinase 3β (GSK 3β), extracellular signal-regulated kinases (ERK) and nitric oxide [5, 6].

Proinflammatory cytokines are small regulatory proteins produced by number of cells which helps in the promotion and modulation of systemic inflammation and pain. It includes a functionally distinct group of cytokines such as IL-1β, IL-6, IL-12, IL-18 TNF-α and IFNγ. Since pain is an unpleasant subjective emotional experience been linked with potential tissue injury, hence the expression of such cytokines can modulate pain [7]. Also it was found that IL-1β and IL-6, are interleukins which works synergistically with TNF- α in controlling many inflammatory factors including inducible nitric oxide synthase that has a key role in pain nociception [8, 9]. PI3K is a crucial kinase which targets an important downstream protein called serine/threonine protein kinase PKB or Akt. Ample evidences have shown that activation of PI3K/Akt can leads to the phosphorylation of nuclear factor kappa B (NF-κB) which was activated by IL-1and TNF-α [10]. Different isoforms of PI3K are expressed in leukocytes where they play specific roles such as activation and recruitment of innate cell into the

inflammatory site and development and differentiation of cytokine and modulation of its function [11]. Recently it was found that PI3K downstream activation of Akt can leads the production of inflammatory cytokine as a consequence of NF-kB activation in dendritic cells [12]. In line with the above fact it is also reported that PI3K can govern the synthesis of IFN-1 by translocation of IRF-7 in predendritic cells in response to TLR activation [13]. Also, it is reported that PI3K catalytic subunit P110-β is activated by GPCR and p110- γ is activated by type-1 cytokine receptor and TLR which have a crucial role in inflammation [14]. PI3K activation is also found to be required for the synthesis of ROS in humans and animals [15]. Keeping in view the central role of PI3K in initiating the inflammatory response, it is important to speculate and overlook the inhibition of this kinase in context of clinically reported pain during various human pathologies. Once proinflammatory cytokines production is initiated it can induce the activity of various enzymes including nitric oxide synthase (NOS). NOS activate NO which itself can be found to be an important modulators of pain [16].It might be an important investigation in development of successful therapeutic agents for pain management. PI3K can activate a diverse group of intracellular proteins including Akt. Different cellular functions have been attributed to the activation of Akt such as, insulin signaling, immune response, cell survival and growth [5]. Exploring a unique substrate specifically to address the chronic pain is still an unmet problem. Class-1 of PI3K can activate Akt (Protein kinase B). The activation of Akt is dependent on the phosphorylation at position number 308 threonine which leads to partial activation of Akt. Complete activation of Akt is dependent upon the phosphorylation of serine 473. Different types of chronic pain such as pain initiated by nerve injury, diabetic neuropathy, spinal cord injury, cancer and tolerance induced hyperalgeisa is associated with PI3K/akt pathway activation [5, 17].

Hence, we cannot ruled out the importance of PI3K and its downstream signaling molecules like Akt, proinflammatory cytokines and nitric oxide as a potential target in chronic pain management.

COMPETING INTERESTS

The author declares no competing interests.

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