

Imiquimod, an immune response modifier, is dependent on the OGF-OGFr signaling pathway

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Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have discovered that the efficacy of imiquimod, a clinically important immune response modifier with potent antiviral and antitumor activity, is dependent on the Opioid Growth Factor (OGF)-OGF receptor (OGFr) axis for its action.

This discovery, reported in the August 08 issue of *Experimental Biology and Medicine*, provides new insights into a widely used drug that may lead to development of new agents that will enhance effectiveness and attenuate side-effects.

Imiquimod and resiquimod are imidazoquinoline compounds. Imiquimod (Aldara, R-837, S26308), the best characterized and most widely used, is highly efficacious in the treatment of external genital and anal warts, basal cell carcinoma, actinic keratoses, Kaposi's sarcoma, chronic hepatitis C infection, and intraepithelial carcinoma. Therefore, the underlying mechanism of imiquimod action is of clinical importance. Imiquimod has been reported to be a toll-like receptor-7 agonist, and its anti-tumor effect exerted by modification of the immune response and stimulation of apoptosis. The mechanism of imiquimod on cell proliferation is unclear.

The research team, led by Dr. Ian S. Zagon, Distinguished University Professor, and Dr. Patricia J. McLaughlin, Professor, along with a pre-

doctoral student Renee N. Donahue, in the Department of Neural & Behavioral Sciences and collaborator Moshe Rogosnitzky of MedInsight explored mechanisms responsible for the remarkable clinical action of this class of drugs. Specifically, using tissue culture models, the investigators found that imidazoquinolines upregulate OGFr which in turn stimulates the interaction of the OGF-OGFr axis.

This native, tonically active inhibitory pathway is known to regulate cell proliferation by modulating cyclin dependent kinase inhibitors, resulting in a retardation of cells at the G1-S interface of the cell cycle.

Neutralization of OGF or knockdown of OGFr by siRNA technology eliminated the inhibitory effects of imidazoquinolines on cell replication. "Thus our data," Dr. Zagon said, "brings a paradigm shift to our thinking about a drug widely used in the clinics. Rather than imiquimod activity being mediated by induction of various cytokines, including interferon (IFN)- α , IFN- β , tumor necrosis factor- α (TNF α) interleukin (IL)-1 α , and IL-12 as currently thought, an entirely new pathway - native to body chemistry - has been discovered to regulate cell proliferation by imidazoquinolines."

Co-author, Moshe Rogosnitzky adds: "The elucidation of imiquimod's immune-independent mechanism of action in cancer also creates exciting new therapeutic possibilities for a number of non-cancer conditions, and these are now being further explored. Such studies could lead to new off-label applications for imiquimod as well as development of imiquimod analogues and unique combination therapies."

Dr. Steven R. Goodman, Editor-in-Chief of Experimental Biology and Medicine stated "Through decades of elegant and ground-breaking work, Zagon and colleagues have identified the role of met-enkephalin (the opioid growth factor –OGF) and the OGF receptor in regulating cell proliferation. The current study demonstrates that the mechanism of imidazoquinoline activity is via OGF and OGFr which will have a

profound impact on its use as a therapeutic for cancer and many other non-cancerous disorders."

Source: Society for Experimental Biology and Medicine

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