1. **Molecular pathways of IL-16 in relation cancer therapy and prevention: An integrative approach examining its mechanisms of immune regulation in neurological diseases and experimental autoimmune encephalomyelitis (EAE)**

**Global Integrative Oncology: Use in Cancer Prevention**

**Background**:An integrative approach, as opposed to individual therapy for each disease should benefit by incorporating knowledge of mechanisms related to other diseases, including autoimmune neurologic.

Cancer relapse and progression pose drawbacks for therapy. We present our experimental data, of interest for experimental oncology, in multiple sclerosis (MS) and its experimental autoimmune encephalomyelitis (EAE) model, which support similarities in IL-16 immune regulation of progressive and relapsing-remitting (RR) MS and EAE.

**Aim**: To provide an introductory review of IL-16 genetic association as well as molecular pathways of IL-16 relevant for cancer, by focusing on the IL-16/CD4, p56lck-mediated desensitization of CCR5 signaling. We present our selected research data on IL-16 regulation in MS and EAE and neutralizing therapy of relapsing-remitting EAE.

**Methodology**:Mouse RREAE, in (B6 x SJL) F1 mice, recapitulates clinical RRMS and histopathology subtype, inclusive of oligodendrogliopathy. RREAE was induced with H-2b autoimmune, MOG35-55, relevant to B cell and antibody responses in RRMS.

**Results**:The CD4+ T cell specific chemotactic cytokine, IL-16 was detected in and adjacent to CD4+, CD8+, NKT and B cells. Caspase-3, necessary for pro-IL-16 cleavage, paralleled IL-16 levels in EAE and corresponding MS lesions, peaking at relapses. Concomitant DNA damage (elevated PARPp85), and axonal and glial-cell dysfunction, were observed in EAE relapses. Neutralizing IL-16 therapy, reversed paralysis, lengthened remission and reduced: relapses, demyelination and axonal damage, in RREAE. Therapy abrogated CD4+ T, followed by B220+ and Mac3+ infiltrates.

**Conclusion**:IL-16 may be of particular interest to cancer based on: genetic and epigenetic association (breast, CTCL, MM); cancer-related (prostate), and integrative data; conserved sequence; efficacy of available neutralizing IL-16 antibodies and blocking peptides; regulation of: the chemokine signaling (CCR5, CXCR3, CXCR4), cell cycle progression, cell-cell cross-talk and cell activation and migration. All these should facilitate either, prediction (relapse and therapy biomarker), new combinational therapies, for example with chemokine drugs, impacting economic burden.

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