

## Concept Clearance

**Branch: ERTB**

**Council Period: 201910**

**Concept Title: RESolution of Inflammation in EnviroNmentally Related diseaseE (RESTORE)**

### Introduction

Inflammation is an acute and dynamic protective response to infection, tissue injury, or environmental exposure. The acute inflammatory response is a complex and highly coordinated process involving molecular, cellular, and physiological alterations. Initially it was perceived that the restoration of tissue homeostasis after an inflammatory response was a passive balancing act achieved by anti-inflammatory molecular and cellular players. While the anti-inflammation mechanisms dampen inflammation by inhibiting pro-inflammatory factors that drive inflammation, the resolution of inflammation involves promoting factors essential for removal of the inciting stimulus as well as dampening proinflammatory signaling to prevent collateral damage. Over the past decade, emerging discoveries suggest that resolution of inflammation is also a dynamic, actively regulated process. One such endogenous pathway that lead to a paradigm shift in our understanding of resolution of inflammation is the discovery and characterization of specialized pro-resolving mediators (SPMs) from poly-unsaturated fatty acids (Serhan and Petasis, 2011).

It has been increasingly recognized that the failed resolution of an acute inflammation results in chronic inflammatory state. This can result from either excessive or subnormal inflammatory response to a stimulus, non-removal of stimulus or repetitive stimuli that lead to incomplete resolution of inflammation. Such recurrent, chronic inflammation is implicated in chronic disease conditions such as allergic asthma, cancer and ageing.

Despite a decade of concerted effort by a handful of investigative teams, the field of resolution biology is largely unexplored and opens several opportunities to address the fundamental distinctions between resolution and anti-inflammatory mechanisms including:

- (1) identification and molecular and cellular characterization of resolution mediators their tissue and species specificity, and the downstream phenotypic effects on the transformation of immune cells from pro- to anti-inflammatory states;
- (2) comprehensive understanding on how an unresolved or dysregulated resolution resulting from acute inflammation may lead to a chronic inflammatory status;
- (3) understanding the role of genetic and other susceptibility factors in failed or dysregulated inflammation resolution pathways in diverse chronic inflammatory disease conditions such as ageing, asthma, cancer, obesity, diabetes, etc.;
- (4) Comprehensive screening efforts for identification of novel therapeutic targets in key resolution pathways and explore their physiology and pharmacology.

In the field of environmental health, we have accumulated a vast knowledge base suggesting that numerous environmental exposures are known to induce acute inflammatory responses. The majority of these investigations focus specifically on the initiation of inflammation but not on resolution. We are also beginning to understand that some environmental agents, for example air pollutants, induce chronic systemic inflammation through repeated insults. Greater understanding of the mechanisms of inflammation resolution will provide understanding on how chronic exposure-induced systemic inflammation may result from dysregulated resolution pathways. Gaining this knowledge is important in addressing environmental health morbidities particularly in susceptible populations such as the elderly and children with compromised/underdeveloped immune systems.

To initiate a coordinated effort on this emerging field, the NIEHS hosted a Trans-NIH workshop on “Inflammation Resolution Biology” in March 2019. The one-and-half-day workshop deliberations and panel discussion sessions identified both long-term and short-term goals to promote research in this field. The recommendations include characterization of resolution pathways across the spectrum; expanding our current knowledge on the transition from acute inflammation to chronic inflammation; linking resolution biology to chronic disease conditions; and translation of mechanistic findings from animal models to human disease conditions.

### **Research Goals and Scope**

Given the broader scope of this field that overlaps with the mission of several ICs, the following two-pronged approach is proposed. As a trans-NIH effort, we will issue a Notice of Special Interest (NOSI) aimed at filling the gaps and needs identified by the participating ICs by stimulating multidisciplinary research efforts to characterize fundamental molecular, cellular and physiological pathways involved in the resolution of inflammation as outlined above. Along with this global effort, the NIEHS intends to issue an FOA, in parallel, to support a more narrowly focused research program to examine the impacts of the environmental exposures on the resolution of inflammation, specifically in the context of air pollution exposure and its multiorgan impacts.

Both acute and chronic exposure to air pollutants- ozone and PM<sub>2.5</sub> have been found to induce lung inflammation. Studies carried out in the late 1990s and early 2000s, both in animal models and limited human studies, strongly suggested induction of lung inflammation and its delayed resolution on chronic exposure to ozone and PM<sub>2.5</sub>. An American Heart Association statement issued in 2012 suggested the potential for chronic PM<sub>2.5</sub> exposure to cause a systemic inflammatory state and its associated impact on extrapulmonary systems. Limited studies that explored nutritional interventions to reduce inflammation both in animal models and human subjects had mixed response. These efforts were aimed at inhibiting inflammation, rather than promoting its complete resolution. Gaining insights into how air pollutants may contribute to unresolved or impaired resolution of inflammation is critical to developing a strong scientific underpinning for preventive or intervention strategies. To fill this gap, there is a need to develop a focused research program aimed at air pollution-induced cardiopulmonary, neuronal inflammation, as well as chronic inflammatory conditions, such as diabetes and obesity. Research outcomes from these efforts may aid in extending these findings to other exposures in the future.

The NIEHS FOA will support the research inquiries ranging from transcriptional, epigenetic, metabolomic approaches to profile different phases of inflammation and resolution on exposure to air pollutants. A variety of model systems including chronic disease models may be used to investigate air pollution and its constituents known to induce or exacerbate acute inflammatory response. Chronic exposure studies may include use of neonatal, adult, or older adult animals of both genders, as well as nutritional or pharmacological interventions that

may aid in the characterization of chronic inflammation phenotype or disease exacerbations as a result of exposure to air pollutants.

### **Mechanism and Justification**

A Trans-NIH NOSI will solicit research on the fundamental mechanisms of inflammation resolution and the features which distinguish resolution from pro- and anti-inflammatory pathways. This will be linked to an NIEHS focused FOA that will utilize the R01 mechanism to encourage multi-PI projects to bring multidisciplinary expertise required to understand the impact of environmental exposure on resolution in chronic exposure and disease states.

This solicitation will stimulate research in this understudied area of inflammation resolution in the context of environmental exposure. The research outcomes from this effort will have potential translational value to explore nutritional intervention and preventive strategies. In addition, this research program will support the NIEHS 2018-2023 Strategic Plan Theme 1, Goal 2 “Advancing Environmental Health Sciences, Individual Susceptibility” and Theme 2, Goal 4 “Promoting Translation – Data to Knowledge to Action.