

# Research

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## **Inflammation, Cancer epigenetics and Metabolism**

Inflammation involving the innate and adaptive immune systems is a normal response to infection. However, it is now known that when allowed to continue unchecked, chronic inflammation is a key underlying cause for the development of autoimmune disorders, neurodegenerative diseases, metabolic syndromes such as diabetes and cancer. Our lab studies a transcription factor called NFκB which is a master regulator of inflammation. Indeed deregulated activity of NFκB precedes and is causally linked to chronic inflammation and the development of several human ailments including metabolic syndromes and cancers. However, given that NFκB signaling is also essential for many housekeeping cellular and developmental events in normal human beings, simply blocking NFκB to curb inflammation is not an option. Hence deciphering the regulation of NFκB signaling is crucial to understanding the mechanism and role of uncontrolled/unwanted NFκB activity seen in human ailments and in developing better and safer anti-inflammatory drug. We are focusing our efforts to identify targets that will help develop drugs which will block NFκB /inflammation more selectively and not generically and hence may have less side effects.

### a) Mechanisms that initiate and maintain chronic inflammation in cancer

Chronic Inflammation such as that triggered by infectious agents is a key driver of human cancers. Two sets of Nobel prizes were awarded in last 7 years (a) to discovery of Helicobacter as cause of gastric cancers (2005) and (b) to the discovery of Human Papilloma Virus as a causative agent for cervical cancer (2008). However, even in cancers where these infectious agents are not present, inflammation is now known as a key driver. That is why people on aspirin (an anti-inflammatory drug) have significantly lower risk of some cancers and on the other hand, obese individual (who have chronic inflammation) without infectious agents have more cancers of certain kind. But what activates and sustains chronic inflammation in cancers is not understood at all. Another hallmark of all human cancers is that cancer cells divide endlessly and for this they need an enzyme called telomerase (discovery of which received Nobel prize in 2009). But many pieces of evidence suggest that telomerase enzyme has other roles apart from making cells divide endlessly. We find time that telomerase enzyme, is the key missing link that in addition to its role in cell division also kick starts and maintains chronic inflammation in cancers. Our findings have immense therapeutic implications and we are developing drugs blocking this enzyme and find that in experimental settings such therapies are showing promising results in blocking cancer inflammation and cancer cell division.

### b) New epigenetic controls of inflammation

Deciphering the regulation of critical regulators of inflammation such as NFκB is crucial to understanding the mechanism and role of constitutive NFκB activity seen in human ailments. Given that over 200 physiological stimuli activate NFκB, which in turn regulates an equally large number of genes, understanding how specificity is generated in such a pleiotropic pathway is also a major challenge. Using large-scale functional genomics and proteomic approaches, our group has identified several novel modifiers of NFκB activity. Using genetic and epigenetic approaches, we are keen to decipher the mechanisms by which these novel regulators modulate NFκB and hence chronic inflammation in human ailments.

#### c) Mechanisms that regulate chronic inflammation in metabolic syndrome

Type 2 diabetes (T2D) and one of its major risk factors, obesity are pandemic problem. Inherent genetic predispositions in combination with inappropriate diet and sedentary lifestyle contribute to the pathogenesis of these disorders. A better understanding of inflammatory signaling is critical for development of therapeutic strategies towards T2DM and obesity. As part of a directed screen to identify molecules that respond to dietary and inflammatory cues in adipose tissue during development of obesity and insulin resistance, we have identified several signaling molecules. Of particular mention is a protein called NUCKS (Nuclear Ubiquitous Casein and cyclin-dependent Kinase Substrate), expression of which is inversely correlated with body mass index in humans and body fat in mice. Ablation of NUCKS results in weight gain, increased body fat accumulation, glucose intolerance and insulin resistance. NUCKS is a key chromatin modifier and transcriptional regulator of a number of signaling genes. We are characterizing the roles of proteins like NUCKS in metabolic syndromes.

#### **Prospective Graduate Students:**

##### **SINGA fellowships:**

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renowned researchers in A\*STAR labs. This award will normally be for students in the later years of a Bachelor or Master level program. Students considering PhD studies in A\*STAR are encouraged to apply.

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