

## Loss of immune surveillance in aging (unresolved inflammation): Common denominator in chronic diseases and cancer

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Despite heavy public investment in the war against cancer for over four decades, progress in understanding the biology of cancer and how to cure it has been too slow, fragmentary and fuzzy. Few, if any, of the many heavily funded projects in cancer research, drug development or clinical trials proven worthy of translation into diagnosis, prevention or therapy, while the incidence of cancer is projected to rise even higher in the next decade around the globe. Claimed 'targeted' therapies or 'personalized' medicine using potent inhibitors of growth factors have failed patients at the rate of about 90%, due to life-threatening side effects. This presentation will focus on a fundamental but forgotten role that the loss of cancer (immune) surveillance or chronic inflammation plays in the induction of a wide range of chronic diseases and cancer during aging. The results of our 'accidental' discoveries in 1980's on experimental models of acute and chronic inflammatory diseases are suggestive of the first evidence for a direct association between inflammation and tumorigenesis and angiogenesis. Analyses of data that led to first report on developmental phases of inflammation-induced immune dysfunction were extended at NCI/NIH since 1998 for the design of clinical trials, utilization of patient biospecimen, cancer molecular diagnosis and prevention. Acute inflammation was recently defined as an inherent and highly regulated property of immune system cross talks with non-immune systems (vasculature and neuro-endocrine) that protect the body throughout life. It possesses 2 biologically opposing arms, termed 'Yin' (pro-inflammatory, apoptosis or tumoricidal) and 'Yang' (anti-inflammatory, wound healing or tumorigenic) processes. Chronic (sustained oxidative stress, sub-clinical, persistent or unresolved) inflammation was defined as the loss of balance between 'Yin' and 'Yang' (tumoricidal v tumorigenic) properties of immune system that would create immunological chaos in target tissues. Unresolved inflammation, in all likelihood, is a common denominator in the induction of nearly all age-associated chronic diseases such as allergies, autoimmune and neurodegenerative diseases, diabetes and cardiovascular complications or cancer. Chronic inflammation or potent pathogen-induced severe alterations in immune dynamics (immune tsunami) could differentially impact tissues/organs that are naturally immune-responsive (e.g., epithelia, endothelia, stroma, vasculature) or immune-privileged (e.g., blood brain barrier/BBB, CNS, cornea, neuroretina, reproductive system, hair follicles) and damaging architectural integrity of susceptible tissues and the induction of acute (e.g., sepsis) or chronic diseases or cancer. Future directions in design of clinical trials will be proposed based on promotion of inherent ability of immune surveillance, or the maintenance of balance between 'Yin' and 'Yang' of acute inflammation. The ultimate goal is to help resolve the mystery around cancer biology and end the misery of cancer-stricken public.

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