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Unresolved inflammation: Immune dynamics of aging process and tumorigenesis

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For over 150 years increasing publications reported on circumstantial association between injuries/inflammation and cancer. However, until recently no data were available on a direct link between inflammation and tumor development. In 1980's, we established experimental models of acute and chronic inflammatory diseases in conjunctival associated lymphoid tissues (CALTs) in guinea pigs by topical application of fluoresceinyl ovalbumin (FLOA) for up to 30 months. Analyses of series of clinical and immunopathological findings demonstrated at least three distinct developmental phases of immune responses: a) Acute phase, involving IgE-Fc receptor aggregation and mast cell degranulation, histamine and prostaglandin release and vascular hyperpermeability; b) Intermediate phase, involving desensitization phenomenon, loss/exhaustion of mast cells function, infiltration of inflammatory cells (e.g., eosinophils) into subepithelium and goblet cells and neovascularization; c) Chronic phase, induction of massive lymphoid hyperplasia, follicular formation with germinal centers, increased swollen goblet cells, increased degranulation of mast cells ('leaky'), increased activity of macrophages, extensive epithelial thickening and thinning, changes in local antibody profiles (IgG1/IgG2 ratios) and angiogenesis.

The results are suggestive of a first evidence for direct association between inflammation and development of tumor-like lesions in lymphoid tissues, extensive changes in adjacent epithelium and angiogenesis. Mast cells are effector cells within innate immunity and play important roles, being 'tumoricidal' in their granulated (mature-resting) status during acute inflammation, while they possess 'tumorigenic' properties when partially granulated ('leaky') under persistent inflammation.

Designs of Clinical Trials and Drug Development: Unresolved inflammation is loss of balance between 'tumoricidal' vs. 'tumorigenic' (pleiotropy or 'Yin' and 'Yang') properties of acute inflammation. Promotion of innate and adaptive immune cells plays key roles in tumor surveillance ability of host tissues. Designs of suitable clinical trials and drug development will be discussed based on a concept that chronic inflammation is a common denominator in the genesis and progression of nearly all age-associated chronic diseases including cancer.

Recent Selected References:

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