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NF-kB: A Novel Therapeutic Target for Cancer

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Usually, the onset of all types of cancers is characterized by a genetic mutation leading to cell proliferation, which further increases the probability of genetic damage. Similar to genetic causes, external stimuli is equally important for the initiation and progression of cancers. If environmental factors such as radiation and exposure to carcinogens are excluded a potential candidate for cancer causation is chronic inflammation (Balkwill, 2004). Chronic inflammation accounts for 20% of all types of human cancers (Coussens et. al., 2004). Population studies have demonstrated the increase susceptibility of cells to be come cancerous when exposed to chronic inflammation. Although, a lot is known regarding the pathological links between inflammation and cancer, the signal transduction pathways underlying them is still unresolved. The study by Pikarsky et. al., (2004) explored this question. They proposed the nuclear factor (NF-kB) to be a pivotal protein in the link between inflammation and cancer. NF-kB characterizes all inflammatory responses (Li et. al., 2002) and is also a major hallmark of tumors (Lin et. al., 2003; Mayo, 2000).

In order to study this link they chose to use Mrd2 knockout mice, which are characterized by hepatocellular carcinoma (HCC; Nakamoto, 1998). HCC progresses through distinct stages of inflammation, dysplasia, carcinoma and metastasis, thereby making it an ideal system for studying the connection between inflammations and cancer (Block, 2003). When compared to control mice, Pikarsky et. al., (2004) noted high expression of NF-kB in HCC mice demonstrating a potential link between NF- kB and cancer. To further confirm the direct relationship between NF-kB and the progression of cancer, they treated HCC mice with anti-inflammatory drugs, which resulted in the rescue of cells from becoming cancerous. The study also showed that the expression levels of NF- kB varied with the stage of the cancerous cell thereby showing a regulatory mechanism for NF-kB expression.

To investigate the regulatory mechanism that controls NF-kB levels, Pikarsky et. al., (2004) chose the tumor-necrosis-facor (TNF-alpha), since it is a common pro-inflammatory mediator that is actively expressed by neighboring cells that directly controls inflammatory responses. Treating the HCC mice liver extracts with anti-TNF-alpha antibodies that inhibited TNF-alpha activity showed ablation of cancer progression and decrease levels of MF-Kb. From the perspective of tumorogenesis, NF- kB can thus be placed as one of the several proteins that expedite the progression of cancer. By definition, cancer refers to uncontrolled cell division with the complete inhibition of apoptotic mechanisms of normal cells. To test the possibility of NF-kB inhibiting apoptosis, Pikarsky et al., (2004) demonstrated increased apoptosis in cells treated with anti-inflammatory drugs. This further confirms the significant role of NF-kB in HCC progression.

Experimentally, Pikarsky et. al., clearly demonstrates the link between NF-kB and cancer through TNF-alpha. However, the study has not answered the question of whether the anti-cancerous properties of NF-kB and TNF-alpha is linked with its roles in the signal transduction pathways underlying inflammation. Since, they have not investigated the cytokine expression with the changes in NF-kB and TNF-alpha. It is important to investigate cytokine expression because they are the workhorses of the inflammatory system. Therefore, it possible for us to propose a model where over expressed NF-kB and TNF-alpha are acting as oncogenes through unknown molecular pathways. However, most recent studies by Greten et. al., (2004) that showed increased cytokine and TNF-alpha in cancerous microenvironment supports the model of Pikarsky et. al., (2004). From a therapeutic viewpoint, the most crucial discovery by Pikarsky's group was the late effect of NF-kB in cancer progression. They did not see any effect of NF-kB over expression in the initial stages of tumorogeneisis. However, NF-kB inactivation in the later stages led to the suppression of tumor formation suggesting that drugs targeting NF-kB can potentially act us good therapies for cancers at late stages. The late effect of NF-kB also indicates the complexity associated with cancer progression. This further expands the field with more novel questions such as the regulatory mechanisms other than TNF-alpha for NF-kB.

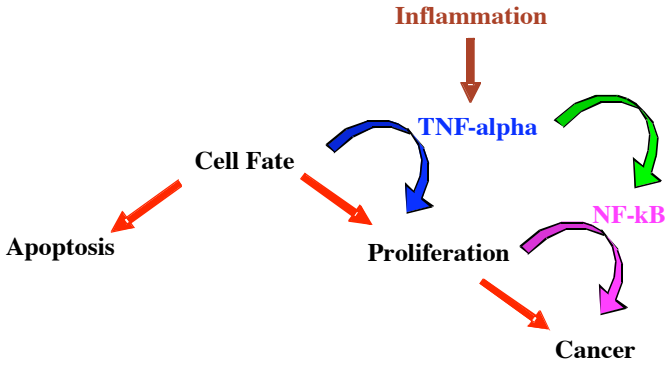

Figure 1. Control of Cell Fate by NF-kB and TNF-alpha
During inflammatory responses, cytokines and several other unknown signals activate TNF-alpha. Once activated, TNF-alpha can induce excessive cell proliferation and therefore cancer. Activation of TNF-alpha also activates NF-kB, which can further enhance the proression of proliferating cells to tumors.

In the second part of Pikarsky's study shows the anti-apoptotic properties of NF-Kb and uses it as a premise to propose the therapeutic potential of NF-kb. However, we should also consider the impact of inhibiting a major inflammatory protein such as NF-kb or TNF-alpha for tumor suppression. Since, it may affect the normal immuno and inflammatory responses of our body. Thus, if either NF-kB or TNF-alpha is used as a target for tumor suppressing drugs, the treatment must be done in a way that does not affect the regular homeostasis of the body. Although, Pikarsky's study demonstrates the halting of tumor progression by inhibiting NF-kB or TNF-alpha, the study needs to be repeated in other types of inflammatory cancers for further exploring the potential of using them as targets for cancer-drug development.

In brief, the study exposed the role of NF-kB and TNF-alpha in maintaining the delicate balance between cell proliferation and apoptosis (Figure. 1). The study also reveals two novel targets—a) NF-kB and b) TNF-alpha for developing cancer drugs. When compared to other therapeutic targets of cancer, the novelty is the unique ways in which two molecular targets of the same signal transduction pathway (Figure 1) acts. Blocking TNF-alpha function will allow the eradication of the primary causes of cancer. NF-kB inhibition will help in halt tumor progression and eliminates tumors thereby making it an ideal target for drugs to be used at later stages of cancers.

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