Innate Resistance, Inflammation, and Carcinogenesis

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The interaction of the inflammatory mediators and innate and immune effector cells with carcinogenesis and tumor progression is complicated and results in effects that either favor or impede tumor progression. The simple concept that early inflammation is necessary for carcinogenesis whereas inflammatory and immune response prevent tumor progression has been replaced by a more subtle understanding that the degree of inflammation and the type of inflammatory/immune response are responsible for tilting the balance between tumor progression and regression. Furthermore, it is becoming evident that the processes that the organisms use for resistance to infections are related to the mechanisms essential for tissue homeostasis and morphogenesis. In order to address these mechanisms in carcinogenesis, we studied the role of MyD88-linked innate receptors in skin and colon chemically induced carcinogenesis.

Role of MyD88 in colon and skin carcinogenesis

MyD88 is required for signaling through all Toll-like receptors except TLR3 and through the IL-1 receptor family. Studies by us and other have shown that expression of MyD88 is required for carcinogenesis in the skin, colon, and liver. In skin carcinogenesis, expression of MyD88 appears to be required for optimal papilloma formation in both radiosensitive hematopoietic cells and radioresistant host cells. In order to investigate whether signaling through MyD88 in keratinocytes was important for tumorigenesis, we transformed in vitro keratinocytes with oncogeneic ras and we found that MyD88 expression in these cells was necessary for production of chemokines, metallo-proteases, and hematopoietic growth factors and also for the ras-mediated inhibition of keratinocyte differentiation. When grafted in vivo ras-transformed MyD-/- formed tumors much slower than wild type cells.. We identified that the lack of expression of MyD88 prevented the expression of the full ras-transformation program by blocking signaling through the interleukin-1 receptor.

MyD88-/- mice are very susceptible to irradiation- and DSS-induced colitis due to defective epithelial mucosa repair possibly reflecting a role of microbial-derived ligands to stimulate TLR-dependent tissue homeostasis in physiological conditions and upon injury. Although highly resistant to all other model of carcinogenesis, MyD88-/- mice are very susceptible to AOM/DSS induced carcinogenesis, possibly due to their defective tissue repair after DSS-induced mucosal damage. IL-18-/- but not IL-1R-/- mice partially reproduce the phenotype of MyD88-/- mice: they are very susceptible to DSS colitis and AOM/DSS carcinogenesis.