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The transient and constitutive inflammatory signaling in tumorigenesis

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It is estimated that about 25% of cancers appear due to chronic infection or other types of chronic inflammation. However, almost all cancers have abnormal or/and constitutive inflammatory signaling activation. Much progress has been made in elucidating the mechanisms by which inflammatory signaling drives tumor progression and metastasis. However, how the abnormal and constitutive inflammatory signaling is initiated and maintained in transforming cells, and its roles in the early stages of tumorigenesis, such as cell transformation, are largely unknown.[1-3] In a recent study,[4] we established an in vitro co-culture cell transformation system. Using this system we discovered that a constitutively activated, feedforward inflammatory signaling circuit normally harnessed by miR-200c is established during cell transformation, and that this circuit plays crucial roles in cell transformation and tumorigenesis. This circuit is comprised of IL6, miR-200c, PTPRZ1 and JNK2 and the transcription factors HSF1, estrogen receptor (ERα), ZEB1, p65/RelA and c-Jun (**Fig. 1A**). Importantly, this constitutive inflammatory signaling circuit is manifest in human cancer cells and in ErbB2 (Neu)-driven breast cancer transgenic mouse models, where deletion of IL6 disables this circuit and dramatically impairs mammary tumorigenesis.

The feedforward nature of this constitutive inflammatory signaling circuit provides explanations for the common phenomenon that many (inflammatory) signaling pathways are interplayed and simultaneously constitutively activated in the same cancer cells. It also demonstrated that the cause and maintenance of the constitutive activation of inflammatory signaling are different from those of the transient activation of inflammatory signaling. For example, the maintenance of constitutive p65 in this circuit is not dependent on IKK, whose activation leads to transient activation of NFκB. Therefore, therapeutic strategies that target constitutively activated pathways should be different from those that target transient activation of pathways.

The roles of transiently and constitutively activated inflammatory signaling in tumorigenesis are different. A transient inflammatory signal is clearly insufficient to transform normal cells. However, as demonstrated in our co-culture model, the transient inflammatory signaling from immune cells can trigger the transformation of those cells (MCF-10a) that have already accumulated some genetic or/and epigenetic alterations that provide the basis for the oncogenic transformation. Although the transient inflammatory signaling initiates the transformation process, the maintenance of the transformed state of malignant cells is dependent on the constitutively activated inflammatory signaling circuit that is formed during the transformation process. Therefore, it is speculated that like MCF-10a cells, "normal" cells in human body accumulated with pre-cancerous mutations will be at highrisk for inflammatory cytokine-driven oncogenic transformation.

Abnormal and constitutive inflammatory signaling in cancer cells may not only be provoked by extrinsic inflammatory signals from the tumor microenvironment, but can also occur in a cancer cell-intrinsic fashion.[6] Activated oncogenes or inactivated tumor suppressors in cancer cells can induce abnormal and constitutive inflammatory signaling through various means.[2,6] While our co-culture model showed that the constitutive activation of this circuit was triggered by transient inflammatory signaling that activates IL6, it is most likely that in other pathological circumstances this circuit can also be triggered by other extrinsic signaling from microenvironment or intrinsic signaling in pre-transformed cells (such as oncogene activation and tumor suppressor inactivation) that activates anyone of p65, JNK2, IL6, STAT3, ZEB1 or HSF1 or suppresses microRNA-200c or PTPRZ1 expression. Once activated, the circuit keeps its constant activation through its positive feedforward nature. While the constitutive activation of the components in the circuit is interdependent, each constitutively activated component regulates its downstream genes that together drive transformation and tumorigenesis (**Fig. 1B**). Therefore, interventions that target any component of the circuit should trigger a therapeutic response.

Another interesting observation from our study was the loss of ERα in transformed cells. The inflammatory signaling circuit was constitutively activated in all tested ER-negative human breast cancer cell lines. ERα signaling suppresses inflammation and ER-negative breast cancers are usually more aggressive and metastatic,[7] which is in accordance with our observations that the cells with the active circuit are more mesenchymal. On the other hand, inflammation also suppresses ERα signaling in ER-positive breast cancer cells,[8] and loss of ERα has been observed during the progression from benign to invasive carcinoma.[9] In addition, deregulation or loss of ERα expression is one of the mechanisms that have been suggested to confer endocrine

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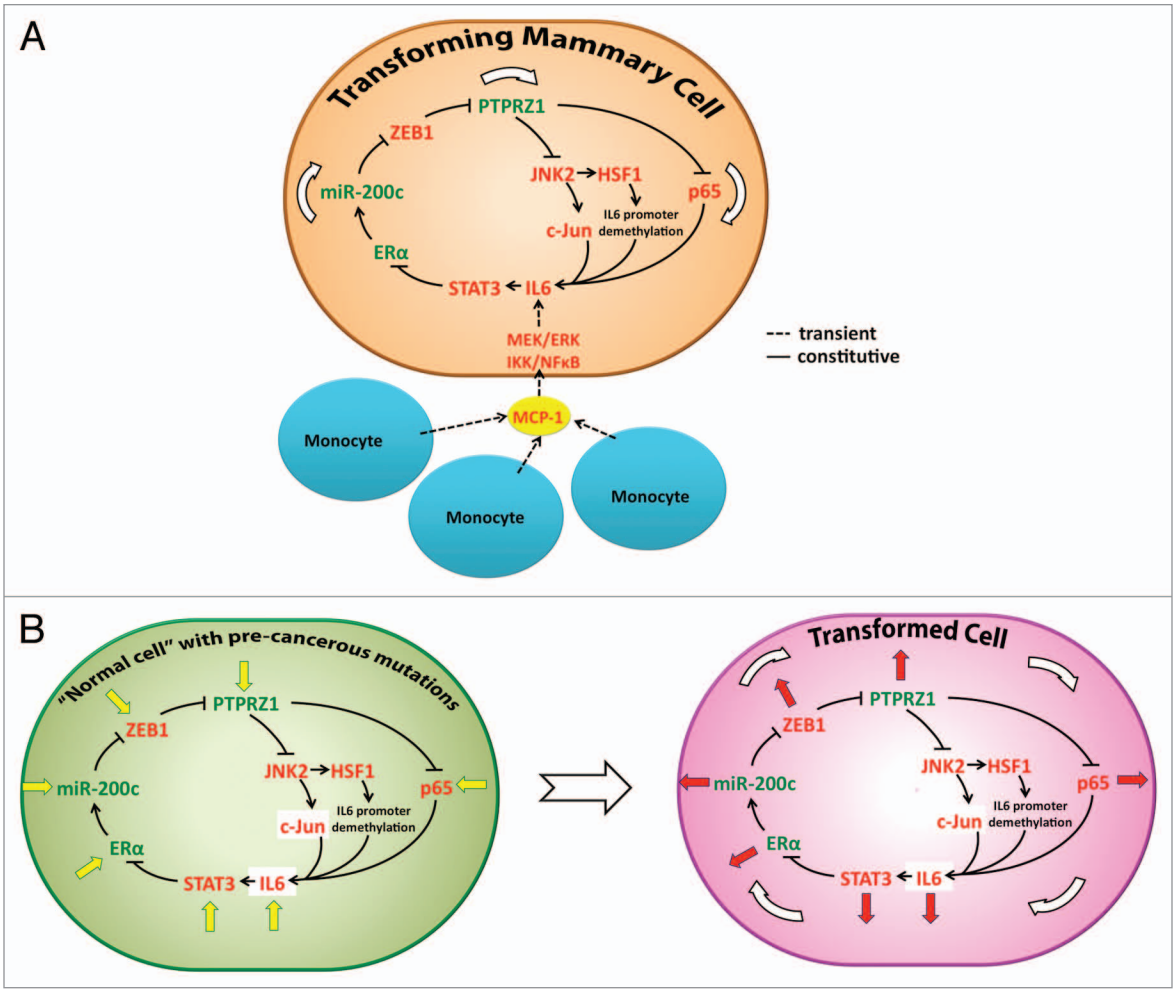

Figure 1. (A) Schematic overview of monocyte-induced transformation of immortal mammary epithelial cells into breast cancer cells. The red components of the circuit are overexpressed or activated and the green ones are repressed/deactivated upon oncogenic transformation. (B) Proposed model of a constitutively activated inflammatory signaling circuit during cell transformation and tumorigenesis. Yellow arrow, triggered by extrinsic or/and intrinsic signaling; red arrow, regulating downstream genes related to tumor development.

resistance in patients with ER-positive breast cancer.[10] Thus, we speculate that the inflammatory circuit described in our study may play an important role in ER-negative breast tumorigenesis and in the development of endocrine resistance in ER-positive breast cancer.

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