

A Putative Link Among the Triad: Inflammation, Reprogramming, and Cancer

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ABSTRACT

Induced pluripotent stem cells (iPSCs) are generated during ex vivo artificial process, referred to as reprogramming process; on the other hand, reprogramming has been demonstrated to be also involved in human pathological process *in vivo*, such as metaplastic change. Moreover, a surprising link between reprogramming and inflammation has been revealed. In this Editorial at the triple crossroads, I discuss a novel link among inflammation, reprogramming, and cancer.

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Key words: Reprogramming; Inflammation; Transformation; Transdifferentiation; *Helicobacter pylori*; Intestinal metaplasia; TLR3

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Accumulating evidence suggests that inflammation is associated with tumorigenesis; for example, *Helicobacter pylori* induces chronic inflammation in gastric mucosa, and subsequently there will be progression from normal gastric mucosa to intestinal metaplasia, from which adenocarcinoma arises. Recent study indicates that, during inflammation, emerging reprogramming process results in development of premalignant lesion^[1], which is the first demonstration of reprogramming within human cancer. Another interesting paper published recently shows that inflammation (innate immunity) and

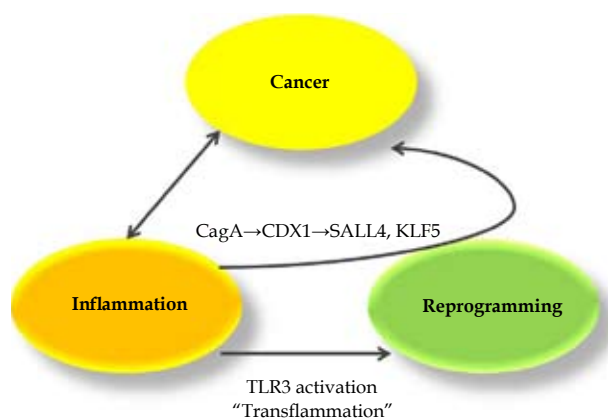


Figure 1 Putative scheme of triad link. Cancerous lesions are known to arise from inflammatory foci. On the other hand, Fujii *et al*^[1] reveal that *Helicobacter pylori* CagA-induced CDX1 activates stemness-associated reprogramming factors SALL4 and KLF5. These factors converted gastric cells into tissue stem-like progenitor cells, which then transdifferentiated into intestinal cells, leading to intestinal metaplasia. Chronic bacterial infection (inflammation) might affect carcinogenesis via induction of reprogramming. Furthermore, Lee *et al*^[2] unmask the link between inflammation and reprogramming. Activation of inflammatory pathways via TLR3 is required for efficient nuclear reprogramming, and this state is referred to as "transflammation". TLR3; toll-like receptor-3.

nuclear reprogramming are linked via toll-like receptor-3 (TLR3) activation^[2]. As shown in figure 1, there is a possibility that the triad (inflammation, reprogramming, and cancer) might be closely related, and in this editorial, the details would be overviewed, followed by the discussion on unanswered questions.

The article by Fujii *et al*^[1] demonstrates that CDX1-induced stemness-associated reprogramming factors (SALL4 and KLF5) convert gastric epithelial cells into intestinal epithelial cells. *Helicobacter pylori*-induced chronic gastritis is a major cause of gastric intestinal metaplasia, from which intestinal-type gastric adenocarcinoma arises. Metaplasia is histological change from one tissue type to another, and is associated with neoplastic transformation via metaplasia-dysplasia-carcinoma sequence. *Helicobacter pylori* CagA aberrantly stimulates β -catenin signaling and induces Wnt target genes including CDX1. It would be significant that the study by Fujii *et al*^[1] has shown that CDX1 induces stemness-associated reprogramming factors SALL4 and KLF5, which is the first demonstration of the involvement of reprogramming factors in

metaplastic changes. Although generation of induced pluripotent stem cells (iPSCs) is known to be *ex vivo* artificial process, it has been shown that reprogramming process is also involved in pathological process *in vivo*, such as metaplastic change. Collectively, chronic infection with *Helicobacter pylori* could lead to gastric intestinal metaplasia via CDX1-induced stemness-associated reprogramming factors SALL4 and KLF5. As Fujii *et al.*^[1] discussed, cancer stem cells possess properties that are shared in common with tissue stem/progenitor cells, suggesting that acquisition of stemness traits may link to cell transformation, and that a transition through intestinal stem/progenitor-like states via dedifferentiation may predispose cells to undergo neoplastic changes; which may explain why intestinal metaplasia is a precancerous lesion of the stomach^[1].

Next, Lee *et al.*^[2] have recently revealed that activation of inflammatory pathways is required for efficient reprogramming. TLR3 activation is identified as a factor for efficient nuclear reprogramming, indicating an unexpected link between innate immunity and nuclear reprogramming^[2]. Indeed, knockdown of TLR3 pathway inhibits nuclear reprogramming. Furthermore, TLR3 activation induces an open chromatin state, which increases cell plasticity as epigenetic modifiers. Lee *et al.*^[2] speculate that this cell state may enhance induction of pluripotency, transdifferentiation, or even malignant transformation, and the authors refer to this state as “transflammation”. Regarding transdifferentiation, as Ding *et al.*^[3] first demonstrated, short transient expression of reprogramming factors is enough to induce a partially reprogrammed state that is suitable for conversion into specific cell types. This is known as lineage conversion by plastic induction.

Based on these findings, it would be interesting to clarify whether TLR3 activation is also involved in intestinal metaplasia, especially in human gastric samples, in the study by Fujii *et al.*^[1]. The hypothesis is that inflammation by innate immunity would promote reprogramming in cooperation with SALL4 and KLF5, which leads to intestinal metaplasia. If so, knockdown of TLR3 might result in change of phenotype, implying the possibility that anti-inflammatory strategy would be linked with prevention of precancerous lesion.

It has been suggested that infection with *Helicobacter pylori* is associated with activation of TLR2, 4, 5^[4], but not TLR3. Since activation of TLR3 is known to be induced by infection of virus including EB virus, and since EB virus-encoded small RNA (EBER) induces signaling from TLR3^[5], it would be also interesting to examine whether the presence of EBER would enhance reprogramming in

cooperation with SALL4 and KLF5 and would accelerate the process of intestinal metaplasia.

As the authors mentioned^[1], SALL4 positively regulates Oct4, c-Myc, Sox2, and Klf4. It would be also helpful if expression of iPSC-four-factors in human gastric samples would be clarified in future. Another interesting question to be addressed is whether local invasion (as well as distant metastasis) from a malignant tumor with a special histological type may result from reprogramming of normal cells. Implication of reprogramming in the pathogenesis should be clarified.

Collectively, the first documentation of reprogramming in human disease would be outstanding, and it would be believed that modulation in the plasticity of lineage commitment might contribute to prevention of cancer in the near future.

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