BID: a potential link between DNA damage and inflammatory responses in tumourigenesis

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Abstract

Introduction
The BH3-only family members BID is a pro-apoptotic protein of the Bcl-2 family that is crucial for mitochondria-mediated apoptosis in many cell systems. However, some recent studies have found that BID may also play a pro-survival role. It can be the intermediate substance of deoxyribonucleic acid damage response, which is connected with the phosphorylation of BID. Likewise, BID−/− cells in mice decrease the release of inflammatory factors. BID is also a mediator of inflammation.

Hypothesis
Based on the above point of view, we hypothesize that BID, a novel convergent molecular, is a potential link between the inflammation and the irreparable deoxyribonucleic acid damage responses in tumourigenesis.

Evaluation of hypothesis
There is clear evidence that inflammation plays a critical role in tumourigenesis, and some of the molecular mechanisms have been elucidated, which show that the inflammation in tumourigenesis is related to the deoxyribonucleic acid damage. Inflammatory cells turn into cancer cells when their deoxyribonucleic acid is destroyed. Most of the times, damaged deoxyribonucleic acid is repaired by BID phosphorylation by the kinase ataxia-telangiectasia mutated involved in the deoxyribonucleic acid repair response. But if it is not repaired, the damaged deoxyribonucleic acid initiates the apoptosis of cells or the organs or tumourigenesis. Moreover, BID drives the production of pro-inflammation cytokine and chemokines resulting in either increasing of stressed cells or a local inflammatory response. So, we consider that inflammation depends on BID to link Deoxyribonucleic acid damage response.

Conclusion
BID plays a key regulatory role in both the inflammation and deoxyribonucleic acid damage responses. However, such as tBID, p-BID acts as its work forms may be activated in different time. In brief, BID, a novel convergent molecular, is a potential link between the inflammation and the irreparable deoxyribonucleic acid damage responses in tumourigenesis. However, much more work needs to be done to demonstrate the hypothesis.

Introduction
BID was originally discovered as a binding partner of both Bcl-2 and Bax, and later identified as a substrate of apical caspase-8 in the apoptotic pathways. The cleaved BID (tBID) by the caspase-8 is an active form, which is modified by myristoylation and translocates into mitochondria, where it activates oligomerisation of Bak or Bax and promotes the release of cytochrome c. Cytochrome c in turn activates the apoptotic cascade of caspases-9 and -3, leading to cell death. BID pro-apoptotic function has been identified and acknowledged. However, according to BID structure, we believe that the function of BID has not been conclusively demonstrated, as for several other aspects of BID activation and function that have been outlined here.

The network of BID in the inflammatory response has been internalized elucidated by Saleh Yeretssian et al. Conjunction with other studies indicates that the function of BID in inflammation and immunity is independent of its apoptotic function, and BID is at the centre of the cellular decision to induce innate immune responses or commit suicide by apoptosis. Depletion of BID leads to a marked reduction in interleukin (IL)-8 production. Meanwhile, IL-6 production was significantly blunted in BID-deficient macrophages. Both of them inhibit activation of NF-κB and MAPKs (ERK1/2, p38 and JNK) pathways. Interestingly, this paper has observed that BID phosphorylation by casein kinases I and II on serine residues proximal to the cleavage site hampers its processing and promotes cell survival. When HT-29 cells are treated by the NOD1 activator γTri-DAP, BID is not cleaved but phosphorylated. Mutation of phosphorylation sites in BID (BID (S64A), BID (S65A) and BID (S65A)) significantly blunted MDP-induced IL-6 production. Contemporarily, compared BID−/− mice with WT mice, the pronounced peritonitis was marked by infiltration of Gr1+ neutrophils when treated with γTri-DAP. Thus, BID phosphorylation is related to the inflammation, and at the same time it survives the cells.

Simultaneously, BID is also involved in DNA damage response. DNA damage leads to generation of DNA single- and double-strand breaks (DSBs). DSBs activate downstream DNA damage response pathways mediated by the phosphoinositide...
3-kinase (PI3K)-related protein kinases (PIKKs)\(^\text{20}\). The PIKK family consists of five serine/threonine kinases, including ataxia-telangiectasia mutated (ATM), ATM and Rad3-related (ATR)\(^\text{21}\). Upon DNA damage, kinase ATM activation is by phosphorylation, which in turn phosphorylates BID at serine 61 (in mouse BID) and serine 78 (in mouse and human BID)\(^\text{16,17}\). BID phosphorylation occurs only in response to DNA double-strand breaks\(^\text{16}\). ATM-mediated BID phosphorylation might serve as a mechanism to inhibit apoptotic activity or alternatively as a mechanism to activate a pro-survival activity of BID. In addition, the BID is specifically required for S-phase arrest\(^\text{16,17}\). Thus, BID has been involved in more mechanisms and biological roles. For example, not only the tBID, but also BID play important roles both in apoptotic pathways and inflammation-survival pathways. Obviously, BID phosphorylation plays an important role in inflammation and DNA damage response. BID phosphorylation facilitates inflammation progress, and promotes the release of pro-inflammatory cytokines. Simultaneously, the phosphorylation of BID is also involved in the DNA damage response.

As we all know, some chronic inflammation that precedes tumour development caused by immune deregulation and autoimmunity, such as inflammatory bowel disease has greatly increased the risk of colorectal cancer\(^\text{22}\). The role of inflammation in tumourgenesis is now generally accepted, and it has become evident that an inflammatory microenvironment is an essential component of all tumours, including some in which a direct causal relationship with inflammation is not yet fully proven\(^\text{23–25}\). Inflammation-induced mutagenesis may also result in inactivation or repression of mismatch repair response genes. Once the mismatch repair system has been dismantled, inflammation-induced mutagenesis is enhanced and several important tumour suppressors, such as Tgfb2 and Bax, which harbour microsatellite sequences, may be inactivated\(^\text{26}\). It remains to be shown that any of these inflammation-induced epigenetic mechanisms actually make a critical contribution to tumour initiation\(^\text{27,28}\). The connection between inflammation and tumour initiation is not a one-way street, and much evidence indicates that DNA damage leads to inflammation and thereby promotes tumourigenesis. This has been proved by the model of hepatocellular carcinoma induced by the carcinogen diethylnitrosamine, in which DNA damage contributes to necrotic cell death, resulting in an inflammation reaction that promotes tumour development\(^\text{29}\). A number of oncoproteins (such as Ras, Myc, RET) activate signalling pathways that drive the production of pro-inflammatory cytokines and chemokines (such as IL-6, IL-8, IL-1b, CCL2, CCL20)\(^\text{30}\). Genotoxic stress can also induce expression of NKG2D family members, which serve as ligands for NK and gdT cell receptors, resulting in either elimination of stressed cells or a local inflammation response\(^\text{31}\). In the same vein, mosaic deletion of the DNA repair gene ATR and Tp53 in the skin results in recruitment of CD11b ‘Gr1’ myeloid cells, as a part of a prototypical immune response to ‘altered self’\(^\text{32}\). As mentioned above, the process of inflammation in tumourigenesis is related to irrepairable DNA damage response, and BID not only attends the repairable DNA damage response, but is also involved in the inflammation process.

**Hypothesis**

According to the above point of view, we hypothesize that BID, a novel convergent molecule, is a potential link between the inflammation and the irrepairable DNA damage responses in tumourgenesis (Figure 1).

**Evaluation of Hypothesis**

The authors have referenced some of their own studies in this hypothesis. The protocols of these studies have

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**Figure 1:** Hypothetical illustration of BID is the link of the inflammation and the irrepairable DNA damage response in tumourogenesis.

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been approved by the relevant ethics committees related to the institution in which they were performed.

There is clear evidence that inflammation plays a critical role in tumourigenesis, and some of the molecular mechanisms have been elucidated, including the inflammation in tumourigenesis related to DNA damage. Moreover, several possible links existing between the inflammation and cancer have been proved in the last decade. We have observed that tumour initiation is stroked by inflammatory cells. The inflammation enhances the proliferation of the mutation cells, and then the body prepares for the DNA damage response. Activated inflammatory cells serve as sources of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) that are capable of inducing DNA damage and genomic instability. We also found p53 mutation in many chronic inflammation cells, which may be caused by the oxidative damage. p53 has emerged as a central player in linking death signals through surface death receptors to the core apoptotic mitochondrial pathway and life signals through surface death receptors. Meanwhile, BID deficiency in the sepsis model of cellagulation and puncture (CLP) is able to rescue mice from septic mortality, and this is associated with reduced apoptosis in lymphoid organs as well as the suppression of local and systemic cytokine/chemokine levels during sepsis. Another study has indicated that BID may play a role in promoting hepatocarcinogenesis in response to DNA damage-induced or replicative stress-induced apoptosis or cell cycle arrest. However, a different view from Strasser et al. reported that BID does not function in the DNA damage response. Likewise, BID has also been shown to be required for the maintenance of myeloid homeostasis and suppression of myeloid tumourigenesis. It was known that BID overexpression regulates proliferation and phosphorylation of Akt and MAPKs in response to etoposide-induced DNA damage in hepatocellular carcinoma cells. The activation of Akt and MAPK signalling pathways is thought to be pivotal mechanisms of apoptotic signals in malignant cells.

Nonetheless, in the inflammation environment, the cells release ROS and RNI, which result in DNA damage and genomic instability. However, it is not clear whether ROS and RNI are produced and released by neutrophils or macrophages. By this time, BID is phosphorylated, in nuclear. Indeed, BID drives the production of pro-inflammation cytokine and chemokines (IL-6, IL-8 and IL-1β), resulting in either increasing of stressed cells or a local inflammatory response. Subsequently, DNA damage is easy. In the same vein, under the DNA damage response, BID may active the S-phase checkpoint response or induce the mitochondrial pathway cell death. So, we consider that chronic inflammation depends on BID to link the inflammation response, and BID plays a very important role in the activation of the NF-κB pathway. Moreover, BID−/− cells have no impact on the phosphorylation of IKK and ERK. But, when treated with the activator of the NOD1 signalling pathway, the BID phosphorylation depends on the concentration of the activator. Obviously, BID−/− cells and BID+/+ mice reduce the release of the cytokine. Probably, BID sets about repairing the inflammatory cells at this very moment. Consequently, further research is needed to validate. So, the full-length BID is represented in another form. The more destroyed the DNA or mutated inflammatory cells, the more likely the inflammation in tumourigenesis. As a result, not only the inflammatory cells change into cancer cells, which can be limitless proliferation, but also many cells may go for apoptosis. For the time being, BID results in pro-apoptotic only in the BH-3 protein for which tBID is the acting factor.

Discussion
BID, tBID were considered as a sub-strate of apoptotic pathway, and its pro-apoptotic function have been identified and widely acknowledged. However, in the inflammatory responses, depletion of BID has influence on cytokines expression, such as IL-8, IL-6. Particularly, BID is not cleaved but phosphorylated, and BID phosphorylation is related to the inflammation. Simultaneously, in DNA damage response, BID phosphorylation occurs in response to DNA double-strand breaks. In addition, BID is specifically required for S-phase arrest. So, the hypothesis that BID as a novel convergent molecule, is the link between the inflammation and the irreparable DNA damage responses in tumourigenesis will be well-established.

Conclusion
BID plays a key regulatory role in both the inflammation and DNA damage responses. However, the acting forms are different, and the working time may be the same or different. In brief, BID, a novel convergent molecule, may be a potential link between the inflammation and the irreparable DNA damage responses in tumourigenesis. However, much more work needs to be done to demonstrate the hypothesis.

Abbreviations list
ATM, ataxia-telangiectasia mutated; PIKK, phosphoinositide 3-kinase-related protein kinase; ROS, reactive oxygen species; RNI, reactive nitrogen intermediates; BH3, Bcl-2 homology domain 3; BID, BH3 interacting domain death agonist; Bcl-2, the anti-apoptotic B-cell lymphoma-2; tBID, truncated BID; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MDP, muramyl dipeptide; IL, interleukin; WT, wide type; γ-Tri-DAP, L-Ala-γ-D-Glu-meso-diaminopimelic acid; ATR, attenuated

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Hypothesis

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Concluding paragraph: A better understanding of cell death mechanisms could provide novel therapeutic targets for the treatment of cancer. Further studies are needed to explore the role of BID in the regulation of apoptosis and inflammation in various contexts.

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38. Li Y, Dai C, Li J, Wang W, Song G. Bid-overexpression regulates proliferation and phosphorylation of Akt and MAPKs.