NF-κB is a potential pharmacological target in triple negative breast cancers

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Triple negative breast cancers (TNBCs), characterized by lack of estrogen, progesterone and HER2 receptors, are a highly heterogenous group of tumors which account for about 20% to 25% of all breast cancers. TNBCs are often associated with epithelial-mesenchymal transition and a high propensity for early metastasis. Since no molecularly-targeted therapeutic agents are clinically available for TNBCs, these tumors, which are frequently resistant to cytotoxic chemotherapy, remain difficult to treat. Nevertheless, progress is being made in the finding of molecular alterations typical of TNBCs toward which to focus therapeutic efforts.

There is increasing evidence that aberrant activation of NF-κB signaling is a frequent characteristic of TNBCs. For this reason, we have evaluated by TransAM assays and report here the effects on the constitutive activation of NF-κB shown by three TNBC cell lines (SUM 149, SUM 159 and MDA-MB-231) of different potential NF-κB inhibitors. They include bisindolylmaleimide I (BIS, a selective PKC inhibitor), MG132 (a proteasome inhibitor), curcumin (endowed with pleiotropic activities) and dehydroxymethylepoxyquinomicin (an inhibitor of NF-κB traslocation into the nucleus). In particular, both in cell growth inhibition and in induction of apoptosis assays, the combination of BIS and MG132 produced significant antitumor synergy in SUM 149 and SUM 159 cells, but not in MDA-MB-231 cells. These data were corroborated by the synergistic antitumor effects obtained also by combining UCN-01 (a PKC pan-inhibitor) and MG132 or bortezomib (another proteasome inhibitor) and BIS.

Further, we have analyzed the effects of BIS and MG132, both alone and together, on the expression in the cells of some NF-κB targets (like Survivin and the other IAPs, BclXL, Bcl2, RKIP, YY1 and SNAIL) at mRNA and protein levels.

Finally, overexpression of MDA-9/Syntenin associated with increased cell migration/invasion has been reported in different human cancers. In our TNBC models, we have verified whether MDA-9/Syntenin has a role in NF-κB activation, as observed in other cancer types. Indeed, silencing the factor with a siRNA anti-MDA-9/Syntenin produced a very strong reduction of NF-κB activation in all the three TNBC cell lines.

In conclusion, different approaches targeting NF-κB activation might be useful for the development of new antitumor therapies for TNBCs and their relative merits are worthy to be further investigated.