Molecular Interaction of Vitamin D Binding Protein - Derived Macrophage Activating Factor with Vitamin D Receptor: A New Perspective in Endometrial Cancer Treatment

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Introduction 1

- Interaction of vitamin D with its receptor (VDR) induces genomic and non-genomic responses that inhibit cancer cell proliferation, metastatic potential and angiogenesis.
- Here we demonstrate that another member of the vitamin D axis, i.e., the vitamin D-binding protein-derived macrophage activating factor (GeMAF), may directly interact with VDR and exert anti-cancer effects.

Materials and Methods

- Purified, activity-tested GeMAF was from Immuno Bionics Ltd.
- Analyses were carried out on the nucleotide and amino-acid sequences of the gene coding for vitamin D binding protein GeMAF (GenBank accession g9 324021743艰辛; 0.99192325-1) and VDR (g1 28311928; g2 93660032-1) in Homo sapiens.
- Three primers were taken into account: sequence identity, sequence similarity, hydrophobic profile.

Introduction 2

- The efficacy of GeMAF as an anti-cancer agent is due to the multiple biological properties of the molecule that are:
  1. Activation of tumoricidal macrophages.
  2. Inhibition of cancer cell proliferation.
  3. Inhibition of cancer cell metastatic potential.
  4. Inhibition of cancer cell-induced angiogenesis.

Results

- There are 22 hydrophobic amino acids near the amino terminus of GeMAF (MKRLVLLLLAVAFGHALREGRQDY) and 23 amino acids near the carboxyl terminus of the VDR (SFQPECSMKLPPLVEYLQINGS——).
- According to the model depicted in the figure, the last 23 hydrophobic amino acids of VDR (on the right of Fig. 1A), located at the outer part of the plasma membrane, is inserted into the first, 23 hydrophobic amino acids of GeMAF (on the left of the figure) located at the external part of the plasma membrane, with vitamin D (represented in yellow) sandwiched in between the two vitamin D-binding proteins.
- Oleic acid, taken as an example of an unsaturated fatty acid bound to GeMAF (Biochem Biophys Res Commun. 1998; 25:1019-24), stabilizes the complex at the level of the plasma membrane.

Discussion 1

- Endometrial cancer is considered vitamin D-sensitive because of activation of VDR.
- Activation of VDR leads to anti-mutagenic, pro-apoptotic and pro-differentiating signaling that contribute to anti-cancer effects (Anticancer Res. 2009; 29:3697-98).
- GeMAF, by activating VDR, elicits a variety of anti-cancer effects that synergize with those of vitamin D itself.

Discussion 2

- These observations at the molecular level are corroborated by observations at the clinical level.
- Here we report the preliminary observation of a series of clinical cases describing the results obtained administering GeMAF to patients with diverse types of cancers at advanced stages.
- In all cases, GeMAF treatment was initiated at late stages of tumour progression.

Discussion 3

- The response to GeMAF was robust and, even though statistical analysis is inappropriate in such an heterogeneous recollection of clinical stories, certain trends emerge evident.
- All patients (n=19), but one, presented with aggressive levels well above the threshold of normal values.
- This indicates high tumour burden and relative immune deficiency (Cancer Lett. 2000; 158:61-4).
- All patients, but one, showed significant decrease of nadirage levels following GeMAF weekly injections.
- In all cases, but two, such decrease was associated with improvement of the clinical condition.
- Conversely, in one patient, clinical improvement was not associated with a decrease of nadirage level.
- No adverse side effects were reported.

Discussion 4

- They open the way to further studies aimed at assessing the precise role and indications for GeMAF in the immunotherapy of endometrial cancer.