Supporting Information For:

Absence of Runx3 expression in normal gastrointestinal epithelium calls into question its tumor suppressor function

Ditsa Levanon[1], Yael Bernstein[1], Varda Negreanu[1], Karen Rae Bone[1], Amir Pozner[1], Raya Eilam[2], Joseph Lotem[1], Ori Brenner[2] and Yoram Groner[1,*]

Departments of [1]Molecular Genetics and [2]Veterinary Resources The Weizmann Institute of Science, Rehovot 76100, Israel.

*Corresponding author: Yoram Groner, Department of Molecular Genetics The Weizmann Institute of Science, Rehovot 76100, Israel. Phone: 972-8-9343972, FAX: 972-8-9344108, Email: Yoram.groner@weizmann.ac.il

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Evaluation of anti-Runx3 antibodies reliability.

In this manuscript we used a variety of methods to show unequivocally the absence of Runx3 expression in GIT epithelium. Among other measures we performed IHC with five different anti-Runx3 Abs on sections from either embryos or adult mice and demonstrated that all five Abs failed to reveal the pronounced Runx3 expression in GIT epithelium reported by Li et al (Li et al, 2002). More recently, the group of Yoshiaki Ito raised several monoclonal anti-Runx3 Abs against the Runx3 protein and identified their recognition regions (Ito et al, 2009).

In an attempt to clarify the immunohistochemical basis for the conflicting results regarding the expression of Runx3 in GIT epithelium, we exchanged anti-Runx3 Abs with Yoshiaki Ito. Our lab provided the poly-G anti-Runx3 Abs (Fig 1 and 2) to Ito's lab and obtained three anti-Runx3 Abs designated R3-8C9, R3-3F12 and R3-1E10 (Ito et al, 2009). Mapping of the epitopes recognized by these Abs as reported by Ito K. et al (Ito et al, 2009) is shown herein in Fig S1A. R3-8C9 recognizes an epitope at the C-terminal end of the protein, whereas the epitope recognized by R3-3F12 and R3-1E10 maps immediately downstream of the RUNT domain (Fig S1A), in a region defined by Ito Y. et al as GIT epithelium "exposed" (Ito, 2008). An additional GIT epithelium "exposed" region (Ito, 2008), is located at the N-terminus of Runx3 (Fig S1A). This region coincides with the region recognized by the two anti-Runx3 Abs, Pep-J and GS, which readily detected Runx3 in GIT leukocytes, but failed to do so in the GIT epithelium (Fig 2A&D).

Using the Poly-G Abs, which we provided, Ito K. et al. (Ito et al, 2009) confirmed our previous observations (Levanon et al, 2001; Levanon & Groner, 2004); and data presented in the manuscript Fig 1 and 2), that Poly-G detect Runx3 in DRG, but not in GIT epithelium (Ito et al, 2009). Using R3-3F12 and R3-8C9 Abs in IHC of GIT sections we found that the GIT leukocytes in each section were clearly stained, whereas the GIT epithelium was not (Fig S1B). Similar results were obtained with Poly-G (Fig S1B). Of note, to avoid the high background staining, that occurs when using mouse primary antibodies on mouse tissues, the analysis presented in Fig S1B&C**,** was conducted with the MOM kit (Vector laboratories Burlingame, CA, USA), designed specifically to use with mouse primary Abs on murine tissues. This protocol was particularly important because GIT epithelial cells are notorious for their high degree of nonspecific antibody binding.

It was previously reported by Ito K. et al (Ito et al, 2009) that of the three monoclonal anti-Runx3 Abs (R3-1E10, R3-3F12 and R3-8C9) R3-1E10 displayed an inverse reactivity pattern compared to Poly-G, namely, it detected Runx3 in GIT epithelium, but not in the DRG (Ito et al, 2009). This was a peculiar finding since Runx3 expression in DRG is considered the undisputed golden standard of the Runx3 expression-signature (Inoue et al, 2002; Kramer et al, 2006; Levanon et al, 2002; Levanon et al, 2001; Li et al, 2002; Marmigere & Ernfors, 2007). To explain the

unusual activity of R3-1E10 Abs the authors postulated that in GIT epithelium the C-terminal region of Runx3 is sequestered in an epithelial-specific manner (Ito et al, 2009; Ito, 2008). Two uncommon mechanisms were suggested. The first postulated that the GIT epithelial C-terminal region of Runx3 undergoes a conformational change due to an epithelial-specific modification of the protein. The second suggested that an unidentified epithelial protein was specifically bound to the C-terminal region and masked certain epitopes (Ito et al, 2009; Ito, 2008). Based on these assumptions, neither of which were supported by any experimental evidence, the authors concluded that the reason Poly-G failed to detect Runx3 in GIT epithelium is because it was raised against the C-terminal region of Runx3, which is inaccessible in epithelial cells (Ito et al, 2009).

Using R3-1E10 Abs on sections of either DRG or GIT tissues, we confirmed the finding of Ito et al (Ito et al, 2009) that R3-1E10 Abs did not detect Runx3 in DRG (Fig S1C), but we further found that R3-1E10 neither reacted with GIT epithelial cells nor with GIT-embedded leukocytes (Fig S1C). Of note, the inability of R3-1E10 to detect Runx3 in DRG and/or in leukocytes, the two major and undisputed sites of Runx3 expression, disqualifies it as a valid anti-Runx3 Ab. Supporting this conclusion are the findings that Mono-G Abs, which were raised against the same GIT epithelium "exposed" region (Fig S1A) readily reacted with Runx3 in DRG, but not in GIT epithelium (Fig S1C). Hence, results attained using R3-1E10 should be interpreted cautiously, in particular its reaction with GIT epithelium (Ito et al, 2009). Together, the combined outcome of the IHC experiments (Fig S1B-C) and the comprehensive evidences for the absence of Runx3 in GIT epithelium described in the manuscript, exclude the possibility of a GIT epithelium-specific sequestering of Runx3 (Ito et al, 2009; Ito, 2008) and demonstrate that R3-1E10 is not a valid anti-Runx3 Ab.

In all, more than seven anti-Runx3 Abs were tested, either in the present manuscript or by Ito et al (Ito et al, 2009); of these, only R3-1E10 did not detect Runx3 in DRG and leukocytes. Therefore, as noted before, it is unfortunate and scientifically unsound that of all available anti-Runx3 Abs, R3-1E10 was the one recently used to detect Runx3 expression in GIT epithelium (Ito et al, 2008) without a proper disclosure of any information regarding its unique properties. Given that GIT

epithelial cells are notorious for their high degree of nonspecific antibody binding, it is important to note that of the seven anti-Runx3 Abs raised by different laboratories not a single one produced a reliable signal when reacted with GIT epithelium (Fig 2 and Fig S1). This finding poses a serious challenge to published data documenting Runx3 expression in GIT epithelium that was solely based on IHC. The data presented herein which using various measures demonstrate that Runx3 expression in undetectable in GIT epithelium strongly support this conclusion.

Supporting Information References

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Supporting Information Figure 1

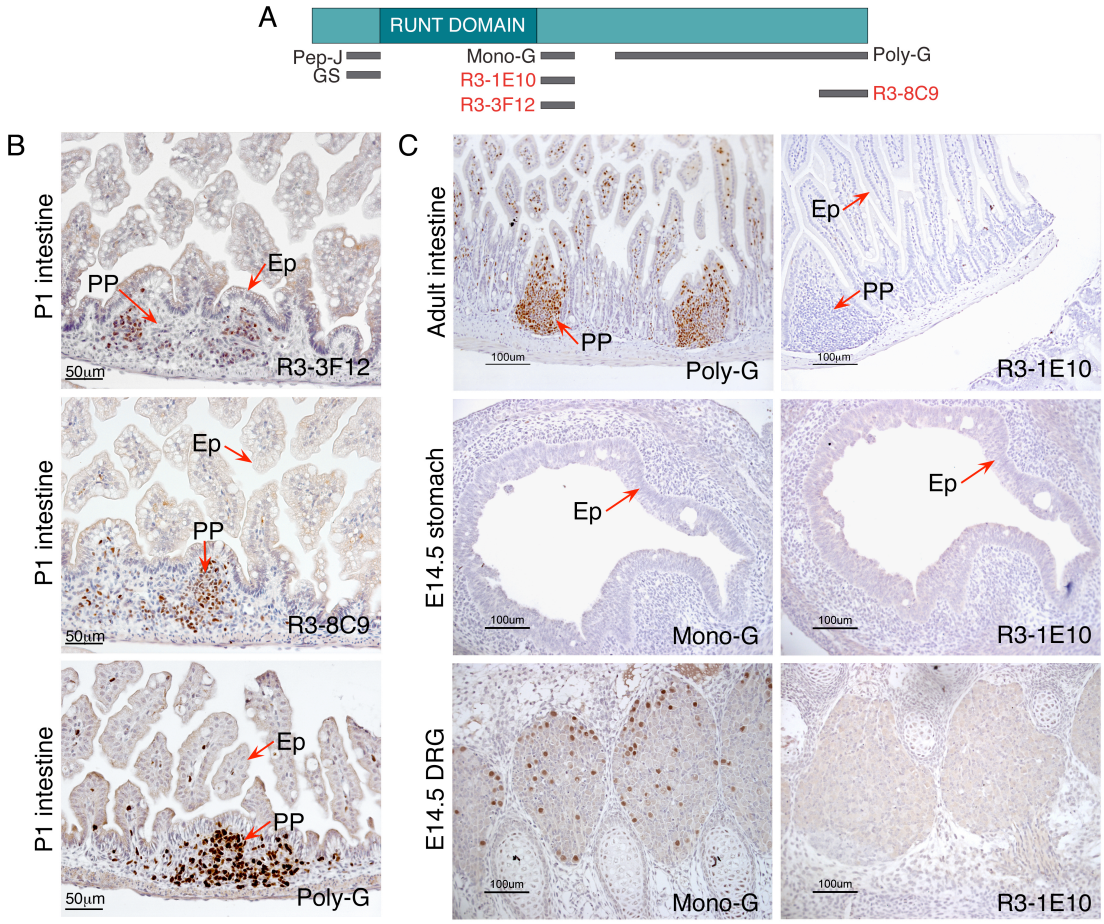

Figure S1. Rigorous evaluation of anti-Runx3 Abs demonstrates that R3-1E10 is an unreliable reagent for detection of Runx3 expression.

A. Scheme of Runx3 protein structure indicating the positions of the peptides used for generation of the Abs (Poly-G, Mono-G, Pep-J and GS), or the epitopes recognized by the anti-Runx3 Abs (R3-8C9, R3-3F12 and R3-1E10).

B. *Bona fide* anti-Runx3 Abs raised either by Ito's group (R3-3F12 and R3-8C9) or by us (Poly-G) failed to detect Runx3 in GIT epithelium. Transverse section of one-day-old (P1) intestine from WT mice immunostained either by R3-3F12, R3-8C9 or Poly-G Abs using the MOM kit (Vector laboratories). Runx3 was detected in GIT leukocytes

located in the Peyer's patches (PP), but was not detected in the surrounding GIT epithelium (Ep).

C. The R3-1E10 Ab does not have Anti-Runx3 specificity. Transverse section of adult intestine and E14.5 stomach or DRG immunostained with Poly-G, Mono-G or R3-1E10 Abs. In adult intestine (top panels), Poly-G detected Runx3 in Peyer's patches (PP) leukocytes and GIT-embedded IEL, whereas R3-1E10 did not. Neither Poly-G nor R3-1E10 detected Runx3 in the intestinal epithelium. The stomach of E14.5 embryos (middle panels) is practically devoid of leukocytes. Neither Mono-G nor R3-1E10 detected Runx3 in the stomach epithelium. Of note, these two monoclonal anti-Runx3 Abs (Mono-G and R3-1E10) were raised against similar Runx3 region (A). In E14.5 DRG (bottom panels) Runx3, which is highly expressed in TrkC neurons (Inoue et al, 2002; Kramer et al, 2006; Levanon et al, 2002; Levanon et al, 2001; Li et al, 2002; Marmigere & Ernfors, 2007), is readily detected by Mono-G, but not by R3-1E10.

Supporting Information Figure 2

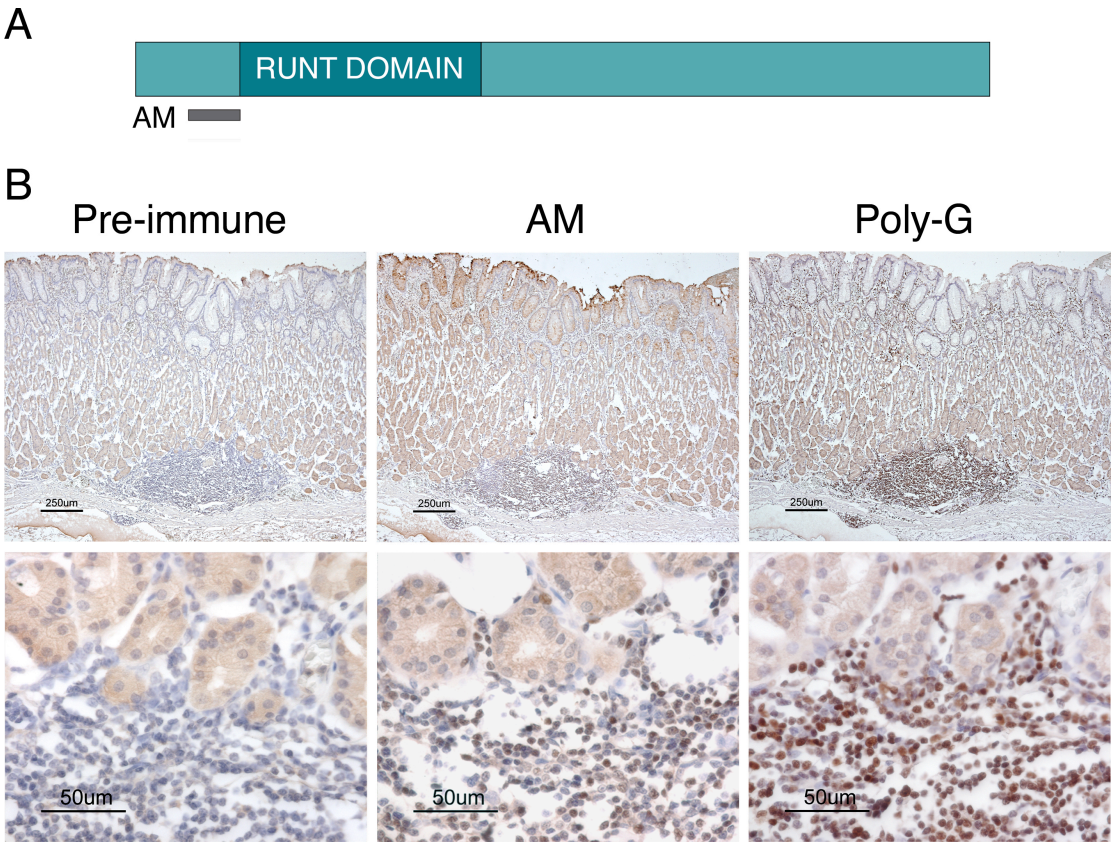

Figure S2. Anti-RUNX3 antibodies detect RUNX3 protein in leukocytes but not in epithelium of human stomach.

A. Scheme of RUNX3 protein structure indicating the position of the peptide used for generation of the Active Motif (AM) anti RUNX3 antibody. The position of Poly-G is shown in Fig S1.

B. Human cardiopyloric stomach sections (Upper panels x4, lower panels x40) were reacted with pre-immune serum (left panels), with AM Ab (middle panels), or with Poly-G anti RUNX3/Runx3 Ab. The pre-immune serum as well as the AM and Poly-G Abs reveal the characteristic high background staining in the epithelium. Specific staining of leukocytes is detected in the AM and Poly-G but not the pre-immune panels.

Supporting Information Table 1

Table S1. List of publications addressing associations of Runx3 loss with tumor development in wide spectrum of cancers

The list was compiled from PubMed using "Runx3" and "Cancer" as search terms. The original retrieved list of 333 articles was reduced to the 286 articles listed below following evaluation for relevancy. The list is up-to-date as of May 8 2011

Ahlquist T, Lind GE, Costa VL, Meling GI, Vatn M, Hoff GS, Rognum TO, Skotheim RI, Thiis-Evensen E, Lothe RA (2008) Gene methylation profiles of normal mucosa, and benign and malignant colorectal tumors identify early onset markers. Mol Cancer 7**:** 94

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