

LETTER TO EDITOR

Conserved histocompatible machinery in marine invertebrates?**B Rinkevich***Israel Oceanography & Limnological Research, National Institute of Oceanography, Tel Shikmona, PO Box 8030, Haifa 31080, Israel**Accepted May 26, 2015*

To the Editor

How would we best inquire the challenging query for the likely shared allorecognition properties between taxonomically distant marine invertebrates? Are the customary comparisons made with the mammalian immune systems satisfactory? The below discussion challenges this routinely employed research approach.

As organismal genetic-homogeneity is assumed to be evolutionary beneficial in preventing inner-organism conflicts (Dawkins, 1990; Pal and Papp, 2000), numerous natural and experimental transplantation situations have spawned considerable interest in the evolution of allorecognition, the non-pathogenically directed property of immunity (Stewart, 1992; De Boer, 1995; Rinkevich, 1999). Therefore, it has been proposed that preserving 'individuality' from soma and the germline littering by conspecific alien cells might have been the primeval function of the immune system, a theory that sees allorecognition as the possible key common background on which the diverse immunity has been developed (Magor *et al.*, 1999; Rinkevich, 1999, 2012). Following the aforementioned rationale, and if preservation of the individual identity was the original and salient function of the primitive immune system before it was harnessed to defend from invasive pathogens, we may expect to find intimate linkages between the allorecognition machineries in various phyla of multicellular organisms (Grosberg, 1988).

Indeed, allorecognition phenomena exhibit suites of effector mechanisms, are ubiquitously recorded in diverse taxa of marine sedentary invertebrates, including sponges, cnidarians, bryozoans and urochordates, and are frequently documented in the field following direct tissue contacts between conspecifics (e.g., Oka and Watanabe, 1960; Hildemann, 1979; Rinkevich, 1999, 2002; Cima *et al.*, 2004; Hughes *et al.*, 2004; Cerrano *et al.*, 2007; Fernández-Busquets, 2008). These tissue-to-tissue contacts beget surprisingly complex sets of allorecognition phenomena, typified

by extreme allotypic diversity, a wide range of effector arms (many of which are simultaneously used for other purposes, such as feeding and competition; Williams, 1991; Rinkevich, 2011), allogeneic maturation, highly tuned immunological specificity, quasi-immunological memory, alloincompatible necrotic zones and fusion events that lead to chimerism (reviewed in Oka and Watanabe, 1960; Grosberg, 1988; Leddy and Green, 1991; Rinkevich 1996a, b, 1999, 2002, 2004, 2011; Gaino *et al.*, 1999; Cima *et al.*, 2004; Cerrano *et al.*, 2007). The genetics of allorecognition in marine invertebrates were elucidated in two model systems, the hydrozoan *Hydractinia symbiolongicarpus* (Cadavid *et al.*, 2004; Nicotra *et al.*, 2009) and the colonial urochordate *Botryllus schlosseri* (Sabbadin *et al.*, 1992; Rinkevich, 1993; Voskoboynik *et al.*, 2013a).

While the commonalities of allorecognition phenomena are above dispute (Loker *et al.*, 2004), the evolutionary basis for the effector mechanisms is not easily understood or illustrated yet. Many of the related evolutionary claims, which are based on the striking superficial similarities between some genes and processes in marine invertebrates, are based on the claimed erroneous notion, that vertebrate immunity and marine invertebrate allorecognition are homologous, 'stemming from the rationale that the early appearance of host defense indicates that same immune constituents are shared by most multicellular organisms; a sort of anthropocentrism' (Rinkevich, 2011). Also, synthetic comparisons of marine invertebrates' genes with seemingly counterpart vertebrate immune genes (the common approach taken by scientists) result in very limited valid information regarding the nature of allorecognition in marine invertebrates, as does the employment of deduced genomic sequences or gene homology comparisons (Loker, 2004; Rinkevich, 2011, 2012). The same holds true when the comparisons are made on the cellular level (Peddie and Smith, 1995; Ballarin *et al.*, 2001; Khalturin *et al.*, 2003; Dunn, 2009). The literature thus reveals that we still do not really know what allorecognition in marine invertebrates is. As complex as allorecognition phenomena in marine invertebrates are, the historecognition attributes that accept/reject alien tissues are probably not associated with host-parasitic and disease

Corresponding author:

Buki Rinkevich
Israel Oceanography & Limnological Research
National Institute of Oceanography
Tel Shikmona, PO Box 8030, Haifa 31080, Israel
E-mail: buki@ocean.org.il

responses; thus host-parasitic/disease events (that are customary compared with the mammalian immune systems) have emerged as a serious obstacle to elucidating the nature of allorecognition (Rinkevich, 2012).

Based on the aforementioned, we may re-examine the following query: Are the salient properties of allorecognition systems in marine invertebrates conserved and thus shared by unlike taxa? This would be best summoned by analyzing allorecognition in one of the most morphologically simplest extant metazoans that do not possess a circulatory system (e.g., Cnidarians; Dunn, 1999) and comparing the results with results from one of the most developed metazoan groups that has a circulatory system operating in self/non-self recognition (e.g., colonial Urochordates; Rinkevich, 2002). Both groups present copious *in situ* documentations for allogeneic and xenogeneic encounters. As the cellular components of allorecognition in both phyla are clearly dissimilar (e.g., the nematocysts in cnidarians and the morula cells in the tunicates; Rinkevich *et al.*, 1998; Dunn, 1999; Ballarin *et al.*, 2001; Rinkevich, 2012), it is advisable to establish cross-phyla comparisons at the molecular constituents that actually manifest allorecognition responses (in lieu of molecular comparisons with lists of mammalian immune related genes). This approach is further eased by the recent development in genome sequences in marine cnidarians and urochordates (e.g., Rast and Messier-Solek, 2008; Steele *et al.*, 2011; Voskoboynik *et al.*, 2013b).

A recent study (Oren *et al.*, 2013) illuminates the scientific insight that surfaced when employing the cross-invertebrate phyla comparisons approach and the need for additional, similar studies. Oren *et al.* (2013) compared two independently developed allogeneic rejection transcriptomes, one from incompatible challenged colonies of the stony coral *Stylophora pistillata* and the other from allo-rejecting partners of the ascidian *B. schlosseri*. This revealed common expression patterns of specific immune-related genes and shared functional attributes expressed during allogeneic rejection. Oren *et al.* (2013) disclosed 74 similar blast matches in the immune-related categories of the coral and the ascidian expression libraries, accounting for 37.2 % of the total immunerelated matches. Within these matches, 43/74 cases were exact matches. Two highly noticeable genes within this shared list of expressed genes were the immunophilins, Cyclophilin A (CypA) and the FK506-binding protein (FKBP). The mRNA expressions of the coral and ascidian immunophilins in allorecognition challenged colonies were restricted to the specific effector cell populations (nematoblasts and nematocytes in the coral and morula cells in the ascidian). Furthermore, gene expressions were limited to only some of the effector cells within a population, disclosing disparities in numbers and location between naïve and immune challenged colonies. Administration of the immunosuppression drug Cyclosporine-A during ascidian allogeneic interactions inhibited both the fusion and the rejection reactions, probably through the inhibition of the ascidian morula cells' movement and activation.

The results of Oren *et al.* (2013) illuminated the evolutionary shared immunocyte activation mechanisms that take place during allogeneic responses in these remotely affiliated taxa. These remarkable similarities are present at all allogeneic levels and include a similar inhibitory effect of immunosuppressive agents. Cumulatively, the results showcase the need for additional studies targeting cross-invertebrate phyla comparisons (and less studies that target vertebrates/invertebrates comparisons) on the molecular pathways characteristic to allorecognition responses.

Acknowledgements

This study was supported by a grant from the Israel Science Foundation (68/10).

References

- Ballarin L, Franchini A, Ottaviani E, Sabbadin A. Morula cells as the major immunomodulatory hemocytes in ascidians: evidences from the colonial species *Botryllus schlosseri*. Biol. Bull. 201: 59-64, 2001.
- Cadavid LF, Powell AE, Nicotra ML, Moreno M, Buss LW. An invertebrate histocompatibility complex. Genetics 167: 357-365, 2004.
- Cerrano C, Calcinaï B, Di Camillo CG, Valisano L, Bavestrello G. How and why do sponges incorporate foreign material? Strategies in Porifera. Porifera Research: Biodiversity, Innovation and Sustainability. Série Livros 28: 239-246, 2007.
- Cima F, Sabbadin A, Ballarin L. Cellular aspects of allorecognition in the compound ascidian *Botryllus schlosseri*. Dev. Comp. Immunol. 28: 881-889, 2004.
- Dawkins R. Parasites, desiderata lists and the paradox of the organism. Parasitology 100: S63-S73, 1990.
- De Boer RT. The evolution of polymorphic compatibility molecules. Mol. Biol. Evol. 12: 494-502, 1995.
- Dunn SR. Immunorecognition and immunoreceptors in the Cnidaria. Inv. Surv. J. 6: 7-14, 2009.
- Fernández-Busquets X. The sponge as a model of cellular recognition. In: Sourcebook of Models for Biomedical Research, Humana Press, pp 75-83, 2008.
- Gaino E, Bavestrello G, Magnino G. Self/non self recognition in sponges. Ital. J. Zool. 66: 299-315, 1999.
- Grosberg RK. The evolution of allorecognition specificity in clonal invertebrates. Q. Rev. Biol. 63: 277-412, 1988.
- Hildemann WH. Immunocompetence and allogeneic polymorphism among invertebrates. Transplantation 27: 1-3, 1979.
- Hughes RN, Manriquez PH, Morley S, Craig SF, Bishop JDD. Kin or self-recognition? Colonial fusibility of the bryozoan *Celleporella hyaline*. Evol. Dev. 6: 431-437, 2004.
- Khalturin K, Becker M, Rinkevich B, Bosch TC. Urochordates and the origin of natural killer cells: identification of a CD94/NKR-P1-related receptor in blood cells of *Botryllus*. Proc. Natl. Acad. Sci. 100: 622-627, 2003.

- Leddy V, Green DR. Historecognition of the Cnidaria. In: Warr GW, Cohen R (eds), *Phylogenesis of immune functions*, CRC Press, Boca Raton, pp 103-116, 1991.
- Loker ES, Adema CM, Zhang SM, Kepler TB. Invertebrate immune systems—not homogeneous, not simple, not well understood. *Immunol. Rev.* 198: 10-24, 2004.
- Magor BG, Tomoso A, Rinkevich B, Weissman IL. Allorecognition in colonial tunicates: protection against predatory cell lineages? *Immunol. Rev.* 167: 69-79, 1999.
- Nicotra ML, Powell AE, Rosengarten RD, Moreno M, Grimwood J, Lakkis FG, *et al.* A hypervariable invertebrate allodeterminant. *Curr. Biol.* 19: 583-589, 2009.
- Oka H, Watanabe H. Problems of colony-specificity in compound ascidians. *Bull. Mar. Biol. Sta. Asamushi, Tohoku Univ.* 10: 153-155, 1960.
- Oren M, Paz G, Douek J, Rosner A, Amar KO, Rinkevich B. Marine invertebrates cross phyla comparisons reveal highly conserved immune machinery. *Immunobiology* 218: 484-495, 2013.
- Pal C, Papp B. Selfish cells threaten multicellular life. *Trends Ecol. Evol.* 15: 351-352, 2000.
- Peddie CM, Smith VJ. 'Lymphocyte-like' cells in ascidians: Precursors for vertebrate lymphocytes? *Fish Shellfish Immunol.* 5: 613-629, 1995.
- Rast JP, Messier-Solek C. Marine invertebrate genome sequences and our evolving understanding of animal immunity. *Biol. Bull.* 214: 274-283, 2008.
- Rinkevich B. Immunological resorption in *Botryllus schlosseri* (Tunicata) chimeras is characterized by multilevel organization of histocompatibility alleles. A speculative endeavor. *Biol. Bull.* 184: 342-345, 1993.
- Rinkevich B. Immune responsiveness in colonial marine invertebrates revisited: the concourse of puzzles. In: Söderhäll K, Vasta G, Iwanaga S (eds), *Invertebrate Immunology*, SOS Publications, Fair Haven, pp 55-90, 1996a.
- Rinkevich B. Links between alloresponses and their genetic background in colonial urochordates and cnidarians: evidence for the recognition of "nonself" as opposed to "self". In: Stolen JS, Fletcher TC, Bayne CJ, *et al.* (eds), *Modulators of immune responses, the evolutionary trail*, SOS Publications, Fair Haven, pp 1-13, 1996b.
- Rinkevich B. Invertebrates versus vertebrates innate immunity: in the light of evolution. *Scand. J. Immunol.* 50: 456-460, 1999.
- Rinkevich B. The colonial urochordate *Botryllus schlosseri*: from stem cells and natural tissue transplantation to issues in evolutionary ecology. *BioEssays* 24: 730-740, 2002.
- Rinkevich B. Allorecognition and xenorecognition in reef corals: A decade of interactions. *Hydrobiologia* 430/531: 443-450, 2004.
- Rinkevich B. The 'immunology trap' of anthozoans. *Inv. Surv. J.* 8: 153-161, 2011.
- Rinkevich B. Neglected biological features in cnidarians self-nonself recognition. In: Lopez-Larrea C (ed.), *Ancient origin of self recognition systems in nature*, Landes Bioscience, pp 46-59, 2012.
- Rinkevich B, Tartakover S, Gershon H. Contribution of morula cells to allogeneic responses in the colonial urochordate *Botryllus schlosseri*. *Mar. Biol.* 131: 227-236, 1998.
- Sabbadin A, Zaniolo G, Ballarin L. Genetic and cytological aspects of histocompatibility in ascidians. *Ital. J. Zool.* 59: 167-173, 1992.
- Steele RE, David CN, Technau U. A genomic view of 500 million years of cnidarian evolution. *Trends Genet.* 27: 7-13, 2011.
- Stewart J. Immunoglobulins did not arise in evolution to fight infection. *Immunol. Today* 13: 396-399, 1992.
- Voskoboynik A, Newman AM, Corey DM, Sahoo D, Pushkarev D, Neff NF, *et al.* Identification of a colonial chordate histocompatibility gene. *Science* 341: 384-387, 2013a.
- Voskoboynik A, Neff NA, Sahoo D, Newman AM, Pushkarev D, Koh W, *et al.* The genome sequence of the colonial chordate, *Botryllus schlosseri*. *eLife* 2: e00569, 2013b.
- Williams RB. Acrorhagi, catch tentacles and sweeper tentacles - a synopsis of aggression of actinarian and scleractinian Cnidaria. *Hydrobiologia* 216: 539-545, 1991.